Australian Government

National Health and Medical Research Council

REVIEW OF THE USE OF MICROWAVE THERAPY FOR THE TREATMENT OF PATIENTS WITH CANCER

VOLUME 1 - FINAL REPORT TO THE MINISTER FOR HEALTH AND AGEING

REVIEW COMMITTEE ON MICROWAVE CANCER THERAPY
NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL

SEPTEMBER, 2005

ISBN Print: 1864963387

ISBN Online: 1864962313

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This report and its recommendations were prepared by the Review Committee on Microwave Cancer Therapy. The systematic literature review and technical writing were undertaken by Dr Adèle Weston, Dr Kristina Coleman, Dr Sarah Norris and Mr Lachlan Standfield of Health Technology Analysts Pty Ltd.

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Australian Government
National Health and Medical Research Council

The Hon Tony Abbott MP
Minister for Health and Ageing
Parliament House
CANBERRA ACT 2601

Dear Minister

In reference to your request of 3 September 2004 for the National Health and Medical Research Council (NHMRC) to assess the therapeutic effectiveness of the microwave cancer therapy practised by Dr Holt in Western Australia, I am pleased to present the final report *Review of the use of microwave therapy for the treatment of patients with cancer*.

This report was considered by the NHMRC at its 158th Session on 8-9 September 2005 with the final conclusions and recommendations receiving the full support of the Council.

Yours sincerely

Professor John Shine AO FAA
Chair
National Health and Medical Research Council

12 September 2005

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BACKGROUND

In September 2004, the Commonwealth Minister for Health and Ageing, the Hon. Tony Abbott, MP, requested that the NHMRC undertake a review of the therapeutic effectiveness and safety of microwave (UHF) cancer therapy.

TERMS OF REFERENCE

The Terms of Reference for the 2004-2005 Review of Microwave Cancer Therapy were as follows:

> The NHMRC has established the Review Committee on Microwave Cancer Therapy (UHF radiowaves in the range 300 MHz to 300 GHz)[1] which will, having regard to the best available evidence and following consultation with relevant individuals and organisations:
>
> 1. Establish and describe the scientific basis of microwave therapy in the treatment of cancer; and
> 2. Assess the effectiveness and safety of microwave cancer treatments including the use of the Tronado machine; and
> 3. Identify gaps in research knowledge.

TERMS OF REFERENCE 1: ESTABLISH AND DESCRIBE THE SCIENTIFIC BASIS OF MICROWAVE THERAPY IN THE TREATMENT OF CANCER

Description of Technology

UHF cancer therapy aims to expose tumour tissue to electromagnetic radiation, delivered within the radiofrequency range of 300 MHz–300 GHz (which includes ultra high frequency, UHF; super high frequency, SHF; extra high frequency, EHF)[2]. Of particular relevance to the current review is ultra high frequency (UHF) therapy (specifically at a frequency of 434 MHz) as used by Dr John Holt in Western Australia for the treatment of people with cancer. However, other UHF frequencies commonly used elsewhere include 200–300 MHz, 915 MHz, and 2450 MHz, and therefore evidence relating to these frequencies was also included within the review.

Proposed mechanism of action

Internationally, UHF cancer therapy is almost always administered in combination with radiotherapy. Dr Holt offered this combined therapy until 1991. Since then, as Dr Holt has not had access to radiotherapy, he advised that he had been administering UHF cancer therapy in combination with low dose cyclophosphamide, cystine disulphide or penicillamine disulphide (referred to by Dr Holt as 'glucose blocking agents'). The use of these compounds in combination with UHF cancer therapy appeared to be unique to Dr Holt's practice in Western Australia.

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1 Hereafter referred to as '**microwave cancer therapy**','**microwave therapy**' or '**UHF**'.

2 It is acknowledged that the definition of the 'microwave' portion of the electromagnetic spectrum varies. For the purposes of this review, a broad definition of 300 MHz to 300 GHz has been used (UNSW 2004).

The therapeutic effect of UHF cancer therapy is generally thought to result from heating of cancer cells, either directly or indirectly. Dr Holt has hypothesised an alternative mechanism of action, independent of hyperthermia. He argues that there is a specific non-thermal radio-sensitising effect of UHF (Holt 1988), although there are currently no high-quality published animal or human data to support this hypothesis.

TERMS OF REFERENCE 2: ASSESS THE EFFECTIVENESS AND SAFETY OF MICROWAVE CANCER TREATMENTS INCLUDING THE USE OF THE TRONADO MACHINE

This term of reference was addressed in four ways:

- A systematic review of the published literature was conducted to identify evidence related to the therapeutic effectiveness and safety of UHF treatment for cancer;
- A national public consultation was conducted to invite submissions from patients, clinicians and other interested parties;
- An audit of Dr Holt's patient records between 1973 and 2003 was conducted to review clinical data and outcomes; and
- A separate data matching study, was conducted to compare data from WA residents with invasive cancer treated at the Perth Radiation Oncology Centre with Western Australian Cancer Registry data to more systematically identify any potential survival benefits from UHF cancer therapy treatment using a larger sample with more complete data.

All four of these investigations are reported below.

SYSTEMATIC REVIEW

Within the scope of the broader review, the NHMRC commissioned an independent systematic review of the published medical literature relating to the therapeutic effectiveness and safety of UHF cancer treatment for cancer. In total, 2876 publications were identified by the literature search strategy. After application of inclusion/exclusion criteria, 58 relevant studies were included in the review.

Whilst there is a considerable volume of published literature, the study methods were generally not adequate to resolve issues of therapeutic effectiveness. In particular, formal controlled comparisons of patients allocated to differing treatments were lacking. Furthermore, outcomes from these previous clinical studies are inconsistent. There is currently no published evidence to support the effectiveness of UHF cancer therapy in addition to radiotherapy for the treatment of cancer. A possible exception is in the treatment of patients with cancers of the head and neck region where, on balance, there is a suggestion of benefit, although there are methodological limitations with regard to study design, conduct and to overextrapolation of the data.

Importantly, evidence that relates to the use of UHF cancer therapy *with* concurrent radiotherapy should not be extrapolated to the use of UHF cancer therapy *without* radiotherapy. There is currently no published scientific evidence that shows benefit of UHF cancer therapy alone *or* when combined with 'glucose-blocking agents' (GBA) as treatment for patients with cancer.

There are no peer-reviewed publications or single or double-blind randomised controlled trials available to support the use of UHF in combination with radiotherapy (RT).

Reporting of adverse events in the literature was generally poor with results not systematically recorded. Some studies reported the adverse events per patient, some per field and some per lesion. Others reported adverse events as narratives only, with no quantification of the relevant denominator. Therefore, it was not possible to quantitatively summarise the frequency at which adverse events occur with UHF therapy

PUBLIC CONSULTATION

The NHMRC undertook a public consultation process to seek input from patients, clinicians and other interested parties. It was considered that submissions and personal testimonies received from patients, their carers and medical practitioners, might provide additional information regarding treatment effectiveness and safety for the Review Committee to consider.

• Submissions from Individual Patients, Carers and Medical Practitioners

A total of 293 submissions were received, of which 74 contained clinical information relating to individual patients. Information provided in the submissions from patients and carers was generally in the form of testimonials and patient reports of perceived benefits associated with treatment received from Dr Holt between 1974 and 2004. Minimal information was provided regarding the stage of disease at diagnosis or at the time of UHF cancer treatment, and details about use of other concurrent treatments was limited, making it difficult to interpret the information provided. A large proportion of the patients treated prior to 1991 had received UHF cancer therapy in conjunction with conventional radiotherapy, but the radiotherapy dose was not reported. It was therefore impossible to determine if the positive effects of treatment reported were a consequence of UHF cancer therapy or radiation therapy or other treatments (e.g., chemotherapy, surgery). There was minimal reporting of measurable outcomes such as tumour response and time to disease progression.

For these reasons, it was not possible for the Review Committee to reliably determine from these submissions whether or not patients had experienced extraordinary clinical responses as a consequence of receiving UHF cancer therapy.

• Submissions from Cancer Organisations or Government Bodies

Fourteen submissions were received from cancer organisations and government bodies. A number of submissions noted that there was a lack of empirical evidence, including well-designed randomised trials, to establish the therapeutic effectiveness of this treatment, and that a review of Dr Holt's clinical data and outcomes, with a matched cohort of patients treated with conventional therapy, should be undertaken to determine whether this method of cancer treatment warrants further consideration.

Two additional issues were raised in these submissions:

1. Approval of the equipment used by Dr Holt had not been sought through the Therapeutic Goods Administration (TGA).
2. Reimbursement of the treatment is provided through the Australian Government Medicare Benefits Schedule (MBS), although UHF cancer therapy itself is not listed on the MBS.

ASSESSMENT OF PATIENT MEDICAL RECORDS

In addition to the review of submissions, and the systematic literature review of existing empirical evidence, a clinical audit was undertaken to review the medical records of some of Dr Holt's patients and a data matching study was conducted to more systematically identify any potential benefits from UHF cancer therapy.

• Clinical Audit

In order to better understand the therapeutic effectiveness and safety of UHF cancer therapy, the Review Committee, in consultation with Dr Holt, undertook to conduct a patient audit. Despite best efforts, considerable difficulties were encountered in identifying and locating adequate numbers of patient records. As a result, the audit was limited to the following series:

A. 34 bladder cancer patients treated with radiotherapy (RT) alone (between 1973 and 1992);

B. 12 bladder cancer patients treated with combined UHF and RT (between 1974 and 1991);

C. 18 bladder cancer patients treated with combined GBA and UHF (between 1992 and 2005);

D. 56 consecutive cancer patients treated with UHF and RT (between 1980 and 1990);

E. 49 consecutive cancer patients treated with GBA and UHF (between 2001 and 2003); and

F. 10 cases identified by Dr Holt as representing superior clinical outcomes.

In consultation with Dr Holt, bladder carcinoma was selected as it is often localised, treated with radiotherapy rather than chemotherapy or radical cystectomy and often managed with repeat cystoscopy and biopsy to assess response. Also, this tumour was nominated by Dr Holt as one tumour that he regards as being particularly sensitive to treatment with RT + UHF and, perhaps to a lesser extent, to treatment with UHF + GBA. In a previous published report by Dr Holt, 31 of 31 patients (100%) treated with Stage T1 (confined to mucosa) or Stage T2 bladder cancer (involving bladder wall muscle) had complete resolution of their primary cancers following treatment with RT and UHF and patients with Stage T3 (extra-vesical spread) lesions had a control rate of 80% (Holt, 1988).

It is acknowledged that the inability to match for stage makes comparison between the series difficult. Despite the small patient treatment groups, some trends were evident in this audit. Firstly, the complete remission rates were not high in any group. The study did not confirm Dr Holt's previous reports of a 100% response rate for bladder tumours (Holt, 1988). The initial response rate (complete response and partial response) was 50% for RT alone, 34% for RT + UHF and 17% for UHF + GBA. Following salvage surgery, the overall response rate (complete response and partial response) was higher for patients treated with RT alone (44%) compared to RT+UHF (25%) or UHF + GBA (11%).

In the patient groups comprising patients with any type of invasive cancer, the complete response rate was 45% for patients treated with RT + UHF and 4% for those treated with UHF + GBA. The overall response rate (complete response and partial response) was 70% for the RT + UHF group and 10% for UHF + GBA. Following initial and all known subsequent treatments, the complete remission rates at last follow-up or death were 38%

for RT + UHF and 8% for UHF + GBA. However, follow-up time after treatment was short as patients were usually discharged back to their referring doctor and long-term response or survival data was lacking.

In the best ten patient series, one patient had non-invasive ductal carcinoma in-situ (DCIS), and therefore results regarding this patient should not be considered to reflect results for treatment of patients with invasive cancer. This patient also had a salvage mastectomy showing DCIS after UHF therapy. Of the nine remaining patients, eight patients had complete remission or stable disease within three months of initial treatment. However, four subsequently had disease progression. Following study treatment, seven patients received subsequent treatment, including RT alone, UHF + RT, UHF + GBA and/or surgery. Nine patients had complete remission or stable disease at last follow up.

- ### Data Matching Study

The relatively small number of patients obtained through the data audit, short follow-up period and lack of long-term survival data made reliable comparisons between different treatment groups impossible. In view of this, a separate study was undertaken, matching data from 3788 WA residents treated for cancer at the Perth Radiation Oncology Centre with data housed by the Western Australian Cancer Registry. Patients were excluded from the analysis if treatment was given more than 12 months after initial diagnosis to ensure better uniformity between the two treatment groups, RT alone versus RT + UHF as patients treated later were more likely to have more advanced disease. Information available included age at registration, site of the cancer and treatment modality but not disease stage.

This analysis showed a survival disadvantage for patients with four of the seven most prevalent cancers (breast, lung, lymphoma and prostate) who were treated with RT + UHF, and no significant difference in long-term survival for patients with cancers of the head and neck region, bowel or bladder, according to treatment type (RT or RT + UHF). It is unclear whether the survival disadvantage from RT + UHF was due to stage differences between the groups or possibly due to patients treated with RT + UHF receiving suboptimal doses of radiation. Patients receiving RT + UHF had lower total doses of radiation and lower doses per fraction than patients receiving RT alone.

SYMPTOM CONTROL

From the retrospective data audit, symptom control for all tumour sites for the three treatment modalities was as follows; RT alone (83%), RT + UHF (71-74%), UHF + GBA (50 – 57%).

Patients with invasive bladder cancer treated by RT alone seemed to have better disease symptom control compared to patients treated with RT + UHF.

It should be noted that there was no systematic recording of symptom improvement or of quality of life, using validated patient-report measures though this was not unexpected for routine clinical records outside a clinical trial setting.

SAFETY

There is insufficient information to make a reliable assessment of the safety of the treatment delivered by Dr Holt. According to the medical literature, UHF cancer therapy, when used to produce a hyperthermic effect (as in the bulk of the published literature), may be associated with significant side effects/toxicities. However, exact quantification of the rate and severity of side effects is difficult, as many studies have not routinely reported complete safety data. Dr Holt emphasised that any benefits from his treatment is not due to a hyperthermic effect (Holt, 1988). Furthermore, side effects associated with UHF cancer therapy should be considered in the context of the disease and its progression, and of the side effects associated with concurrent treatment options.

Based on results from the data audit, RT + UHF appeared to result in a higher degree of moderate to severe toxicity when compared to RT alone or UHF + GBA for patients with bladder or other invasive cancers. Of the patients with bladder cancer, 56% of patients treated with RT alone, and 62% of patients treated with UHF +GBA, had no or only mild toxicity. Fewer patients (25%) treated with RT + UHF experienced no or only mild toxicity. These results were consistent with the mixed group of patients with any invasive cancer, where a greater degree of toxicity was noted for patients treated with RT + UHF compared with UHF + GBA.

In summary, a meticulous audit of available medical records and a comprehensive cancer registry data matching exercise found that:

- UHF + RT (Dr Holt's preferred treatment) was inferior compared to standard conventional RT, with respect to cancer control or survival, for patients with breast cancer, lung cancer, lymphoma or prostate cancer.
- There was no significant difference in survival between RT or UHF + RT for patients with head and neck cancer, colorectal cancer or bladder cancer when treated with either UHF + RT, or RT alone.
- Although data was limited, in the retrospective audit, UHF + GBA, compared to RT + UHF or RT alone, was inferior in terms of symptom control for all patients with invasive bladder cancer, or any invasive cancers.
- Although nine patients in the "best ten" series had complete remission or stable disease at last follow-up, it was difficult to interpret tumour response in this group as four patients had prior surgery and six patients underwent a combination of post-study treatments including RT alone, RT + UHF, UHF + GBA and surgery.

TERMS OF REFERENCE 3: GAPS IN CURRENT RESEARCH KNOWLEDGE

The development of scientific knowledge generally involves a series of studies, which aim, firstly to establish the theoretical foundation for an area of investigation, animal and human testing, the feasibility and safety of conducting an intervention study, and the testing of a hypothesis to determine if there is preliminary data to support a randomised controlled trial (RCT). If the findings from these studies demonstrate scientific merit and do not appear to result in greater harm to the patient than would be the case with standard treatment, then a RCT is appropriate.

The systematic review, overall, did not provide evidence of significant benefit for the use of UHF as treatment for patients with cancer and raised some concerns about safety. Subsequent examination of the clinical data and the data matching study did not provide

evidence of improved survival and symptom control, and in fact showed poorer survival for people with breast cancer, lung cancer, lymphoma or prostate cancer. Therefore, there appears to be no current justification for further research at present on the use of UHF for the treatment of patients with cancer.

The Review Committee has, however, identified the following gaps in research knowledge aimed at improving the communication and interpretation of information about medical treatments:

- Understanding how to improve communications to patients with cancer, and their families and carers about the risks and benefits of potential treatments;
- Understanding how patients obtain, interpret and apply medical information about health and disease to themselves and others; and
- Understand how to assess the quality and scientific validity of medical information.

CONCLUSIONS

There is no published scientific evidence or clinical data currently available to the Review Committee that supports the effectiveness of UHF either alone or in combination with RT or GBA treatment for cancer in humans.

Notwithstanding the limitations of the retrospective patient audit, the comprehensive literature review, the patient audit and data matching study found that:

- There is no high-quality published scientific evidence which shows benefit in terms of therapeutic effectiveness of microwave (UHF) cancer therapy alone or when combined with RT or GBA for the treatment of cancer.
- UHF in combination with RT was inferior compared to standard conventional radiotherapy with respect to disease control and survival for patients with breast cancer, lung cancer, lymphoma or prostate cancer.
- There was no significant difference in survival between RT alone or RT + UHF for patients with head and neck, colorectal or bladder cancer.
- UHF + GBA was inferior to RT in terms of symptom control and disease control in all sub-groups in the retrospective audit for patients with bladder or any invasive cancer.
- There is insufficient information to make a reliable assessment of the safety of UHF in combination with RT, or UHF in combination with GBA for the treatment of patients with cancer.
- RT alone had better symptom control rates in bladder cancer patients, than UHF + RT or UHF + GBA.
- UHF + GBA appeared to have a lower rate of toxicity than UHF + RT and RT alone.

RECOMMENDATIONS

1. On the basis that, after review of all the available data, there is no evidence that UHF alone, or in combination with GBA has significant activity against human cancer and that there is no evidence that UHF adds to the effectiveness of RT, and the suggestion that UHF may increase toxicity and potentially reduce the therapeutic effectiveness of RT if sub-optimal doses are prescribed, the Review Committee recommends that the Minister for Health and Ageing:

- Notes that at present there is no basis to recommend additional clinical studies into UHF cancer therapy.
- Considers the appropriateness of ongoing public funding of this treatment through the MBS.
- Requests the Therapeutic Goods Administration to investigate the approval of UHF devices for the treatment of patients with cancer; and
- Disseminates the outcomes of this review to health professionals, patients, their families and carers, and to the Australian community.

2. As it is important that the Australian public is able to make informed individual choices about their health care which are informed by accurate assessments of the best available scientific evidence, the Review Committee also recommends that the Minister for Health and Ageing:.
   - Explores ways to assist patients, their carers and families, and the community to understand and evaluate information about the benefits and risks of treatments for cancer and other diseases so that fully informed decisions can be made; and
   - Considers referring the issue of media reporting of medical therapies through the Minister of Communications, Information Technology and the Arts, to the Australian Communication and Media Authority requesting a review of policies on the nature of the reporting of treatments for cancer and other diseases.

CHAPTER 1: INTRODUCTION

In September 2004, the Commonwealth Minister for Health and Ageing, the Hon. Tony Abbott, MP, requested that the NHMRC undertake a review of the therapeutic effectiveness and safety of microwave cancer therapy (The NHMRC process report is presented in **Appendix 1**). The review was to be inclusive of the ultra-high frequency (UHF) microwave therapy provided by Dr John Holt in Western Australia. It is important to note however this centre no longer administers radiotherapy in conjunction with microwave therapy.

The Terms of Reference for the 2004 Review of Microwave Cancer Therapy were as follows:

> The NHMRC has established the Review Committee on Microwave Cancer Therapy (UHF radiowaves in the range 300 MHz to 300 GHz)[3] which will, having regard to the best available evidence and following consultation with relevant individuals and organisations:
>
> 1. Establish and describe the scientific basis of microwave therapy in the treatment of cancer; and
> 2. Assess the effectiveness and safety of microwave cancer treatments including the use of the Tronado machine; and
> 3. Identify gaps in research knowledge.
>
> (see Appendix 2)

A Review Committee was established to oversee the conduct of the review. The membership of the Review Committee is presented in **Appendix 3**. A Sydney-based consultancy (Health Technology Analysts Pty Ltd) was contracted to undertake a systematic review of the published clinical evidence and to summarise the findings of the Review Committee.

Within the scope of these Terms of Reference, the Review Committee determined that the review may include some or all of the following components:

- Prepare a description of microwave cancer therapy as conducted in Western Australia and elsewhere and consider the proposed scientific basis of any therapeutic effect.
- Conduct a systematic review of the published medical literature relating to the therapeutic effectiveness and safety of microwave cancer therapy.
- Call for and consider public submissions from patients, clinicians, medical colleges, cancer organisations and other interested parties.
- Examine clinical information from a sample or series of patients treated with microwave therapy in Western Australia (subject to availability).
- Identification of gaps in research knowledge relating to microwave therapy.

This report presents the methodology and findings of these processes.

[3] Hereafter referred to as 'microwave cancer therapy', 'microwave therapy' or 'MT'.

CHAPTER 2: SUBMISSIONS RECEIVED

The NHMRC undertook a public consultation process to seek input from patients, clinicians and other interested parties. Consultation took the form of invitations to make a submission (i) by public notices placed in *The Weekend Australian* and all major metropolitan newspapers on Saturday 2 October; (ii) by a notice placed on the NHMRC website and (iii) by letters sent to known stakeholders and other interested parties (see **Appendix 4** for a copy of the public notice calling for submissions and **Appendix 5** for a list of organisations and individuals who were invited by letter to make a submission). In particular, it was hoped that submissions and personal testimonies would be received from patients, their carers and medical practitioners, and that these would provide additional therapeutic effectiveness and safety data for consideration by the Review Committee[4].

A total of 293 submissions were received. Of these, 176 provided no information addressing the Terms of Reference of the review and therefore were not considered within this report. The content of these submissions is summarised in **Table 1**. Eight of these submissions expressed concern regarding the conduct of the review. Issues raised by these submissions were conveyed to the Review Committee for their consideration.

Table 1 Submissions that did not contain information relevant to Terms of Reference

Total number of submissions	**293**
Reason for exclusion	
Requesting information regarding microwave therapy, Dr Holt's contact details, an appointment with Dr Holt or other clinical advice	77
Requesting information regarding the review process or a copy of the report	37
Expressing support for Dr Holt, his therapy or the review process in general terms only	38
Expressing concerns about the review process	8
Provided clinical details but no use of microwave therapy	5
Expressing concern over being rejected for therapy	2
Other (eg. insufficient information, contact details only, not cancer)	9
Total submissions not containing information relevant to the Terms of Reference	**176**

The remaining 117 submissions that contained information of relevance to the Terms of Reference were categorised as shown in **Table 2**.

Table 2 Submissions containing information relevant to Terms of Reference

Category	**Number**
Submissions received from patients (or their carers) who had been treated with microwave therapy and containing individual patient characteristics and outcome data	71
Submissions received from patients (or their carers) who had been treated with microwave therapy and containing individual patient characteristics, but still awaiting results	10
Submissions from individual clinicians [a]	6
Submissions from medical and cancer organisations and government bodies	14
Submissions from other organisations and individuals	16
Total submissions containing information relevant to the Terms of Reference	**117[a]**

[a] Two submissions from clinicians also contained individual patient data

[4] Persons making submissions had the option to mark patient data as confidential.

The majority of the submissions received from patients expressed support for Dr Holt or his treatment. The Review Committee did not consider the anecdotal support for Dr Holt treatment as constituting scientific evidence. Submissions containing individual patient data relating to the therapeutic effectiveness and safety of UHF cancer therapy are discussed in more detail in **Chapter 4, Part 2**.

Several submissions provided scientific material that contributed to discussion of the scientific basis and proposed mechanism of action of microwave therapy (**Chapter 3**). A complete list of all submissions received appears in **Appendix 6**.

CHAPTER 3: DESCRIPTION OF TECHNOLOGY AND PROPOSED MECHANISM OF ACTION

DESCRIPTION OF TECHNOLOGY

Microwave cancer therapy aims to expose tumour tissue to electromagnetic radiation, delivered within the radiofrequency range of 300 MHz–300 GHz (includes ultra high frequency, UHF; super high frequency, SHF; extra high frequency, EHF)[5]. Of particular relevance to the current review is the ultra high frequency of 434 MHz that was available as cancer therapy in Australia. However, other microwave frequencies commonly used elsewhere include 200–300 MHz, 915 MHz, and 2450 MHz, and therefore evidence relating to these frequencies is also included within the current review. The therapeutic effects of lower radiofrequencies not considered to be microwave (eg. 8 MHz, 13.56 MHz, 27.12 MHz) have also been extensively studied, however these are not the subject of the current review.

Microwave cancer therapy can be delivered in many different ways. The microwaves may be delivered externally through the skin, or via more invasive internal routes (eg, intraluminal, interstitial, intraoperative, transrectal delivery). The focus of the current review is upon the external delivery of microwave therapy, as other methods are not routinely used for cancer therapy in Australia at present.

The vast majority of microwave cancer therapy in Australia appears to be undertaken at a single clinic in Perth, Western Australia[6] under the direction of Dr John Holt. This clinician has offered microwave cancer therapy since 1974, although the treatment regimen has been modified several times over the past three decades. Prior to 1991, patients treated by Dr Holt with microwave therapy in Western Australia usually received concurrent external beam radiotherapy. However, since that time the therapy has been administered by Dr Holt without radiotherapy (see **Appendix 12** for more detail).

The Western Australian clinic operated by Dr Holt used the following treatment regimen[7]:

- Intravenous injections of cyclophosphamide (2.5–5 mg), cystine disulphide (1 g) and/or penicillamine disulphide (1 g). These compounds are collectively referred to by Dr Holt as 'glucose-blocking agents'. Higher doses of cyclophosphamide are recognised elsewhere as cytotoxic chemotherapy; cystine disulphide is a non-essential amino acid; and penicillamine disulphide is a detoxifying (chelating) agent for heavy metal poisoning. Doses are not titrated to body weight.
- Waiting period of 10–20 minutes.
- 20 minutes of 434±1 MHz microwave therapy delivered by four generators operating at 0.6kW each (this may be divided into 2 x 10 minute sessions).
- Treatment (inclusive of both injections and microwave therapy) is repeated on working days for a period of three weeks (ie., 3 x 5 = 15 days total).
- Patients do *not* receive radiotherapy.

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5 It is acknowledged that the definition of the 'microwave' portion of the electromagnetic spectrum varies. For the purposes of this review, a broad definition of 300 MHz to 300 GHz has been used (UNSW, 2004).

6 NHMRC is aware that treatment is currently being performed / may soon be available in Victoria and Queensland.

7 Dr Holt ceased practicing at the Radiowave Therapy Centre on 30 June 2005.

Despite a considerable volume of research undertaken over the past 20 years, microwave therapy in other countries remains experimental, rather than forming a part of routine cancer treatment (**Appendix 7** provides a list of researchers known to have investigated MT). Whilst the dose regimens and the total thermal dose administered vary greatly between users of microwave cancer therapy internationally, it is almost always given in combination with radiotherapy. Typically, the microwave exposure occurs soon after the radiotherapy (eg, 15-30 mins later). Individual exposures to microwave therapy are usually 30-60 minutes in duration, although this is often limited by patient tolerance to heat. Concurrent tissue cooling is applied by most users, although the methods vary. Cold water bladders, sprays or cold air are all commonly used. Analgesics or anaesthetics are often used to minimise pain associated with heating.

A further difference between the use of microwave therapy in Western Australia and elsewhere is the role of low dose cyclophosphamide, cystine disulphide and penicillamine disulphide (referred to by Dr Holt as 'glucose blocking agents'). There are no published reports of the use of these compounds by other groups internationally[8]. Neither is there any peer-reviewed pre-clinical or clinical data on the efficacy, mechanism or safety of this combination. The use of these compounds in combination with microwave therapy appears to be unique to the Western Australia clinic.

REGULATORY AND REIMBURSEMENT STATUS IN AUSTRALIA

Microwave equipment used in a therapeutic context is regulated as a medical device by the Therapeutic Goods Administration (TGA) according to the requirements of the *Therapeutic Goods Act 1989* and the *Therapeutic Goods (Medical Devices) Regulations 2002*. The TGA have notified the NHMRC (submission #224) that no medical devices used to deliver microwave cancer therapy have been approved for supply in Australia, and that the TGA has not been informed of any clinical trial being (or that has been) undertaken involving such a medical device. Similarly, microwave therapy is not approved by the Food and Drug Administration in the United States for the treatment of malignancies. Cyclophosphamide, cystine disulphide and penicillamine disulphide are all approved by the TGA, albeit for different indications.

The current cost of a course of microwave treatment in Western Australia is A$6,550[9]. The microwave procedure itself is currently not listed on the Commonwealth of Australia Medicare Benefits Schedule (MBS) for public reimbursement. However, consultations related to the treatment are claimed under MBS item numbers 104 and 105 and an additional item number available under a special arrangement made with the Department of Health in 1976 (MBS item number 105-UF). The Health Insurance Commission have advised that this item number is currently reimbursed as a 105 item. In addition, item number 13915, for the administration of cytotoxic chemotherapy, is used by the Western Australian clinic for the administration of glucose blocking agents. **Table 3** presents the MBS item descriptors. In summary, Dr Holt advises patients that $2,251.60 is rebatable for the initial and repeat consultations and for the cytotoxic chemotherapy, whilst up to 80% of the $4,298.40 balance may be rebated under the new Medicare safety net arrangements. The information currently provided to patients regarding the admission, treatment and follow-up procedures of the Western Australian clinic are presented in **Appendix 8**.

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[8] Excluding case reports, only one published study was located that investigated the clinical efficacy of using external microwave hyperthermia in conjunction with cyclophosphamide, but without radiotherapy, however these researchers used a cyclophosphamide dose typical of routine chemotherapy - CDDP 50 mg/m2 + adriamycin 10 mg/body + cyclophosphamide 200 mg/body (Hayashi *et al.* 1999).

[9] Dr Holt support group website, accessed 09/02/2005.

Table 3 Commonwealth Government Medicare Benefits Schedule item number

MBS item number	Item descriptor	Schedule fee
104	SPECIALIST, REFERRED CONSULTATION - SURGERY OR HOSPITAL (Professional attendance at consulting rooms or hospital by a specialist in the practice of his or her speciality where the patient is referred to him or her) - INITIAL attendance in a single course of treatment, not being a service to which item 106 applies	$72.60
105	Each attendance SUBSEQUENT to the first in a single course of treatment	$36.40
105-UF[a]		
13915	CYTOTOXIC CHEMOTHERAPY, administration of, either by intravenous push technique (directly into a vein, or a butterfly needle, or the side-arm of an infusion) or by intravenous infusion of not more than 1 hours duration - payable once only on the same day, not being a service associated with photodynamic therapy with verteporfin	$55.20

Source: Australian Government Department of Health and Ageing Medicare Benefits Schedule Book, 1 November 2004.

[a] The Health Insurance Commission and the Department of Health and Ageing advise that a descriptor is not currently available for this item, and that it is reimbursed as item 105.

PROPOSED MECHANISMS OF ACTION

The entire spectrum of electromagnetic waves can interact with human tissues, but the nature of the interaction is highly dependent upon the frequency. Radiation that is of sufficiently high frequency to cause biological molecules to produce electrically-charged particles is called ionising radiation. Examples include X-rays and Gamma rays (as used in radiotherapy) which exert their cytotoxicity by damaging the cell's DNA. In contrast, microwave radiation is an example of non-ionising radiation. Whilst they do not cause ionisation as they move through human tissue, non-ionising electromagnetic waves do have the potential to heat human tissue.

Non-ionising electromagnetic waves (including microwaves) lose velocity as they move through human tissue and they are refracted, diffracted and dispersed as they encounter heterogeneity within the tissue. Within this portion of the spectrum, energy transfer into the tissue (deposition) increases as the frequency increases and therefore at higher frequencies less energy reaches the deeper tissues (ie., 434 MHz will result in greater energy deposition than 8 MHz, all other things being equal). However, it is important to recognise that another important factor influencing the extent of energy deposition is the nature of tissue through which the waves pass. A conflicting characteristic of microwave delivery is that at lower frequencies (ie, those able to reach deeper tissues), the localisation of the energy deposition is poor. This places a fundamental constraint to the external delivery of microwaves, whereby localised penetration is restricted to depths of less than 2–5 cm below the skin (Dewhirst *et al.* 2000).

In accordance with the laws of electrodynamics, the penetration of microwaves is further reduced when microwaves have to travel through tissue boundaries in a perpendicular direction. A clinically relevant consequence of these boundary conditions arises when one attempts to deliver microwave energy to a tumour with an overlying fat layer. If the electromagnetic field is perpendicular to the fat layer, energy deposition in the fat layer will be 10-times higher than in the underlying tumour tissue (Dewhirst *et al.* 2000).

Therefore, microwave devices that configure the electromagnetic field perpendicular to the skin rarely achieve effective delivery of energy through subcutaneous fat thicknesses greater than ~2 cm.

Hyperthermia-based hypothesis:

It has been proposed that the delivery of microwaves to tumour tissue may have a therapeutic effect. The overwhelming majority of microwave therapy researchers believe that any therapeutic effect of microwave therapy is related to heating of the tumour cell, either directly or indirectly (Arcangeli *et al.* 1985; Hornback *et al.* 1986; Overgaard *et al.* 1995; Lindholm *et al.* 1987; Howard and Bleehen 1988; Ohizumi *et al.* 2000; Valdagni *et al.* 1988; Egawa *et al.* 1989). It is indeed well-known that microwaves can elevate tumour temperature (Arcangeli *et al.* 1985; Gabriele *et al.* 1990; Hornback *et al.* 1986; Overgaard *et al.* 1995), and it is also known that high cell temperatures (approximately ≥42˚C) can result in cell death (Lepock *et al.* 1983; Seegenschmied and Feldmann 1996). The molecular mechanisms of hyperthermic cytotoxicity are continuing to emerge, but it appears to differ from that of ionising radiation, which acts by preferentially damaging the cell's DNA. Nevertheless, it has been hypothesised that microwave cancer therapy may be able to deliver sufficient heat to be cytotoxic to tumour cells and therefore lead to a reduction in tumour size. Indeed, there is some evidence to suggest a relationship between the extent of tumour heating and the therapeutic benefit (Arcangeli *et al.* 1985; Hand *et al.* 1997; Hiraoka *et al.* 1984; Luk *et al.* 1981), although in practice the delivery of adequate heat has proved difficult (Gonzalez Gonzalez *et al.* 1995; Overgaard *et al.* 1995). Assuming heat can be adequately delivered to the tumour, it is theoretically plausible that there may be a) a direct effect of hyperthermia per se, in which case microwave therapy alone would be effective; b) an indirect effect whereby microwave therapy alone has no effect, but microwave-induced hyperthermia increases the effectiveness of concurrent radiotherapy[10]; or c) truly independent but additive effects of microwave-induced hyperthermia and radiotherapy. In practice it is difficult to experimentally distinguish between the latter two possibilities in humans.

Preliminary *in vivo* studies have also suggested that the local metabolic environment may influence the cytotoxicity of hyperthermia. For example, induction of acute intracellular acidosis may increase the sensitivity to heat (Song 1984; Song 1993). Such an environment can be induced by reduced tumour perfusion, or a stimulation of glycolytic rate induced by hyperglycaemia. However, optimisation of the intra-tumour metabolic environment for sensitivity to heat may not be straightforward, as the conditions which *enhance* thermal damage are typically those that *reduce* radiotherapy-induced damage (Seegenschmied and Feldmann 1996). This does however provide an attractive rationale for the combination of radiotherapy and hyperthermia. Similarly, it has been suggested that local hyperthermia may enhance the cytotoxicity of chemotherapy in an animal model (Wiedemann *et al.* 1992).

Non-hyperthermia hypothesis:

An alternative mechanism of action, that is independent of hyperthermia, has been hypothesised by Dr Holt in Western Australia (Holt 1988; Holt 1991). Specifically, Dr Holt states that there is a specific non-thermal radio-sensitising effect related to fluorescence of the cancer in the presence of microwaves (Holt 1988). This hypothesis appears to be based primarily upon observed differences in the reflected radiation from tumour tissue when compared to that from normal tissue (Holt 1988). This is an entirely biologically plausible observation given the differences in density and conductivity of tumour and

10 For example, it has been proposed that heat-exposed cells can not repair the single strand breaks and chromosome aberrations induced by ionising radiation (Overgaard 1989).

normal tissue, and therefore is not an unexpected observation. However, how this would impart any therapeutic effect is not clear. Holt (1988) also contends that this effect only occurs at frequencies between 425 MHz and 440 MHz, but not at the frequencies commonly used elsewhere (13 MHz, 27 MHz, 915 MHz or 2,450 MHz). There is no reference to this hypothesised mechanism of action amongst other proponents of microwave therapy internationally (Arcangeli *et al.* 1985; Gabriele *et al.* 1990; Hornback *et al.* 1986; Overgaard *et al.* 1995). Although proposing a radio-sensitising mechanism of action that is independent of hyperthermia, Dr Holt's clinic in Western Australia delivered microwave therapy in Western Australia without concurrent radiotherapy.

Dr Holt states that heating is *not* the basis for the therapeutic effect of his treatment (Holt 1988; Holt 1991) and, in keeping with this, the microwave therapy he delivered resulted in minimal heating of the patient[11]. This is likely to have an impact upon the safety of the treatment, with fewer heat-related adverse events such as burns and blisters (Ben Yosef and Kapp 1992; Kapp *et al.* 1992). However, it also has the potential to impact upon the effectiveness of the treatment, as several researchers have reported the magnitude of response is directly related to the elevation of temperature at the tumour (Arcangeli *et al.* 1985; Hand *et al.* 1997; Hiraoka *et al.* 1984; Luk *et al.* 1981).

In Western Australia microwave therapy was administered 10–20 minutes after an intravenous injection of cyclophosphamide, cystine disulphide and/or penicillamine disulphide. It is proposed by Dr Holt that compounds such as these reach the target tumour, inhibit glucose metabolism in the tumour cell and reduce cancer load (Holt 2004a; Holt 2004b). Specifically, Dr Holt states that "the application of 434–434 MHz UHF results in an increase in the cancer cell growth rate (by a factor of up to 10 times the normal growth rate)". He states that this rapid cancer cell growth rate "is attributable to the fact that cancer cells conduct electricity, so absorb energy at a greater rate than healthy cells, in turn growing faster" and that "this accelerated growth rate is then destroyed by preventing the cancer cell using glucose from the blood as its energy source or by treating with X ray therapy after UHF"[12]. There is currently no published animal or human evidence to prove these hypotheses[13].

Submissions were received from two leading biological scientists based at the Peter MacCallum Cancer Centre[14] (Dr Ian Radford, Group Leader, Cellular Radiation Biology Group and Dr Roger Martin, Group Leader, Molecular Radiation Biology Group) who had critiqued the Holt 2004 publication. Dr Radford comments that Dr Holt's paper "presents neither sound reasoning nor experimental evidence to support his opinions", whilst Dr Martin notes that within the paper "the author draws on a diverse collection of observations, hypotheses and interpretations of published work but fails, in my opinion, to combine these many threads into an intelligible thesis". In general, the reviewers consider that the hypotheses presented within the paper are not supported by empirical evidence, and in many cases are based upon unconventional or out-dated scientific beliefs.

Irrespective of any theoretical rationale by which microwave therapy could result in tumour cell death (via hyperthermia or other mechanisms), it must be confirmed that such an effect actually occurs in the complex *in vivo* environment in humans, and that

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11 In the 1970s and 1980s, Dr Holt delivered microwaves at a considerably higher power (~2400 kW compared to 2.4 kW at present). With respect to microwave deliver, power is a major determinant of the magnitude of the local temperature elevation.

12 J Pickworth on behalf of J Holt, Personal communication, March 2005.

13 Dr Holt has recently sponsored limited *in vitro* investigations of the impact of 915 MHz microwave upon cell lines at the University of New South Wales. Recent relevant publications from this research group are summarised in **Appendix 17**.

14 Within submission 103.

the effect is of sufficient magnitude to be of therapeutic relevance. Pivotal to this is the ability of microwaves to reach the tumour, and ultimately the ability to objectively measure a clinically relevant effect.

Evidence of a clinically-relevant benefit should be assessed by patient-relevant outcomes. Ideally these should include overall survival, improvements in quality of life, symptom control and palliation. Whilst they are common indicators of a biological effect in cancer research, surrogate outcomes such as tumour response (shrinkage) may not be relevant to the patient - as shrinkage may not necessarily be associated with an improvement in the patient's quality of life or lead to a prolongation of survival. As is the case with all therapeutic interventions, whether pharmacological or procedural, any measured benefit must be balanced against the associated risks and side-effects.

SUMMARY

Several researchers have proposed mechanisms by which microwave therapy could have a therapeutic effect. Irrespective of these hypotheses, it is essential to have consistent evidence of a clinically-relevant therapeutic effect before endorsing the routine use of microwave therapy in Australia. Furthermore, any evidence must be specific to the technology as it is currently administered in Australia.

CHAPTER 4: ASSESSMENT OF CLINICAL EFFICACY AND SAFETY

Within the context of the current review, the assessment of the efficacy and safety of microwave cancer therapy took various approaches:

SYSTEMATIC REVIEW OF THE MEDICAL LITERATURE

In the first instance, the published medical literature was systematically searched for evidence relating to both the efficacy and safety of microwave therapy. Whilst the current review was primarily interested in microwave therapy as currently available in Australia, the literature review was broadened to encompass a wider range of microwave frequencies - with or without concurrent radiotherapy. Furthermore, literature was included whether or not any additional non-cytotoxic compounds were used (e.g. 'glucose-blocking agents'). However, evidence relating to the efficacy and safety of these compounds alone (without concurrent use of microwave therapy) was not sourced.

INDIVIDUAL PATIENT DATA FROM PATIENTS, CARERS OR MEDICAL PRACTITIONERS

The NHMRC undertook a public consultation process to seek input from patients, clinicians and other interested parties. In particular it was hoped that submissions and personal testimonies would be received from patients, their carers and medical practitioners, and that would provide additional clinical efficacy and safety data for consideration by the Review Committee[15].

AUDIT OF PATIENT MEDICAL RECORDS

Following the completion of the literature review, an audit of the medical records of a number of series of patients with cancer treated with microwave (UHF radiowave) therapy in combination with glucose blocking agents or radiotherapy, was undertaken to compare outcomes with patients treated with conventional therapy.

A summary of the evidence arising from the literature review and assessment of individual patient data is presented below. A summary of the patient audit is presented in Chapter 5.

[15] Persons making submissions had the option to mark patient data as confidential.

PART 1: SYSTEMATIC REVIEW OF THE MEDICAL LITERATURE

Within the scope of the broader review, the NHMRC commissioned a systematic review of the published medical literature relating to the clinical efficacy and safety of microwave treatment for cancer. The systematic literature review was undertaken by Health Technology Analysts Pty Ltd, under the auspices of the NHMRC Review Committee on Microwave Cancer Therapy.

SYSTEMATIC LITERATURE REVIEW: METHODOLOGY

The research question to be answered by this systematic literature review was defined by the Review Committee in conjunction with the reviewers:

*Is external microwave therapy an **effective** and **safe** cancer treatment?*

The key components of the research question are as follows:

- **Patient population**
  Adult or paediatric patients with cancer of any type (including lymphoma)

- **Intervention**

  Radiotherapy + Chemotherapy + Microwave therapy[a]

  Radiotherapy + Microwave therapy[a]

  Chemotherapy + Microwave therapy[a]

  Microwave therapy[a] alone

- **Comparator**

  Radiotherapy + Chemotherapy alone

  Radiotherapy alone

  Chemotherapy alone

  Any recognised cancer treatment or no treatment

  [a] For the purpose of this review, microwave therapy is defined as externally-delivered microwaves within the 300 MHz–300 GHz range, with or without concurrent non-cytotoxic compounds.

- **Outcomes**

  Patient relevant efficacy outcomes: quality adjusted survival, overall survival, progression-free survival, tumour response[16], quality of life and symptom improvement. Safety outcomes: mortality and any adverse events.

Although the frequency used for microwave cancer therapy in Australia is 434 MHz, the broadest definition of microwave cancer therapy spans the frequency range of 300 MHz–300 GHz. Other microwave frequencies commonly used for cancer therapy elsewhere in the world are 200–300 MHz, 915 MHz and 2,450 MHz. All of these microwave frequencies were included in the current literature review. Furthermore, the review was inclusive of situations where microwave therapy was used in conjunction with non-cytotoxic agents such as glucose blocking agents. However, although more invasive routes of microwave delivery are used elsewhere, the current literature review is limited to the external delivery of microwave therapy.

Literature search strategy

A search of the literature was undertaken in the MEDLINE and EMBASE databases using EMBASE.com. In addition, the bibliographies of included papers were examined for relevant studies. The Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) were searched to help identify existing systematic reviews. Searches were limited to English-language publications.

[16] Wherever possible, complete tumour response is preferentially reported.

The search was conducted in October 2004. Therefore, studies published after this date were not eligible for inclusion in the systematic review. The search strategy used and the resulting number of citations identified are outlined in **Table 4**.

Table 4 Search strategy

Database	Date searched	Search no.	Search terms	Citations
EMBASE.com (EMBASE + MEDLINE)	<1966 – 7 October 2004	1	'neoplasm'/exp	1824674
		2	Metastatic OR metastasis OR metastases OR tumour OR tumours OR tumor OR tumors OR cancer OR cancerous OR malignant OR sarcoma OR melanoma OR carcinoma	1874257
		3	'hyperthermic therapy'/exp OR 'microwave therapy'/exp OR 'microwave irradiation'/exp OR imicrowave irradiation'/exp	14955
		4	'microwave hyperthermia' OR 'localised hyperthermia' OR 'localized hyperthermia' OR 'local external hyperthermia' OR 'radio-frequency hyperthermia' OR 'clinical hyperthermia' OR 'microwave-induced hyperthermia' OR 'local hyperthermia' OR 'regional hyperthermia' OR 'controlled hyperthermia' OR 'local ultrasound hyperthermia' OR 'intermittent hyperthermia'	1579
		5	'hyperthermia *3 radiotherapy' OR 'radiotherapy *3 hyperthermia' OR 'hyperthermia *3 chemotherapy' OR 'chemotherapy *3 hyperthermia' OR 'hyperthermia *3 radiation' OR 'radiation *3 hyperthermia' OR 'hyperthermia *3 irradiation' OR 'irradiation *3 hyperthermia'	2401
		6	'434 mhz' OR '434 megahertz' OR '433 mhz' OR '433 megahertz' OR '430 mhz' OR '430 megahertz'	91
		7	microwave OR microwaves	12928
		8	tronado OR 'radio-frequency-induced currents' OR vhf OR 'ultra-high-frequency radiation' OR 'immobilizing mitotic energy' OR thermoradiotherapy	395
		9	(#1 OR #2) AND (#3 OR #4 OR #5 OR #6 OR #7 OR #8)	7310
		10	Limit #9 to English and Human	3631
		11	Limit 10 to Editorial OR Letter OR Review	775
		12	#10 NOT #11	2856
		Sub-total	**after exclusion of duplicate citations**	**2825**
Bibliographies of included studies and other sources				51
Non duplicate citations				**2876**

Note: Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effectiveness were searched. No relevant systematic reviews were identified.

In total, 2876 non-duplicate citations were identified. Inclusion/exclusion criteria were applied in a number of stages, as outlined in **Table 5**. After application of initial exclusion criteria to the titles/abstracts, a total of 271 full papers were retrieved and assessed for inclusion. After application of the inclusion/exclusion criteria to the full papers, 58 included citations remained, and were included in the review. Reasons for exclusion for each of the full papers assessed are included in **Volume 2**. Papers with less than 10 patients in each arm are excluded from the efficacy review but are included in the review of safety (n=19).

In order to ensure all relevant information was retrieved, all papers previously published by Dr John Holt were reviewed, irrespective of whether or not they had met the criteria for inclusion in the formal systematic literature review. The content of each of these publications is briefly summarised in **Appendix 15**.

Table 5 Inclusion/exclusion of citations

Exclusion criteria	Number
Total citations	2876
Title/abstract (first pass) • Not a full publication of a clinical study: exclude non-systematic reviews, letters, editorials, notes and in-vitro studies. • Not in patients with cancer. • Not microwave therapy: frequency <300 MHz or >300 GHz (ie, excludes hyperthermia induced by radiant heat source, laser, infrared, ultrasound and ferromagnetic implant). • Not in English.	2320
Title/abstract (second pass) • Study design does not answer clinical question (ie, does not provide information of the effect of microwave therapy as distinct from other concurrent treatment modalities).	236
Title/abstract (third pass) • Wrong mode of administration (ie, not external). Excludes microwave therapy delivered using the following methods: interstitial, transurethral, transpupillary, intraluminal, endoscopic, laparoscopic, intrathoracic, intraoperative, transvaginal, intraabdominal and transrectal.	49
Full papers reviewed:	271
Full paper: • Reasons outlined above:	
• Not clinical study (ie., review, protocol, note, meeting, abstract only, animal, in vitro);	48
• Not microwave 300 Mhz–300 GHz[a,b,c];	53
• Wrong study design to address research question;	59
• Wrong mode of administration;	33
• Wrong outcomes (eg. sub-clinical, technical) or no usable results; and	8
• Other reason (see **Volume 2**).	12
Total included citations[d]	58

[a] Where the frequency was not specified, the paper was included, but results were not extracted.
[b] Several papers use a frequency defined as 280–300 MHz. As some patients at least will have received 300 MHz these have been included.
[c] Several papers used a combination of low RF (eg. 8 MHz) and microwave (eg. 434 or 915 MHz). Where possible, results are extracted just for the patients who received microwave. Where the results were not reported separately for the different frequencies, the entire groups results have been reported.
[d] NB. 19 papers with < 10 patients were excluded from the efficacy review, however these papers are include in the final number of included citations as they were included in the safety review.

Dimensions of evidence

The aim of this literature review was to find the highest quality evidence to answer the review question. In accordance with NHMRC guidance (National Health and Medical Research Council 2000), the following dimensions of evidence were considered for each of the included studies (**Table 6**). It is important to recognise that the value of a piece of evidence is determined by all of these dimensions, not just the level of evidence.

Table 6 NHMRC Dimensions of evidence

Dimension	Reviewers definition
Strength of the evidence	
Level (see Table 7 below)	The study design used, as a indication of the degree to which bias has been eliminated by the design alone. The levels reflect the effectiveness of the study design to answer the research question.
Quality	The methods used to minimise bias within an individual study (ie., other than design *per se*).
Statistical precision	An indication of the precision of the estimate of effect reflecting the degree of certainty about the existence of a true effect, as opposed to a effect due to chance.
Size of effect	Determines the magnitude of effect and whether this is of clinical importance.
Relevance of evidence	The considers the relevance of the study to the specific research question and the context in which the information is likely to be applied, with regard to a) the nature of the intervention, b) the nature of the population and c) the definition of the outcomes.

The levels of evidence defined by the NHMRC (2000) were used to categorise the study design of the individual studies. This hierarchy of evidence is summarized in **Table 7**.

Table 7 Hierarchy of evidence

Level	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly-designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from a case-series, either post-test or pre-test/post-test.

The highest level of evidence available is a systematic review of randomised controlled trials, which are considered the study type least subject to bias. Individual randomised controlled trials also represent good evidence. However, comparative observational studies such as cohort and case-control studies or non-comparative case series may often be more readily available. Nevertheless, these lower levels of evidence remain subject to considerable bias.

Quality assessment

Even within the levels of evidence stated above there is considerable variability in the quality of evidence. In accordance with NHMRC guidelines, it was necessary to consider the quality of each of the included studies. The characteristics and quality of each included study were assessed using a number of quality criteria, as shown in **Table 8**, with studies rated as good, fair or poor quality. In accordance with standard systematic review methodology, if efforts to minimise bias were not reported in the publication (eg. independent or blinded assessment of outcomes, adjustment for confounders), they were assumed not to have occurred. Factors underpinning the quality ratings of original studies are shown in the data extraction tables in **Appendix 9**.

Table 8 Original studies: quality criteria

Quality criteria
(A) Has selection bias (including allocation bias) been minimised?
(B) Have adequate adjustments been made for residual confounding?
(C) Was follow-up for final outcomes adequate?
(D) Has measurement or misclassification bias been minimised?

Data relating to other dimensions of evidence (eg. statistical precision, relevance of evidence to the Australian setting) were also extracted from each study.

Data extraction

Data was extracted onto specifically designed data extraction forms, and included information regarding study design, patient characteristics, details of intervention, relevant outcomes, study quality and relevant results. Data was extracted by one reviewer and in 20% of cases checked for accuracy by a second reviewer.

Where the microwave frequency was not specified, the paper was included, but results were not extracted. Furthermore, several papers used low RF (eg. 8 MHz) for some patients and microwave (eg. 434 or 915 MHz) for others. Where possible, results are extracted just for the patients who received microwave. However, where the results were not reported separately for the different frequencies, the entire group's results have been reported.

Unless otherwise specified, the data that was most adjusted for confounders and/or multiple comparisons are reported. Furthermore, where subgroup analyses are available, these were reported if they are deemed relevant.

Data presentation and synthesis

Results are presented complete with the statistical comparison reported in the published paper. If a statistical comparison had not been undertaken by the investigators (and if sufficient data were available) the reviewers have conducted a *post hoc* statistical comparison. Where the comparison has been undertaken by the reviewer, this is clearly stated in the text or footnote.

Furthermore, if the investigators had performed an analysis based upon only evaluable patients, the reviewers have attempted to perform an intention-to-treat (ITT) analysis. This was only possible for dichotomous outcomes, where it was possible to determine the number of randomised patients. Where post-hoc ITT analyses have been undertaken by the reviewer this is clearly stated in the text or footnote.

Methodological limitations of the systematic literature review

All types of study are subject to bias, with systematic reviews being subject to the same biases seen in the original studies they include, as well as biases specifically related to the systematic review process. Reporting biases are a particular problem related to systematic reviews and include publication bias, time-lag bias, multiple publication bias, language bias and outcome reporting bias (Egger *et al.* 2001). Other biases can result if the methodology to be used in a review is not defined *a priori* (ie, before the review commences).

Some of these biases are potentially present in this review of microwave cancer therapy. Only data published in peer-reviewed journals is included. No attempt was made to include unpublished material, as such material typically has insufficient information upon which to base quality assessment, and it has not been subject to the scrutiny of the peer-review process. In addition, the search was limited to English-language publications only so language bias is a potential problem also. Outcome reporting bias and inclusion criteria bias are unlikely as the reviewers had no detailed knowledge of the microwave cancer therapy literature, and the methodology used in the review and the scope of the review was defined *a priori*.

Perhaps most importantly, systematic reviews are only as good as the quality of the information contained within the included studies. There are many biases that may impact on the internal validity of individual clinical trials such as selection bias, performance bias, detection bias and attrition bias (Egger *et al.* 2001). Observational studies are particularly subject to selection bias as well as information bias and may be profoundly affected by confounding.

Biases commonly present in observational studies in microwave cancer therapy research include;

- selection of patients suitable for microwave therapy
- differences in the intervention that is purportedly common to both arms (eg. the radiotherapy)
    - acutely for concurrent controls
    - historically for controls gathered from an earlier time period
- failure to blind patient and clinician to the nature of the treatment
- failure to adequately define outcome measures
- failure to assess outcomes in a manner that is blind to treatment assignment
- inadequate follow-up of patients, and failure to account for missing patients in analyses

In addition, many studies suffer from small patient numbers and therefore are susceptible to type II error (ie., failure to detect a true difference).

SYSTEMATIC LITERATURE REVIEW: RESULTS

Methodological information and results extracted from the included studies are presented below. The reader is referred to the original publications for more detailed information. Only data relevant to the current review is presented here.

In almost all cases, the effect of microwave therapy upon cancer outcomes has been investigated by comparing radiotherapy alone (RT) to radiotherapy plus microwave therapy (RT + MT). It is important to recognise that outcomes achieved when microwave therapy is used in conjunction with radiotherapy may not be transferable to the use of microwave therapy without radiotherapy.

Efficacy results

All included studies containing relevant efficacy data are presented below. In the vast majority of cases, the effect of microwave therapy upon cancer outcomes was determined by a study design that compared radiotherapy alone (RT) versus radiotherapy plus microwave therapy (RT + MT). On some occasions chemotherapy was also given. A small number of uncontrolled studies presented data for a case series of patients receiving microwave therapy alone.

Published efficacy evidence is presented by cancer type then by level of evidence. It should be noted that two subsections contain data from multiple cancer types: 'superficial tumours' and 'various cancer types', where it was not possible to extract data for the individual cancer types from the publication. The superficial tumours sub-section includes studies which specifically stated they had investigated superficial tumours. Tumour types included in these studies were those that were situated within a short distance from the skin surface and included many types including squamous cell carcinoma, melanoma, sarcoma and various carcinomas among others. The various cancer types sub-section includes studies comprising a variety of cancer types. A summary presenting the information from all cancer types is presented later in the chapter.

Cervical cancer

One study provided information regarding the efficacy of external microwave therapy[17] in patients with cervical cancer. The main characteristics of this study are summarised in **Table 9**.

The paper by Hornback *et al.* (1986) reports on the findings of a retrospective chart review of women with cervical cancer, treated with RT + MT or RT alone. This study is considered to be of poor methodological quality due to use of historical control, no adjustment for potential confounding and unblinded assessment of outcomes.

Table 9 Study characteristics: cervical cancer

Citation	Study type *Study quality*	Population	Intervention	Comparator	Outcomes
Intervention Level III-3 evidence					
(Hornback *et al.* 1986)	Retrospective review with historical control Poor	Women with primary stage IIIB squamous cell carcinoma of the cervix, treated between Nov 64 and Jan 79 a N=33	**RT + MT** 4000 cGy over 4.5-5 weeks given as daily 150-200 cGy fractions 434 MHz for 40-45 mins, 10-15 min after external radiation N=18	**RT** 4000 cGy over 4.5-5 weeks given as daily 150-200 cGy fractions N=15	Tumour control Survival Adverse events

Abbreviations: MT, microwave therapy; RT, radiotherapy.

[a] Forty-six patients treated between Nov 1964 and Jun 1975 were excluded from this analysis as they received a different type of radiotherapy (cobalt) to those receiving microwave therapy (25-MeV photon beam).

[17] Several higher quality studies have been undertaken using lower radiofrequencies (eg. 100 MHz), however these were not within the scope of the current review.

The results of the Hornback *et al.* (1986) study are summarised in **Table 10**. When a post-hoc statistical comparison was undertaken by the reviewer, none of these results were significantly different. However, it is possible that the trial was not large enough to detect a difference. Nevertheless, the poor quality of the study, and hence the substantial potential for bias, should be considered when viewing these results.

Table 10 Non-RCT results: cervical cancer

Outcome	RT + MT n/N (%)	RT n/N (%)	*P* value[b]
Hornback *et al.* (1986)			
Local tumour control [a]	13/18 (72)	8/15 (53)	ns
Absolute survival at 1 year	13/18 (76)	10/15 (67)	ns
Absolute survival at 3 years	9/18 (50)	6/15 (45)	ns
Absolute survival at 5 years	4/18 (22)	4/15 (27)	ns
Median survival	36 months	26 months	

Abbreviations:: MT, microwave therapy; ns, not significant (p≥0.05); RT, radiotherapy.
[a] Local tumour control not defined.
[b] Calculated by reviewer using Chi-square test.

Head and neck cancer

Five studies provided information regarding the efficacy of external microwave therapy in patients with head and neck cancer. The main characteristics of these studies are summarised in **Table 11**.

The Valdagni study (Valdagni and Amichetti 1994; Valdagni *et al.* 1988; Valdagni 1988) is a open-label RCT performed in one centre in Italy. Patients were randomised to RT + MT or RT alone. The study was closed early on the basis of ethical reasons after a statistically significant improvement in complete response rates favouring RT + MT compared with RT alone was found. Long-term follow up of this study examined maintenance of complete response, as well as survival.

The study by Arcangeli *et al.* (1980; 1985) reports on the findings of a non-randomised comparison of the response of individual cervical nodes with patients receiving RT + MT or RT alone. This study is considered to be of poor methodological quality as the assignment of treatment for individual nodes within the same patient was not randomised and it is unclear whether outcome assessment was independent of knowledge of treatment assignment.

The study by Ohizumi *et al.*, (2000) is a non-randomised study with retrospectively selected matched controls conducted in one centre in Japan. This study is considered to be of poor methodological quality and includes patients receiving both microwave and radiofrequency therapy; the number of patients receiving each type was not reported.

The study reported in various papers by Holt and Nelson was a historical comparison of several series of patients treated with different modalities including RT alone, RT under hyperbaric conditions and RT + MT. RT under hyperbaric conditions is excluded from this review. This study is considered to be of poor methodological quality due to the study design and poor reporting of study methodology and results.

In addition, a further paper by Holt (1988) re-presents the results of the aforementioned series (n=52), and also refers to a later series (79 patients on RT + MT and 218 patients on RT alone). Results of this later series are listed under the heading of the "1985

report", which refers to a letter to editor of the Medical Journal of Australia[18], rather than to an original research publication. While the results will be presented in this review, the lack of information provided regarding the selection of patients for MT or for RT + MT, the nature of the interventions, the definition and assessment of outcomes, statistical methods and the number of patients excluded from the analyses, mean that the data shown in Holt (1988) is classified as poor quality evidence.

Table 11 Study characteristics: head and neck cancer

Citation	Study type *Study quality*	Population	Intervention	Comparator	Outcomes
Intervention Level II evidence					
(Valdagni and Amichetti 1994; Valdagni *et al.* 1988; Valdagni 1988)	Open-label RCT Median follow-up RT + MT: 18 mths RT: 12 mths Fair	Patients with (a) nodal involvement of SSC from previous or concomitant T1-T3 head and neck or unknown primary or (b) Fixed and inoperable N3 cervical lymph nodes (< 7cm wide and < 5 cm deep) N=44 nodes (41 patients)	**MT+RT** RT same as comparator Mean dose 67.85 Gy Twice-weekly microwave 280-300 MHz, 20-25 min after RT N=21 nodes	**RT** Total dose 64-70 Gy given as 2.0-2.5 Gy daily 5 times a week Mean dose 67.05 Gy N=23 nodes	Tumour response Projected survival Adverse events
Intervention Level III-2 evidence					
(Arcangeli *et al.* 1980; Arcangeli *et al.* 1985)	Non-randomised study with within-patient controls but selected treatment assignment Poor	Patients with multiple N2-N3 neck node metastases from head and neck cancer N=81 nodes (38 patients)	RT + MT RT same comparator 40-50 mins at 500 MHz immediately after radiation for 7 treatments N=38 nodes	RT 4000-7000 rads given as 3 fractions/day (200+ 150 + 150) on days 1, 3 and 5 N=43 nodes	Tumour response Duration of local control Adverse events
Intervention Level III-3 evidence					
(Ohizumi *et al.* 2000)	Prospective non-randomised study with retrospectively selected (matched) controls Poor	Patients with previously irradiated neck nose metastases from squamous cell carcinoma from the head and neck Oct 84 – Sep 97 N=24 patients	RT + MT Radiotherapy dose/fractionation not stated Mean dose 60.4 ± 9.49 Gy Microwave (2443 MHz; superficial tumours) or RF (13 MHz; large nodes), 1-2 per week prior to RT for 2-7 treatments for 30-50 min N=12	RT Radiotherapy dose/fractionation not stated Mean dose 57.7 ± 10.5 Gy N=12	Tumour response Progression-free survival Adverse events

[18] Letter to the Editor, Medical Journal of Australia (Holt & Nelson, 1985)

Citation	Study type *Study quality*	Population	Intervention	Comparator	Outcomes
Intervention Level III-3 evidence					
(Holt 1977; Nelson and Holt 1977; Nelson and Holt 1978; Holt 1982; Holt 1988)	Non-randomised study with historical control [a] Perth (1 site) Poor	Patients with ear, nose or throat cancer: T3 or T4 (> 5 cm); T2 or recurrent (< 5 cm); N+; N2 or N3 N=156 (104 relevant to review)	RT + MT 5400 rads given as 200 rads 3 times per week over 9 weeks Microwave (434 MHz) once a week over 9 weeks N=52	RT 6000 rads given as 30 x 200 rads over 6 weeks N=52	Patient response (free of cancer) Adverse events
(Holt 1988)	Unknown. No recruitment information or study methodology provided[b] Poor	Head and neck cancer N=297	RT + MT Nature of RT not reported Microwave (434 MHz), dose regimen not reported N=52	RT Nature of RT not reported N=218	Primary resolution Crude survival

Abbreviations: MT, microwave therapy; N+; Histologically positive nodes; N2 or N3, fixed inoperable nodes; RT, radiotherapy; T3 or T4, late stage > 5cm diameter; T2 or recurrent, < 5 cm diameter.

[a] In Holt (1988) this study is described as being from the "1978 report".

[b] In Holt (1988) this data described as being from the "1985 report" - referring to a letter to the editor in Medical Journal of Australia, 1985. This includes 79 patients on RT + MT and 218 patients on RT alone. There is little information given, however it appears to represent a separate series. While the results will be presented in this review, the lack of information regarding the methodological quality of this data should be kept in mind.

The results of the Valdagni RCT are summarised in **Table 12**. The complete response rate at 3 months was significantly greater in the RT + MT arm compared with the RT alone arm. Although the results suggest that complete response benefit was maintained at 5 years, this was on the basis of an actuarial (extrapolated) analysis, rather than real data. In addition, the actuarial analysis implies a significant benefit of RT + MT over RT alone with regard to 5-year survival. When considered in isolation, the results from this small study appear to suggest a benefit in head and neck cancer for the addition of MT to RT, however it is important to note that median follow-up was only 18 and 12 months respectively for the RT + MT and RT alone groups, therefore the 5 year actuarial estimations are highly extrapolated and may not reflect actual survival. No subsequent paper has been published by this group to confirm the true patient survival.

Table 12 RCT results: head and neck cancer

Outcome	RT + MT	RT	*P* value	Risk estimate [c] RR (95% CI)
Valdagni and Amichetti, (1994);Valdagni et al., (1988);Valdagni,(1988)				
Complete response [a,d] – ITT analysis, n/N (%)	15/21 (71)	9/23 (39)	0.04 [b]	1.83 (1.03, 3.25)
Complete response[d] – evaluable patient analysis, n/N (%)	15/18 (83)	9/22 (41)		
5-year **actuarial** probability of nodal control – evaluable patient analysis (± SD)	68.6% ± 22.19%	24.2% ± 21.1%	0.015	-
5-year **actuarial** probability of survival – evaluable patient analysis (± SD)	53.3% ± 21.03%	0	0.02	-

Abbreviations: CI, confidence interval; MT, microwave therapy; RR, relative risk; RT, radiotherapy; SD, standard deviation.

[a] Four patients (3 on MT+RT and 1 on RT) were excluded from analysis due to protocol violations. For the purpose of performing an ITT analysis for this report they will be included and assessed as non-responders.

[b] Post hoc calculation based on ITT population using Fisher's exact test.

[c] Post hoc calculation for this review (RevMan 4.2).

[d] Complete response was defined as the disappearance of all known nodal disease, measured at 3 months.

The results of the four non-randomised studies are summarised in **Table 13**. All studies were considered to be of poor methodological quality primarily due to the potential for significant selection bias, as well as the lack of blinding of treatment and outcome assessment. As such, the results presented below should be viewed in light of considerable potential for bias.

The results of the Arcangeli *et al.* (1980) study with concurrent controls suggest a substantially greater complete response rate for nodes receiving RT + MT compared to RT alone (both within-patient and historical controls). However, response was only measured at the end of treatment so any longer-term benefits cannot be reliably determined.

The results of the Ohizumi study with retrospectively selected controls suggest no improvement in tumour response when MT is added to RT. In addition, there was no difference in survival or progression-free survival. These results should be viewed with the following in mind: (i) the small patient number; (ii) the highly selected control group; and (iii) the fact that four patients in the RT + MT group received intratumoural injections of interleukin 2, OK 432 or bleomycin before microwave therapy. Furthermore, both microwave and RF therapy were used but the results have not been presented separately.

The study reported in various publications by Holt and Nelson used a historical series to compare the efficacy of RT + MT vs RT alone (Study 1). The results suggest that higher complete response rates are seen for patients treated with RT + MT compared with RT alone from treatment end up to 3 years. Similarly, survival (3-year and 8-year) is greater for patients on RT + MT compared with RT alone.

The additional head and neck study reported by Holt (1988; Study 2) shows similar results to the above study, with greater complete response and survival seen in patients on RT + MT compared with RT alone. However, it is not possible to determine the methodological quality of this study as no details could be ascertained from the available literature[19] regarding (i) how patients were selected, (ii) whether this constituted a consecutive series of patients, (iii) whether the RT regimens used were the same

[19] A letter published in the MJA (1985) was also assessed however this provided no further details of the methodology used.

between treatment groups, (iv) how outcomes were measured and (v) if all patients were included in the analyses. Additional bias may be introduced in the case of historically-controlled series when comparing patients treated before and after the introduction of more advanced imaging techniques (such as CT and bone scans). More accurate staging investigations can result in patients with advanced cancer being included in historical series, but being excluded from more current series. As a result of this, patients treated more recently will appear to have more favourable outcomes. Also, improvements in supportive care and management of treatment complications may result in more favourable outcomes for patients treated in more recent series.

Table 13 Non-RCT results: head and neck cancer

Outcome	RT + MT n/N (%)	RT n/N (%)	*P* value[e]
Concurrent controls			
Arcangeli (1980)			
Complete response [a]	30/38 (79)	18/43 (42)	p<0.01
Complete response at 2 years [b]	22/38(58)	6/43 (14)	-
Historical/retrospective controls			
Ohizumi (2000)			
Complete response	4/12 (33)	5/12 (42)	ns
Partial response	6/12 (50)	5/12 (42)	-
Overall response	10/12 (83)	10/12 (83)	-
(Holt 1988); Nelson (1978); Holt (1977) Holt (1982)			
Percent of patients free of cancer at treatment end [c]	49/52 (94)	17/52 (33)	p<0.01
Percent of patients free of cancer at 1 year [c]	41/52 (79)	11/52 (21)	-
Percent of patients free of cancer at 2 year [c]	34/52 (66)	8/52 (15)	-
Percent of patients free of cancer at 3 year [c]	31/52 (60)	4/52 (8)	-
Crude 3-year survival [d]	28/52 (54)	10/52 (19)	p<0.01
Crude 8-year survival [d]	21/52 (40)	6/52 (11)	-
(Holt 1988) '1985 report'			
Percent of patients free of cancer at treatment end	73/79 (92)	74/218 (34)	p<0.01
Crude 8-year survival	54/79 (68)	37/218 (17)	-

Abbreviations: MT, microwave therapy; ns, not significant (p ≥ 0.05); RT, radiotherapy

[a] Complete response defined as complete macroscopic disappearance of the lesion within/or just after the treatment period.

[b] Actuarial analysis.

[c] Results taken from 1978 publication.

[d] Results taken from 1988 publication.

[e] Post hoc calculation conducted by reviewer using Chi-square or Fishers Exact test as appropriate

Melanoma

Four studies provided information regarding the efficacy of external microwave therapy in patients with melanoma. The main characteristics of these studies are summarised in **Table 14**.

The Overgaard study (Overgaard *et al.*, 1995; Overgaard *et al.*, 1996) was a multi-centre, open-label RCT. The study examined the effect of adding microwave therapy to radiotherapy on complete response over the short-term (3 months) and persistent local control over the longer-term (2 years). It should be noted that the paper states that both microwave and radiofrequency therapy were used; however, the proportion of subjects receiving each is not reported and results are not presented separately. Therefore, this limits the generalisability of the results in the context of the current review.

The study by Shidnia *et al.* (1990) was a single centre, non–randomised comparison of different radiotherapy regimens alone to different radiotherapy regimens + microwave therapy. This study was considered to be of poor methodological quality, in particular because patients were selected for treatment based on tumour size (< or ≥ 2 cm), resulting in selection bias. As this study design is fatally flawed due to inherent selection bias, the results are not presented here.

The study by Arcangeli *et al.* (1987) was a single-centre non-randomised comparison of two different radiotherapy regimens with/without the addition of microwave therapy. The two different radiation schedules resulted in similar response rates so for the purpose of this review they will be considered together. This study was considered to be of poor methodological quality due to potential for selection bias and unblinded assessment of outcomes.

The study by Scott *et al.* (1983) was a single-centre, non-randomised comparison of a RT + MT regimen with three different RT regimens. All included patients had at least 3 lesions and each lesion was assigned to RT + MT and at least two different RT regimens. This study is considered to be of poor methodological quality due to potential for significant selection bias as well as unblinded assessment of outcomes.

Table 14 Study characteristics: melanoma

Citation	Study type *Study quality*	Population	Intervention	Comparator	Outcomes
Intervention Level II evidence					
(Overgaard *et al.* 1996; Overgaard *et al.* 1995)	Open-label multicentre RCT ESHO protocol 3-85 Follow-up from 3-73 months Poor	Patients with advanced, recurrent or metastatic non-lentiginous malignant melanoma N=134 lesions (70 patients)	**MT+RT** RT total dose 24 or 27 Gy [a] given as 3 fractions in 8 days using high voltage photons or electrons Microwave or radiofrequency within 30 mins of radiation fraction N=66 lesions	**RT** RT total dose 24 or 27 Gy [a] given as 3 fractions in 8 days using high voltage photons or electrons N=68 lesions	Tumour response Local control at 2 years Adverse events

Citation	Study type *Study quality*	Population	Intervention	Comparator	Outcomes
Intervention Level III-2 evidence					
(Shidnia *et al.* 1990)	Open-label non-randomised study with concurrent controls but patients with large lesions selected for RT + MT Poor	Patients with malignant melanoma N=188 lesions (92 patients) [b]	**RT + MT** Radiotherapy 200 cGy daily for 30 fractions in 6 weeks 600 cGy twice a week x 6 in 17 days 730 cGy once a week x 5 in 28 days 830 cGy x 4 in 20 days 433, 915 or 2450 MHz within 30 min of RT N=57 evaluable lesions	**RT** Radiotherapy 200 cGy daily for 30 fractions in 6 weeks 600 cGy twice a week x 6 in 17 days 730 cGy once a week x 5 in 28 days 830 cGy x 4 in 20 days N=124 evaluable lesions	Tumour response
(Arcangeli *et al.* 1987)	Open-label non-randomised study with concurrent controls Poor	Patients with cutaneous and nodal metastases from malignant melanoma N=38 lesions (17 patients)	**RT + MT** Radiotherapy a. 40 Gy as 2 weekly fractions of 5 Gy b. 30 Gy as 2 weekly fractions of 6 Gy RF (27 MHz) or MW (500, 2450, 400 MHz) a. Following each fraction at 42.5°C for 45 mins (8 treatments) b. Following each fraction at 45°C for 30 min (5 treatments) N=21 lesions	**RT** Radiotherapy a. 40 Gy as 2 weekly fractions of 5 Gy b. 30 Gy as 2 weekly fractions of 6 Gy N=17 lesions	Tumour response Persistence of complete response

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Citation	Study type *Study quality*	Population	Intervention	Comparator	Outcomes
Intervention Level III-2 evidence					
(Scott *et al.* 1983)	Open-label non-randomised study with concurrent intra-patient control lesions RTOG 77-10 Poor	Patients with extensive disease, limited survival, ≥ 3 superficial lesions and failed all other therapies N=40 lesions (12 patients)	Radiotherapy 1500 rads as 3 x 500 rad fractions at 72 hour intervals Microwave 915 MHz following RT treatments **RT + MT** N=12 lesions	**RT** a. 2100 rads as 3 x 700 rad fractions at 72 hour intervals b. 2400 rads as 3 x 800 rad fractions at 72 hour intervals c. 1800 rads as 3 x 600 rad fractions at 72 hour intervals N=28 lesions	Tumour response Adverse events

Abbreviations: MT, microwave therapy; RF, radiofrequency; RT, radiotherapy.
[a] Similar numbers of subjects received each of the two doses in the intervention and comparator arms of the study.
[b] Only 181 lesions (from 90 patients) considered evaluable and included in study analysis.

The results of the Overgaard open-label RCT are summarised in **Table 15**. The results suggest a significant benefit in tumour response with the addition of MT to RT compared with RT alone. The authors report that complete response at 3 months was four times greater in the RT + MT group and 2-year local control was nearly two times greater. However, the reader should be aware that these relative risks rely heavily upon adjustment for confounders as the unadjusted relative risk calculated by the reviewer for complete response was only 1.75 (1.18–2.58). This suggests the two treatment arms were poorly matched with respect to these factors and this extent of adjustment may not be appropriate.

Table 15 RCT results: melanoma

Outcome	RT + MT n/N (%)	RT n/N (%)	*P* value	RR (95% CI) *p* value [d]
Overgaard (1996; 1995)				
Complete response (3 months) –ITT analysis [a]	39/66 (59)	23/68 (34)	0.006[b]	1.75 (1.18, 2.58)[b]
Complete response (3 months) –evaluable patient analysis	39/63 (62)	23/65 (35)	<0.05[c]	4.01 (1.77, 9.08) [d] 0.0015c
2-year local control – evaluable patient analysis	nr	nr	nr	1.73 (1.07, 2.78)[d] 0.023c

Abbreviations: CI, confidence interval; MT, microwave therapy; nr, not reported; RR, relative risk; RT, radiotherapy.
[a] Six subjects considered not evaluable in the publication (3 in each treatment arm). These patients were included as treatment failures for the ITT analysis conducted for this review.
[b] Post-hoc calculation using Chi-square test (for p value) and RevMan 4.2 (for unadjusted RR) based on ITT population.
[c] Study reported.
[d] Study-reported relative risk adjusted for potential prognostic factors including tumour size, radiation dose, sex, time to recurrence, tumour site and number of tumours.

The results of the non-randomised studies are summarised in **Table 16**. All of these studies were considered to be of poor methodological quality due to potential for selection bias and measurement bias/misclassification.

The results of the Arcangeli *et al.* (1987) study suggest a trend toward a greater complete response rate in lesions receiving RT + MT compared with RT alone, however this result was not statistically significant. The persistence of complete response (between 6 and 24 months follow-up) was measured in lesions which responded completely after treatment and was shown to be 100%, irrespective of treatment assignment.

The study by Scott *et al.* (1983) showed a limited response to both RT + MT and RT alone at completion of therapy. However, at 3 months post-treatment, the greatest complete response rate was seen for RT + MT (67%) followed by RT alone at a total dose of 2400 rads (42%). It should be noted that these results are based on very small numbers of lesions (≤ 12 in each arm).

Table 16 Non-RCT results: melanoma

Outcome	RT + MT n/N (%)	RT n/N (%)			*P* value[b]
Arcangeli (1987)					
Complete response	16/21 (76)	9/17 (53)[a]			ns
Scott (1983)					
Complete response at treatment end	2/12 (17)	(a) 2/12 (17)	(b) 1/12 (8)	(c) 0/12 (0)	-
Complete response at 3 months	8/12 (67)	2/12 (17)	5/12 (42)	0/4 (0)	p<0.05[c]

Abbreviations: MT, microwave therapy; ns, not significant (p≥0.05); RT, radiotherapy.
[a] Two RT regimens combined as small groups and similar results.
[b] Post hoc calculation conducted by reviewer using Chi-square or Fishers Exact test as appropriate.
[c] Comparison of RT + MT vs entire RT group
(a) 700 rad x 3
(b) 800 rad x 3
(c) 600 rad x 3

Breast cancer

Five studies provided information regarding the efficacy of external microwave therapy in patients with breast cancer. The main characteristics of these studies are summarised in **Table 17**.

The Vernon study (Vernon *et al*, 1996; Sherar *et al*, 1997) is a combination of five RCTs conducted in the UK, Canada and Europe. The data were pooled due to poor accrual in the individual trials, despite differences in the study protocols. Nevertheless, in all trials patients were randomised to RT + MT or RT alone. The study investigated local response and survival.

The study by Rui-Ying *et al*, (1990) involved concurrent control cases, however has inherent selection bias as all small lesions were treated with RT alone whilst all larger lesions were treated with RT + MT. For this reason, no results were extracted from this study and it is not considered further.

The study by Perez *et al.* (1986) reports on the findings of historically controlled comparison of lesions to RT + MT or RT alone. Data for the two groups were collected over two different periods of time with some overlap; however, it is not reported how patients were selected for the two treatments during the overlapping period. The nature and dose of RT treatment was different in the two arms, and there is inadequate reporting of baseline disease characteristics and concurrent use of chemotherapy in the two groups. This study is of poor methodological quality, and the results have the potential to be substantially biased.

Masunaga *et al* (1990) compare 30 primary or recurrent tumours treated between 1979-1988 with RT + MT with a historically control from 1962-1979 who did not receive MT (n=55). There is minimal reporting of baseline difference between groups, and is likely to be biased against historical control due to changes in radiotherapy since the 1960/70s.

The breast cancer results for Holt (1982) were reported in a paper that presents an audit of results in many types of cancer. Presentation of the study design, patient characteristics and treatment details for the breast cancer patients for whom there was a historic control group is minimal and unconventional (a single paragraph). For this reason it is impossible to assess the study biases, and therefore the results are difficult to reliably interpret.

Table 17 Study characteristics: Breast cancer

Citation	Study type *Study quality*	Population	Intervention	Comparator	Outcomes
Intervention Level II evidence					
(Vernon *et al.* 1996; Sherar *et al.* 1997)	Combination of five open-label RCTs Minimum follow-up for all patients was 5 months Fair	Patients with measurable breast cancer lesions (primary or recurrent) where local therapy was indicated but surgery not feasible. N=306 lesions (306 patients)	MT+RT RT dose not reported, paper states "the doses administered were the same, regardless of the outcome of randomisation" 434, 915 and 2450 MHz after RT N=171 lesions	RT RT total dose (28-50 Gy) and fractions varied across trials and whether radical or palliative Mean dose: not reported N=135 lesions	Tumour response Survival Adverse events
Intervention Level III-2 evidence					
(Rui-ying *et al.* 1990)	Non-randomised study with concurrent control but all large lesions selected for RT + MT Poor	Primary or recurrent breast carcinoma Patients treated between 1980–1983 N=64	RT + MT: RT total dose 20–80 Gy (mean 48 Gy) given in 2–2.5 Gy/day fractions, 4–5/week 915 MHz & 2450 MHz to achieve 40 mins at 41–44°C, twice weekly, 15–30 mins after RT N=42 lesions	RT: RT total dose 20–80 Gy (mean 47 Gy) given in 2–2.5 Gy/day fractions, 4–5/week N= 22 lesions	Tumour response

Citation	Study type *Study quality*	Population	Intervention	Comparator	Outcomes
Intervention Level III-3 evidence					
(Masunaga *et al.* 1990)	Non-randomised study with historic control Poor	Locally advanced or recurrent breast carcinoma. RT + MT 1979–88 RT 1962–79 N=87	**MT+RT** RT total dose 20–74 Gy given in fractions between 1.8–4 Gy, 2–5 days/wk Cobalt-60 gamma ray, high-energy electrons, soft x-ray Mix of 8, 13.56, 430 or 2450 MHz (Not reported how pts got each), 30–60 mins, 1–2/wk after RT Chemotherapy 2 primary tumours received concurrent chemotherapy N=30 tumours	**RT** RT total dose 30–81 Gy given in fractions of 2–3 Gy, 5 days /wk Cobalt-60 gamma ray or high-energy electrons NB. Time dose fractionation factor of post-RT recurrent tumours was lower in MT+RT gp than in RT gp ($P<0.01$) N=57 tumours	Tumour response Survival Adverse events
(Perez *et al.* 1986)	Non-randomised study with historic control Poor	Recurrence of breast carcinoma (95% chest wall) RT + MT group: Treated between March 1978 and December 1984. RT group: Treated between January 1964 and December 1984. N=164	MT+RT RT dose 2000–4000 cGy in 400 cGy fractions every 72 hr 'Majority' of patients got 915 MHz for 30–60 mins, 15–30 min after RT NB. Some patients received chemotherapy (details not reported) N=48 (although some outcomes report 49)	RT RT dose 2000–6000 cGy in 200–300 cGy daily fractions tid NB. Some patients received chemotherapy (details not reported) N=116	Tumour response Adverse events

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Citation	Study type *Study quality*	Population	Intervention	Comparator	Outcomes
Intervention Level III-3 evidence					
(Holt 1982)	Non-randomised study with historic control Poor	Minimal detail provided. RT + MT group: Stage 1 and 2 post mastectomy and axillary sampling or clearance between July 1974 and July 1979 RT group: 'similar post-operative patients' - no other detail reported N=88	**MT+RT** RT dose 3000 rads over 15 treatments to specific regions, and with 6-9 treatments to whole area with 'combined' therapy to a total of 1200 rads Frequency not reported (possibly 434 MHz), regimen not reported N=44	**RT** RT dose 5000 rads over 25 treatments N=44	Not reported what was measured, but local recurrence and development of metastases are reported Adverse events

Abbreviations: MT, microwave therapy; RT, radiotherapy.

The results of the Vernon RCT are summarised in **Table 18**. The complete response rate at 3 months was significantly greater in the RT + MT arm compared with the RT alone arm. However, this benefit did not translate to a survival advantage. The actuarial probability of survival at 2 years was comparable in both groups, and by three years there appeared to be greater survival in favour of the RT group (only shown pictorially in paper). In summary, these results suggest that any initial tumour response benefit is offset by later disease progression.

Table 18 RCT results: Breast cancer

Outcome	RT + MT	RT	*P* value	Risk estimate OR (95% CI)
Vernon (1996); Sherar (1997)				
Complete response [a] n/N (%)	101/171 (59%)	55/135 (41%)	<0.001	2.3 (1.4, 3.8)[b]
2-year actuarial probability of survival (± SEM)	36 ± 4%	41 ± 5%	ns	-
3-year actuarial probability of survival (estimated by reviewer)	~24%[c]	~38%[c]	0.012[d] (favouring RT)	-

Abbreviations: CI, confidence interval; MT, microwave therapy; nr, not reported; ns, not significant ($p \geq 0.05$); OR, odds ratio; RT, radiotherapy

[a] Complete response was defined as no evidence of tumour according to WHO criteria, at any time but subject to confirmation 4 weeks later.

[b] Odds ratio after stratification by trial (as reported by investigators).

[c] Data read off Fig 3 (not reported or discussed elsewhere in paper).

[d] Post hoc calculation by the reviewer based on ITT population using a Chi-square with Yates correction.

The historically-controlled results of Masunaga *et al* (1990) and Perez *et al.* (1986) are summarised in **Table 19**. In Masunaga *et al* (1990) there was no difference in local response (defined as any tumour regression >80%) between treatments (90% in the RT + MT arm vs 81% in the RT arm, ns). Similarly there was no significant difference between treatments in any subtype of tumour (primary, post-surgery recurrence, post-RT recurrence), although in the primary tumours there was a trend toward a benefit for MT+RT. However it is important to remember that tumour response measurement was neither independent nor blinded. As survival results were only reported for a selected group of patients with primary tumours, who had not required a salvage operation,

they are subject to considerable bias and are not reported here. The reader is reminded that as a non-randomised study with a poorly matched historic control group, all of the results of this study are subject to bias.

In Perez *et al.* (1986) complete tumour response for all lesions was not different between treatment groups (63% in the RT + MT arm vs 57% in the RT arm). Nor was there a difference when small or large lesions were considered separately. Results reported in the abstract are misleading as only those for the subgroup of small lesions that received 3001–4000 cGy are reported, whilst for large tumours all lesions have been included. In addition, as a non-randomised study with a poorly matched historic control group, these results are subject to considerable potential for bias.

The results for Holt (1982) were not reported in the conventional manner. It is not clear when and how tumour measurements were made or by whom - or if this was consistent between the RT + MT group and the historic control group with RT alone. There is no detail provided regarding the duration of follow-up or how missing data were dealt with. Bearing in mind caveats of likely selection bias, intervention bias and measurement bias - together with poor reporting - the reviewer has nevertheless statistically compared the available data. The results showed that neither local recurrence rate nor development of metastatic disease were significantly different between the groups. However, the reader is reminded to consider these results with caution.

Table 19 Non-RCT results: Breast cancer

Outcome	RT + MT n/N (%)	RT (historic control) n/N (%)	*P* value[a]
(Masunaga et al. 1990):			
Local response [b]: all tumours [c]	27/30 (90)	46/57 (81)	ns
Local response [b]: Primary tumours	10/11 (91)	6/11 (55)	ns
Local response [b]: Post-surgery recurrence	5/6 (83)	24/27 (89)	ns
Local response [b]: Post-RT recurrence	12/13 (92)	16/19 (84)	ns
(Perez et al. 1986):			
Complete response: all tumours [d]	31/49 (63)	66/116 (57)	ns
Complete response: 1–3 cm tumours [d]	18/29 (62)	48/73 (66)	ns
Complete response: > 3 cm tumours [d]	13/20 (65)	18/43 (42)	ns
(Holt 1982):			
Local recurrence [e]	3/44 (7)	9/44 (20)	ns
Development of metastases [e]	17/44 (39)	25/44 (57)	ns

Abbreviations: MT, microwave therapy; ns, not significant ($p \geq 0.05$); RT, radiotherapy.

[a] Post hoc calculation by reviewer using Chi-square with Yates correction or Fishers Exact, as appropriate.
[b] Defined as local regression >80%.
[c] Calculated by reviewer, not shown in paper.
[d] Post hoc comparison conducted by reviewer, results for entire group not reported in paper.
[e] No detail of how, when or by whom measurements made, or in how many patients data was missing and how this was treated.

Gastric cancer

One study provided information regarding the efficacy of external microwave therapy in patients with gastric cancer. The main characteristics of this study are summarised in **Table 20**.

The study by Shchepotin *et al.* (1994) was a single centre open-label RCT. The study examined the effect of adding pre-surgical microwave therapy to pre-surgical radiotherapy on survival at three and five years. This study was considered to be of poor methodological quality as it is unclear how many patients were excluded from the analysis (ie, it appears patients who underwent < 4 treatments were excluded) and because of the lack of blinding of outcome assessment.

Table 20 Study characteristics: gastric cancer

Citation	Study type Study quality	Population	Intervention	Comparator	Outcomes
Intervention Level II evidence					
(Shchepotin *et al.* 1994)	Open-label single-centre RCT Follow-up not clear Poor	Patients with newly diagnosed, previously untreated gastric cancer N=293 subjects [a]	MT+RT+ S RT total dose 20 Gy given as 4 fractions over 4 days Microwave 460 MHz ~ 2 hours after each radiation fraction N=95 patients	RT + S RT total dose 20 Gy given as 4 fractions over 4 days N=98 patients	3- and 5-year survival

Abbreviations: MT, microwave therapy; RT, radiotherapy; S, surgery.
[a] Includes a surgery only arm which is excluded from this review (n=100).

The results presented in **Table 21** suggest little difference in survival rates at these two time points. A reliable analysis of the differences could not be conducted for this review as it is unclear how many subjects were included in the analysis in each treatment arm; patients who did not complete the four microwave therapy treatments were excluded from the study analysis. If one assumes the denominators for the treatment arms were indeed n=95 and n=98 respectively, the available data suggest that neither 3-year nor 5-year survival would be significantly different.

Table 21 RCT results: gastric cancer

Outcome	RT + MT	RT
Shchepotin (1994)		
3-year survival (%)	57.6	51.8
5-year survival (%)	51.4	44.7

Abbreviations: MT, microwave therapy; RT, radiotherapy.

Rectal cancer

One study using external microwave therapy provided information regarding the efficacy of microwave therapy in patients with colorectal cancer. The main characteristics of this study are summarised in **Table 22**. However, the reader should be aware that the vast majority of microwave therapy for colorectal cancer internationally is administered using transrectal microwave antenna, and such studies (including several RCTs) were not included within the scope of the current review.

The Trotter study (Trotter *et al*, 1996) is an open-label RCT conducted between 1985 and 1991 in Western Australia using the Tronado machine (434 MHz). However, patients randomised to RT + MT were treated at one centre, whilst those treated with RT alone were treated elsewhere. This introduces considerable potential for intervention bias. Furthermore, the extent to which assessment of patient outcomes were blind to treatment assignment is not clear.

Results of patients with rectal cancer are also presented in two papers by Holt (1982 and 1988). In neither of these publications is there sufficient detail to be able to determine the study design and to evaluate the potential biases in a reliable fashion. Furthermore methods used to measure, analyse and report outcomes are not reported.

Table 22 Study characteristics: Rectal cancer

Citation	Study type Study quality	Population	Intervention	Comparator	Outcomes
Intervention Level II evidence					
(Trotter *et al*. 1996)	Open-label RCT with treatment arms treated at different centres Minimum follow-up not reported Fair/Poor	Patients with locally recurrent or unresectable primary adenocarcinoma of the rectum. N=73 evaluable patients (75 randomised)	**MT+RT** RT median dose 4275 cGy in 150 cGy fractions over 48.5 days NB. Actual RT dose exceeded protocol dose in 64% of pts 434 MHz (Tronado) 2–3 times/day, at least 2 days/wk, within 20 mins of RT dose. N=36 patients	**RT** RT median dose 4500 cGy in 180 cGy fractions over 38 days NB. Actual RT dose exceeded protocol dose in 24% of pts N=37 patients	Tumour response Quality of life Pelvic pain Survival Adverse events
Level unknown (insufficient detail provided to determine level)					
(Holt 1982; Holt 1988)	Insufficient information to determine study design Minimum follow-up not reported Poor	Recurrent rectal cancer treated 1975-1979 N=48	**MT+RT** RT: no information provided Frequency not reported (possibly 434 MHz), regimen not reported N=24	**RT** RT: no information provided N=24	Not reported what was measured in study, but crude survival and pain relief are reported. Adverse events

Abbreviations: MT, microwave therapy; RT, radiotherapy.

The results of the Trotter RCT are summarised in **Table 23**. There was no difference in maximum tumour response, quality of life or median survival between RT + MT and RT alone. However, there was a tendency toward a greater reduction in pelvic pain in the RT + MT arm. It is important to note that not only does this trial suffer from methodological flaws (intervention bias, possible measurement bias), it also may lack sufficient statistical power to detect any differences.

Table 23 RCT results: Rectal cancer

Outcome	RT + MT	RT	*P* value
Trotter (1996)			
Complete response a n/N (%)	2/36 (5.5%)	2/37 (5.4%)	ns
Spitzer quality of life score (averaged over time), mean ± SE	11.5 ± 0.3	11.6 ± 0.2	ns
Reduction in pelvic pain during treatment (reduction in pain score): 0 1 2 3 4 missing data	 38% 22% 25% 13% 3% 11%	 43% 22% 27% 8% 0% 0%	=0.49b (NB. trend in favour of MT+RT)
Estimated median survival	8.5 months (95%CI 5.9-12.7)	12.2 months (95%CI 9.5-17.4)	ns

Abbreviations: CI, confidence interval; MT, microwave therapy; ns, not significant (p ≥ 0.05); OR, odds ratio; RT, radiotherapy.

[a] Complete response graded by CT using UICC criteria, according to 'maximum' response at any time. NB. Not reported if tumour response assessment was made blind to treatment assignment.

[b] Mann-Whitney U-test performed by investigators.

The absence of methodological information and inadequate presentation of data in both of the publications by Holt (1982 and 1988) make it impossible to reliably interpret the results of this study. Therefore, these results are not presented here.

Mesothelioma

One publication provided information regarding the efficacy of external microwave therapy in patients with mesothelioma[20]. The University Hospital Rotterdam performed a retrospective chart review of 303 patients who had received radiotherapy for mesothelioma between 1979 and 1996 (de Graaf-Strukowska *et al*, 1999). Of this group, 18 patients with chest wall recurrences got RT + MT (≥4 Gy fractions). This small group were compared to a selected subgroup (n=24) of the larger group who had received RT alone during this time (see **Table 24**). Minimal information is provided about the baseline characteristics of the two groups. The study attempts to report tumour response for this subgroup comparison.

This study is of poor methodological quality, and the results have the potential to be substantially biased due to selection bias and poor patient follow-up.

[20] The reviewers are aware of a letter to the editor of Reviews in Clinical Oncology (Holt, 2003) that contains clinical data relating to mesothelioma. However, letters present minimal methodological information, usually do not present original data, and are not subject to the peer-review process. For these reasons, letters are excluded from systematic literature reviews by convention, as was the case with the current review.

Table 24 Study characteristics: Mesothelioma

Citation	Study type Study quality	Population	Intervention	Comparator	Outcomes
Intervention Level III-3 evidence					
(de Graaf-Strukowska *et al.* 1999)	Non-randomised study with 'matched' control patients selected from same group, but not clear if during same time period - therefore assumed historic control Poor	Histological diagnosis of mesothelioma with painful chest wall recurrences Patients treated between 1979–1996 N=189, but only 42 included in analyses	**RT + MT:** RT median dose 42 Gy in 4 Gy fractions 433 MHz for 60 mins after RT (median 4 sessions) N=18 patients	**RT:** RT median dose 40 Gy in 4 Gy fractions N= 24 patients	Tumour response

Abbreviations: MT, microwave therapy; RT, radiotherapy.

It is not possible to interpret the results of de Graaf-Strukowska (1999). Tumour response was poorly measured and almost 50% of the patients (11/24) had 'unknown' tumour response. This invalidates any comparison between the treatment arms, and therefore this paper is not discussed further in the current review.

Ovarian cancer

One publication provided information regarding the efficacy of external microwave therapy in patients with ovarian cancer. Hayashi *et al.* (1999) report the results of multimodality treatment at their centre that included surgery, chemotherapy plus microwave therapy. Both groups of patients received the same chemotherapy, including cyclophosphamide[21], however due to an equipment malfunction in 1993, 26 patients received the treatment without microwave therapy and are able to be compared with the remaining group (n=19).

NB. Equipment used to deliver microwave therapy was either the BSD-1000 or the TCA-434. As the frequency delivered by the BSD-1000 was not reported, it is not possible to determine how many patients got microwave therapy within the range 300 MHz-300 GHz. Minimal information is provided with respect to baseline characteristics of the two groups, however there appear to have been more stage III-IV patients (n=18/26, 69%) in the surgery + CT alone group than in surgery + CT + MT group (8/19, 42%). The only reported outcome relevant to the current review is overall survival (Table 25).

Due to the apparent mismatching of patients in the two groups with respect to cancer stage, the results are likely to be confounded. Small patient numbers also limit the usefulness of this study.

[21] The chemotherapy included cyclophosphamide, one of the compounds concurrently administered with MT in Western Australia. However the dose of cyclophosphamide used in the (Hayashi *et al.* 1999) study was a much higher dose than that used in Western Australia, and was in combination with other chemotherapy agents. Cyclophosphamide is referred to by Dr John Holt of the Western Australian facility as a glucose-blocking agent, but used elsewhere as a cytotoxic chemotherapy agent (as used in the Hayashi study).

Table 25 Study characteristics: Ovarian cancer

Citation	Study type Study quality	Population	Intervention	Comparator	Outcomes
Intervention Level III-3 evidence					
(Hayashi *et al.* 1999)	Non-randomised study with historic control due to malfunction of microwave therapy equipment. Implies consecutive series. Duration of follow-up not reported Poor	Stages Ic-IV superficial epithelial ovarian carcinoma treated since 1989. More stage III-IV patients (n=18/26, 69%) in Surg + CT alone group than in Surg + CT + MT group (8/19, 42%) N=45	**Surg + CT + MT:** Cytoreductive surgery, CDDP + adriamycin + cyclophosphamide (see Appendix 9 for detail). 434 MHz or BSD-1000 for 60 mins with chemotherapy N=26 patients	**Surg + CT:** as previous column, without microwave therapy N=19 patients	Overall survival

Abbreviations: MT, microwave therapy; RT, radiotherapy.

The historically-controlled results of Hayashi *et al* (1999) are presented in **Table 26**. No adjustments have been made for confounding. Specifically, there appear to have been more stage III-IV patients (n=18/26, 69%) in Surgery + CT alone group than in Surgery + CT + MT group (8/19, 42%). This invalidates any comparison between the treatment arms as a whole. The authors do present a subgroup analyses for stage I-II and stage III-IV separately, however patient numbers for these analyses are extremely low, so these results are not reported here.

Table 26 Non-RCT results: Ovarian cancer

Outcome	Surgery + CT + MT (%)	Surgery + CT (%)	P value [b]
Hayashi (1999)			
2 year overall survival [a]	89%	66%	P<0.05 [b]
5 year overall survival [a]	68%	33%	

Abbreviations: MT, microwave therapy; CT, chemotherapy
[a] Kaplan-Meier method
[b] Authors state "significantly higher (p<0.05) at almost any given yearly interval" but p value not reported for each time point. Post hoc calculation by reviewer was not possible, as number at risk at each time point not reported.

Pancreatic cancer

One publication provided information regarding the efficacy of external microwave therapy in patients with pancreatic cancer (**Table 27**). Yamada *et al.* (1992) report the results of treatment with a 'radiofrequency capacitive heating device' (Internova Co, Tokyo), however no further information is provided with respect to the frequency used. In this publication, 14 patients were treated with intraoperative radiotherapy plus microwave therapy, and they were compared to a historic control group.

Table 27 Study characteristics: Pancreatic cancer

Citation	Study type Study quality	Population	Intervention	Comparator	Outcomes
Intervention Level III-3 evidence					
(Yamada *et al.* 1992)	Non-randomised Historic control. Duration of follow-up not reported Poor	Pancreatic carcinoma treated at Tohoku University 1977-1987. IORT + MT: 21% stage I-II 79% stage III-IV IORT: 15% stage I-II 85% stage III-IV N=69	**Surg + IORT + CT + MT:** Total RT: 25-30 Gy intraoperatively Non-operative RT (30-45 Gy) given in 12 pts 'Most' cases underwent chemotherapy RF capacitive heating device (freq not stated) N=14 patients	**Surg + IORT + CT:** Total RT: 25-30 Gy intraoperatively Non-operative RT (30-45 Gy) given in 5 pts 'Most' cases underwent chemotherapy N= 55 patients	Pain relief Tumour response (only some pts) Overall survival

Abbreviations: CT, chemotherapy; MT, microwave therapy; IORT, intraoperative radiotherapy.

Due to the lack of information provided regarding the intervention (specifically whether the frequency delivered was between 300 MHz and 300 GHz), the results of this study are not considered further.

Superficial tumours

Studies included in this section described data from "superficial tumours". Superficial tumours generally included those that were within a short distance from the skin surface and included various tumour sites including squamous cell carcinoma, melanoma, sarcoma, various carcinomas among others. Six studies provide data regarding the efficacy of RT + MT in treating superficial tumours. The characteristics and quality of these studies are summarised in **Table 28**.

The study by Egawa *et al.* (1989) was a multi-centre, open-label RCT conducted at 10 sites in Japan. MT (using either microwave or radiofrequency) was added to RT and compared with RT alone. This study is considered to be of poor methodological quality due to potential for post-randomisation selection bias. Although randomised, 21 subjects were considered non-evaluable, including a number who were withdrawn from treatment (and the analysis) due to heat-related side effects.

The study by Perez *et al.* (1991; 1989) was an open-label RCT comparing RT + MT with RT alone. Of the 250 patients eligible for the study, 14 were considered not evaluable and not included in the analysis. This study was considered to be of poor methodological quality as it was unclear which treatment arm the non-evaluable patients had been assigned to and hence an ITT analysis could not be conducted. There was also no blinding of patient outcomes.

The study by Howard *et al.* (1988; 1987) was a non randomised study comparing microwave RT + MT with RT alone. This study was considered to be of poor methodological quality due to potential for selection and measurement biases.

Lindholm *et al.* (1988; 1987) compared tumour response in patients with superficial tumours receiving RT + MT or RT alone. This study was considered to be of poor methodological quality due to selective treatment of largest lesions with RT + MT

and smallest lesions with RT alone, and because single lesions were all treated with RT + MT (ie, selection bias). There was also possible unblinded assessment of a subjective outcome when treatment assignment was known (ie, measurement bias/ misclassification). Due to the fatally flawed study design, with inherent selection bias, this study is not considered further.

The study by Dunlop *et al.* (1986) assessed the addition of microwave therapy (using mostly microwaves but also radiofrequency and ultrasound) to radiotherapy compared with radiotherapy alone. This study was considered to be of poor methodological quality. Lesions were selected for therapy based on previous RT. Patient with multiple lesions received both RT + MT and RT alone, however the basis for choosing lesions for particular therapies is not described. In addition, there was no blinded assessment of patient outcomes.

Scott *et al.* (1983) reports a non-randomised comparison of RT + MT versus RT, where paired lesions received different treatments. This study is considered to be of poor methodological quality due to potential for significant selection bias as well as unblinded assessment of outcomes. Melanoma patients within this publication are reported elsewhere in this review.

Scott *et al.* (1984) examined the effect of RT + MT compared with RT alone on tumour response rates. This study was considered to be of poor methodological quality due to selection bias (MT given preferentially to tumours < 3 cm below skin surface) and measurement bias.

The study by Luk *et al* (1981) describes a comparative series with superficial lesions receiving MT alone or RT + MT. For the purpose of this review the comparison is not relevant so only the MT alone arm is considered. Hence, this study is considered to be a case series.

Table 28 Study characteristics: superficial tumours

Citation	Study type Study quality	Population	Intervention	Comparator	Outcomes
Intervention Level II evidence					
(Perez *et al.* 1991; Perez *et al.* 1989)	Open-label multicentre RCT RTOG protocol 81-04 Follow-up not stated *Poor*	Patients with superficial measurable malignant tumours of epithelial or mesenchymal origin < 5 cm in thickness N=307 subjects however only 236/250 with single lesions considered evaluable	**MT+RT** RT total dose 32 Gy as 8 fractions of 4 Gy twice weekly Microwave mostly 915 MHz twice weekly within 15-30 min of RT N=119	**RT** RT total dose 32 Gy as 8 fractions of 4 Gy twice weekly N=117 lesions	Initial tumour response Continuous control Adverse events

Citation	Study type Study quality	Population	Intervention	Comparator	Outcomes
Intervention Level II evidence					
(Egawa *et al.* 1989)	Open-label multicentre RCT (10 sites) Follow-up not stated *Poor*	Patients with superficially located tumours > 3 cm in diameter Any type except radiosensitive tumours N=113 however only 92 evaluable	**RT + MT** RT total dose 35-75 Gy given as daily fractions 5/week of 2 Gy Microwave (600-915 and 2450 MHz; 52% patients) and RF (8 and 13 MHz; 48% of patients) MT once a week during radiothepy N=44	**RT** RT total dose 35-75 Gy given as daily fractions 5/week of 2 Gy N=48	Tumour response
Intervention Level III-2 evidence					
(Howard and Bleehen 1988; Howard *et al.* 1987)	Open-label non-randomised study with concurrent control *Poor*	Patients with one or more assessable superficial malignant lesions (included SSC, sarcoma, breast carcinoma, melanoma, oesophageal adenocarcinoma) N=41 lesions	**RT + MT** RT total dose 24 Gy given as 6 twice-weekly fractions Microwave 650 MHz within 30 min RT N=20 lesions	**RT** RT total dose 24 Gy given as 6 twice-weekly fractions N=21 lesions	Tumour response Adverse events
(Lindholm *et al.* 1987; Lindholm *et al.* 1988)	Open label non-randomised study with concurrent control. Largest lesions and pts with single lesions all selected for RT + MT *Poor*	Superficial malignant tumours, treatment refractory; ≥ 3 months life expectancy; ≤ 3 cm below skin; verified by fine needle aspiration or biopsy (included SCC, adenocarcinoma, melanoma, angiocarcinoma and other carcinomas) N=85 evaluable lesions (total 98 lesions)	**RT + MT** RT total dose 30 Gy given as 10 3Gy fractions over 2 weeks a Microwave 915 or 2450 MHz 30-90 min or 3-4 hours after RT; 2 days/week for 2 weeks N=57	**RT** RT total dose 30 Gy given as 10 3Gy fractions over 2 weeks [a] N=28	Tumour response Duration of response Adverse events

Continued over page ➤

Citation	Study type Study quality	Population	Intervention	Comparator	Outcomes
Intervention Level III-2 evidence					
(Dunlop *et al.* 1986)	Open-label non-randomised study with concurrent control *Poor*	Patients with small superficial lesions of various histologies (adenocarcinoma of breast, lung and stomach; SCC of lung and head and neck; Kaposi's sarcoma and melanoma). Mostly breast adenocarcinoma. N=86 evaluable lesions [c]	**RT + MT** 25-30 Gy given as 10 fractions [b] Mostly microwave (MHz not specified) also some US and RF, 15-20 min or 4 hours post RT, usually twice-weekly N=45 evaluable lesions	**RT** 25-30 Gy given as 10 fractions [b] N=32 evaluable lesions	Tumour response Adverse events
(Scott *et al.* 1983)	Open label non-randomised study with concurrent control *Poor*	Patients with superficial malignancies N=48 lesions (paired; 24 patients) [d]	**RT + MT** Schedule 1 (no prior RT) 6000-6600 rads as 180-200 rads/day 5 days/week Schedule 2 (prior RT) 4000-5600 rads as 400 rads/day at 72 hour intervals 915 MHz within 30-45 min of RT at 72 hour intervals N=24 lesions (24 patients)	**RT** Schedule 1 (no prior RT) 6000-6600 rads as 180-200 rads/day 5 days/week Schedule 2 (prior RT) 4000-5600 rads as 400 rads/day at 72 hour intervals N=24 lesions (24 patients)	Tumour response Adverse events
(Scott *et al.* 1984)	Open label non-randomised study with concurrent control *Poor*	Patients with superficial malignancies with at least 6 months follow-up. Included SCC, adenocarcinoma, melanoma. N=62 lesions (paired; 31 patients) d	**RT + MT** Most tumours 6000-6500 rads as 200 rads/day for 6-6.5 weeks 5 tumours 4800-5000 rads as 400 rads/day 4 days/week 915 MHz within 30 min of RT twice per week (most patients) or after all radiotherapy (5 patients) N=31 lesions (31 patients)	**RT** Most tumours 6000-6500 rads as 200 rads/day for 6-6.5 weeks 5 tumours 4800-5000 rads as 400 rads/day 4 days/week N=31 lesions (31 patients)	Tumour response Adverse events

Citation	Study type Study quality	Population	Intervention	Comparator	Outcomes
Intervention Level IV evidence					
(Luk *et al*. 1981)e	Case series [f] *Poor*	Patients with easily observed and measurable superficial lesions; include various adenocarcinomas (breast, colorectal, ovary, kidney), SCCs (vagina, lung, head and neck) and others. N=11	**MT alone** 915 or 2450 MHz given 3 times a week for 2-3 weeks. N=11	**Not relevant** [f]	Tumour response Adverse events

Abbreviations:: MT, microwave therapy; RT, radiotherapy; SCC, squamous cell carcinoma.
[a] Five patients received greater doses due to no prior exposure to RT.
[b] Melanomas received 22.5 or 30 Gy as one 7.5 Gy fraction/week for 3 or 4 weeks.
[c] Excluding 9 lesions receiving MT only.
[d] Study also included 34 patients with single lesions who all received RT + MT. Not included here. It is possible that these wo studies contain the same patients; however, due to differences in reporting it was not possible to determine for certain whether this was the case.
[e] A smaller cases series (Luk, 1979) reported preliminary data from a proportion of the same patients, but as n<10 it is not included here.
[f] Study included a comparison group (RT + MT) however this arm was not relevant to this review and is excluded.

The results of the two RCTs are summarised in **Table 29**. The Perez *et al.*, (1991; 1989) study results suggest no difference between RT + MT and RT when all tumours are taken into account. However, when results are stratified in a post-hoc fashion by tumour size, there appeared to be a difference in treatment effects in smaller tumours (< 3 cm). In the Egawa *et al.* (1989) study there was no difference in complete response rate between the RT + MT arm and the RT only arm; It should be noted that statistical analysis for both of these studies were performed only on the evaluable population which excluded some patients eg., those who ceased treatment due to adverse events from microwave therapy. This has the potential to bias the results in favour of RT + MT.

Table 29 RCT results: superficial tumours

Outcome	RT + MT n/N (%)	RT n/N (%)	*P* value
Perez (1991; 1989)			
Complete response (all)	38/119 (32)	35/117 (30)	ns [a]
Complete response (< 3 cm)	14/27 (52)	11/28 (39)	-
Complete response (≥ 3 cm)	24/92 (25)	24/89 (27)	-
Local tumour control (all)	nr	nr	0.12 [b]
Local tumour control (< 3 cm)	nr	nr	0.02 [b]
Local tumour control (≥ 3 cm)	nr	nr	0.81 [b]
Egawa (1989)			
Complete response	20/44 (45)	18/48 (38)	ns [a]

Abbreviations: MT, microwave therapy; nr, not reported; ns, not significant (p ≥ 0.05); RT, radiotherapy.
[a] Post-hoc calculation based on evaluable patients only. Not possible to conduct ITT analysis.
[b] Study analysis based on evaluable patients only (236/250).

The results of the non-randomised controlled studies are summarised in **Table 30**. The results of these studies should be considered taking into account their poor methodological quality, and hence potential for bias.

The Howard study showed similar response rates in lesions receiving RT + MT (45%; 9 lesions) compared with RT alone (23%; 7 lesions). The authors also report complete response by tumour size (< or > median area) with large tumours showing similar response rates (17% vs 28%; 1 lesion vs 2 lesions) while smaller lesions showed different response rates (57% vs 36%; 8 lesions vs 5 lesions).

The study by Dunlop *et al.* (1986) showed no difference in response rate for lesions receiving RT + MT compared with RT alone. The author's state that when RT + MT results are assessed according to number of "useful" heat sessions (ie, minimum tumour heat of 20minEq43), a greater response rate was seen in lesions receiving two or more useful heat sessions (83-89%) compared with no or one useful heat session (30-38%).

The Scott *et al.* (1983) study show no significant difference in complete response rate between lesions receiving RT + MT compared with RT alone, at either treatment end or after 1-18 months follow-up.

The results of the Scott *et al.* (1984) study show that complete response is substantially greater in the RT + MT arm compared with the RT alone arm at treatment end, and at 6 and 12 months. However, by 18-24 months complete response rates are similar between the two arms.

Table 30 Non-RCT results: superficial tumours

Outcome	RT + MT n/N (%) [a]	RT n/N (%) [a]	*P* valuea
Howard (1988, 1987)			
Complete response	9/20 (45)	7/21 (33)	ns
Dunlop(1986)			
Complete response	27/45 (60)	16/32 (50)	ns
Scott (1983) [b]			
Complete response at treatment end	6/24 (25)	5/24 (21)	ns
Complete response at 1-18 months follow-up	19/24 (79)	14/24 (58)	ns
Scott (1984) [b]			
Complete response at treatment end	10/31 (32)	3/31 (10)	p<0.05
Complete response at 6 months	27/31 (87)	12/31 (39)	p<0.01
Complete response at 12 months	19/31 (61)	10/31 (32)	p<0.05
Complete response at 18 months	8/31 (26)	7/31 (23)	ns
Complete response at 24 months	6/31 (19)	5/31 (16)	ns

Abbreviations: MT, microwave therapy; ns, not significant ($p \geq 0.05$); RT, radiotherapy.

[a] Post hoc comparison calculated by reviewer with available data, using Chi-square or Fishers Exact Test, as appropriate.

[b] These two studies may include some of the same patients however it is not possible to determine this for certain due to differences in the reporting of the studies.

The single arm series receiving MT alone reported by Luk *et al* (1981) showed an 18% complete response rate (Table 31). The authors investigated the effect of average and maximum tumour temperatures on response and found that the mean average temperature for complete responders (n=2) vs non-responders (n=7) was 42.2°C vs 40.1°C respectively. The mean maximum tumour temperature for complete responders vs non-responders was 43.9°C vs 43.0°C respectively.

Table 31 Case series results: superficial tumours

Outcome	MT n/N (%)
Luk (1981)	
Complete response	2/11 (18)

Abbreviations: MT, microwave therapy.

Various cancer types

Two case series from the same group describe efficacy and safety of microwave therapy alone in patients with different cancer types. The main characteristics of the studies described in these two papers are summarised in **Table 32**.

There is significant overlap in the time periods covered by the two papers. Hence, it is possible that some data are duplicated between the two studies. However, the two papers used slightly different microwave therapy regimens, and are therefore considered below as separate studies.

The paper by Gabriele *et al.* (1990) reports on the findings of a case series of 57 patients treated with microwave therapy alone. The paper by Gabriele *et al.* (1989) reports on the findings of non-randomised controlled trial of MT versus RT + MT. Only results from the MT arm (26 lesions in an unknown number of patients) are discussed herein (see methods section). Both studies are of poor methodological quality, and the results have the potential to be substantially biased.

Table 32 Study characteristics: various cancer types

Citation	Study type Study quality	Population	Intervention	Comparator	Outcomes
Intervention Level IV evidence					
(Gabriele *et al.* 1990)	Case-series Poor	Men and women with recurrent cancer or metastases in which prior conventional therapies have failed [a] N=57 patient N=60 lesions	**MT alone** 434 MHz or 915 MHz (for superficial lesions) or 27 MHz (for 4 deep lesions) for 45 mins N=50 patient N=60 lesions	None	Tumour response Survival Adverse events
(Gabriele *et al.* 1989)	Case series (Single arm from a non-randomised controlled trial) Poor	Men and women with recurrent cancer or metastases for whom conventional therapies were not appropriate [b] N=50 patients N=66 lesions	**MT alone** 434 MHz or 915 MHz for 30 mins N patients unknown N=26 lesions	Not applicable [c]	Tumour response Adverse events

Abbreviations: MT, microwave therapy.
[a] Includes lesions in the head and neck, chest wall, trunk, and limbs
[b] Includes cancer of the breast, head and neck, cervix, rectum, colon and melanomas
[c] MT plus radiotherapy.

The results of the Gabriele *et al* (1990) and Gabriele *et al* (1989) studies are summarised in **Table 33**. The results of these studies are difficult to interpret as neither study included a relevant comparator group. The response rate observed for MT alone was modest. However, a number of issues must be kept in mind when interpreting the results from both studies: (i) the use of subjective measures to define tumour response, (ii) no blinding of outcome assessment, and (iii) strong possibility of patient selection. Furthermore, the results are of limited value for the current review as they are non-comparative in nature.

Table 33 Case series results: Various cancer types

Outcome	MT alone n/N (%)
Gabriele (1990)	
Complete response rate	10/60 lesions (16.6%)
Percent survival at 11 months	15%
Gabriele (1989)	
Complete response rate	5/26 lesions (19.2%)

Abbreviations: MT, microwave therapy.

Efficacy summary

In an attempt to illustrate the entire body of evidence directly relevant to the current review, **Table 34** and **Table 35** summarise the evidence presented in **Chapter 4** in accordance with the NHMRC dimensions of evidence. Only data for the primary efficacy outcomes of complete tumour response (preferably 3 month response) and overall survival are summarised. Data for other outcomes and more detail is available above, or in **Appendix 9**.

There has been considerable research undertaken to investigate the efficacy of microwave therapy (300 MHz–300 GHz) for the treatment of cancer. In almost all cases, the effect of microwave therapy upon cancer outcomes was investigated by comparing radiotherapy alone (RT) to radiotherapy plus microwave therapy (RT + MT). This represents a logical approach to addressing the research question. In addition, a small number of publications report data from a series of patients receiving microwave therapy alone, however meaningful interpretation of uncontrolled results is more difficult.

Despite the large volume of evidence, the quality of the evidence is weak. Several randomised controlled trials have been undertaken (Level II evidence), however the quality of these was never better than fair. No single or double-blind randomised controlled trials have been undertaken, outcomes were rarely assessed in a blinded fashion, and patient follow-up has generally been inadequate. The remainder of the evidence is poor quality Level III and IV, the majority of which suffers from considerable selection and intervention bias.

Notwithstanding the poor quality of evidence, synthesising the body of evidence as a whole is problematic for several other reasons; (i) the research covers a broad range of cancer types, and typically there are a limited number of studies in each cancer type; (ii) the research relates to both superficial and deep tumours, when it is reasonable to expect that the effect may differ; (iii) the outcomes reported in each study are different and often poorly defined and (iv) follow-up of patients is highly variable. As a result it is not appropriate to statistically meta-analyse the results.

At the present time, no peer-reviewed publications are available to support the specific microwave therapy currently being practiced in Western Australia (ie., 434 MHz microwave therapy *with* glucose blocking agents but *without* concurrent radiotherapy). However, several studies have been undertaken with 434 MHz microwave therapy (but *without* glucose blocking agents and *with* concurrent radiotherapy), and whilst only partially relevant to the Australian practice, they have been identified as relevant in **Table 34** and **Table 35**.

It is worth reiterating that there is an equally large body of evidence investigating the efficacy of lower radiofrequencies (8-300 MHz) and also investigating the use of more invasive methods of microwave administration, including many randomised controlled trials. However, as these modes of therapy were beyond the scope of the current review, they are not included here.

Table 34 Body of evidence: Efficacy of microwave therapy - Complete tumour response

Citation	Cancer type	Strength of evidence				Clinically relevant effect?	Additional benefit of MT evident?	Relevant to current Australian practice?[b]
		Comparison	Level of evidence	Quality of evidence	Statistical precision [a]			
Level I								
none available								
Level II								
(Valdagni and Amichetti 1994; Valdagni *et al.* 1988)	Head & neck	MT+RT vs RT	II	Fair	Yes, p<0.05	Yes (RR 1.83)	✓	No
(Overgaard *et al.* 1996; Overgaard *et al.* 1995)	Melanoma	MT+RT vs RT	II	Poor	Yes, p<0.01	Yes (RR 4.01[c])	✓	No
(Perez *et al.* 1991; Perez *et al.* 1989)	Superficial	MT+RT vs RT	II	Poor	Not significant	N/A	✗	No
(Egawa *et al.* 1989)	Superficial	MT+RT vs RT	II	Poor	Not significant	N/A	✗	No
(Vernon *et al.* 1996; Sherar *et al.* 1997)	Breast	MT+RT vs RT	II	Fair	Yes, p<0.01	Yes (OR 2.3)	✓	No
(Trotter *et al.* 1996)	Colorectal	MT+RT vs RT	II	Fair/Poor	Not significant	N/A	✗	No
Level III-1								
none available								
Level III-2								
(Arcangeli *et al.* 1980)	Head & neck	MT+RT vs RT	III-2	Poor	Yes, p<0.01	Yes	✓	No
(Arcangeli *et al.* 1987)	Melanoma	MT+RT vs RT	III-2	Poor	Not significant	N/A	✗	No
(Scott *et al.* 1983)	Melanoma	MT+RT vs RT	III-2	Poor	Yes, p<0.05	Yes	✓	No
(Howard and Bleehen 1988; Howard *et al.* 1987)	Superficial	MT+RT vs RT	III-2	Poor	Not significant	N/A	✗	No
(Dunlop *et al.* 1986)	Superficial	MT+RT vs RT	III-2	Poor	Not significant	N/A	✗	No
(Scott *et al.* 1984)	Superficial	MT+RT vs RT	III-2	Poor	Yes, p<0.01[d]	Yes	✓[c]	No

Citation	Cancer type	Strength of evidence				Clinically relevant effect?	Additional benefit of MT evident?	Relevant to current Australian practice?[b]
		Comparison	Level of evidence	Quality of evidence	Statistical precision [a]			
Level III-3								
(Hornback *et al.* 1986)	Cervical	MT+RT vs RT	III-3	Poor	Not significant[e]	N/A	✗	No
(Ohizumi *et al.* 2000)	Head & Neck	MT+RT vs RT	III-3	Poor	Not significant[e]	N/A	✗	No
(Holt 1977; Nelson and Holt 1977; Nelson and Holt 1978; Holt 1982; Holt 1988)[f]	Head & Neck	MT+RT vs RT	III-3	Poor	Yes, p<0.01	Yes	✓	No
(Masunaga *et al.* 1990)	Breast	MT+RT vs RT	III-3	Poor	Not significant[e]	N/A	✗	No
(Perez *et al.* 1986)	Breast	MT+RT vs RT	III-3	Poor	Not significante[g]	N/A	✗	No
Level IV								
(Gabriele *et al.* 1990)	Various	MT alone	IV	Poor	N/A	N/A	N/A	Not clear
(Gabriele *et al.* 1989)	Various	MT alone	IV	Poor	N/A	N/A	N/A	Not clear
(Luk *et al.* 1981)	Superficial	MT alone	IV	Poor	N/A	N/A	N/A	No

Abbreviations: ✓, yes; ✘, no; MT, microwave therapy; N/A, not applicable; RT, radiotherapy; S, surgery.

[a] True effect rather than chance finding?

[b] To be applicable to microwave cancer therapy as currently available in Australia, the study must have used a frequency of 434 MHz, administered without concurrent radiotherapy.

[c] Should be viewed with caution - unadjusted RR = 1.75, so treatment arms imbalanced.

[d] CR at 6 months (not reported at 3 months). P<0.05 at 12 months, not significant at 18 and 24 months.

[e] Actually local tumour control - not defined (complete response not reported).

[f] Assumes these studies represent duplicate data.

[g] Results reported in the abstract of the paper refer to a selected subgroup only (without acknowledging this) and are therefore extremely misleading.

Table 35 Body of evidence: Efficacy of microwave therapy - Overall survival

Citation	Cancer type	Strength of evidence				Clinically relevant effect?	Additional benefit of MT evident?	Relevant to current Australian practice?[b]
		Comparison	Level of evidence	Quality of evidence	Statistical precision [a]			
Level I								
none available								
Level II								
(Valdagni and Amichetti 1994; Valdagni *et al.* 1988)	Head & neck	MT+RT vs RT	II	Fair	Yes, p<0.02	Yes	✓	No
(Vernon *et al.* 1996; Sherar *et al.* 1997)	Breast	MT+RT vs RT	II	Fair	Not significant	No	✗	No
(Shchepotin *et al.* 1994)	Gastric	MT+RT+S vs RT+S	II	Poor	Not significant	N/A	✗	No
(Trotter *et al.* 1996)	Colorectal	MT+RT vs RT	II	Fair/Poor	Not significant	N/A	✗	No
Level III-1								
none available								
Level III-2								
none available								
Level III-3								
(Hornback *et al.* 1986)	Cervical	MT+RT vs RT	III-3	Poor	Not significant	N/A	✗	No
(Holt 1977; Nelson and Holt 1977; Nelson and Holt 1978; Holt 1982; Holt 1988)[c]	Head & Neck	MT+RT vs RT	III-3	Poor	Yes, p<0.01	Yes	✓	No
(Hayashi *et al.* 1999)	Ovarian	MT+CT+S vs CT+S	III-3	Poor	Yes, p<0.05	Yes	✓	No
Level IV								
(Gabriele *et al.* 1990)	Various	MT alone	IV	Poor	N/A	N/A	N/A	Not clear

Abbreviations: ✓ yes; ✗ no; CT. chemotherapy; MT, microwave therapy; N/A, not applicable; RT, radiotherapy; S, surgery.

[a] True effect rather than a chance finding?

[b] To be applicable to microwave cancer therapy as currently available in Australia, the study must have used a frequency of 434 MHz, administered without concurrent radiotherapy.

[c] Assumes these studies represent duplicate data.

In summary, the results presented in **Table 34** and **Table 35** above indicate that there is minimal evidence to support the routine use of microwave therapy for the treatment of cancer. Whilst a considerable volume of clinical reports and related information exists, the content is generally inadequate for assessment of treatment efficacy.

Isolated studies in head and neck cancer suggest microwave therapy with concurrent radiotherapy may confer a local tumour response that is over and above that of radiotherapy alone. However, the variability of the results and the suggestion toward a temperature dose response effect, imply that gaining any benefit may well be highly dependent upon successfully elevating the intra-tumoral temperature. In practice this has proved difficult to achieve. It is not possible to determine whether the lack of convincing and consistent evidence, despite considerable research, is due to a) a lack of effect of microwave therapy per se b) a failure in the practice of microwave therapy due to inability to adequately reach or heat the tumour; or c) weak research methodology, including possible selection bias. The last of these certainly applies, but may not be the only reason.

Nevertheless, evidence that relates to the use of microwave therapy with concurrent radiotherapy should not be extrapolated to the use of microwave therapy alone, or microwave therapy with non-cytotoxic compounds such as glucose blocking agents. There is currently no satisfactory evidence to quantify the benefit of such practices relative to conventional cancer treatments.

Safety results

A total of 54 publications met the inclusion criteria for evaluation of the safety of microwave cancer treatment. Details regarding the study design, intervention and patient characteristics for the majority of these studies have already been presented earlier in this chapter. For studies included for the evaluation of safety outcomes only (n=19), these details are presented in **Table 36**.

In the vast majority of included studies, adverse events were *not* an *a priori* defined endpoint and therefore they were not systematically recorded. For this reason, adverse events were reported in these publications in an *ad hoc* fashion.

Table 36 Study characteristics: Studies reporting safety data only

Citation	Study type	Population	Intervention	Comparator	Outcomes
Intervention Level III-2 evidence					
(Ben Yosef and Kapp 1995)	Non-randomised study. A cohort of patients were treated with both microwave and ultrasound MT applied to the same field during the same treatment course	Various cancers	**MT** **±RT±CT:** MWMT, 60-100 MHz applicators used for eccentric lesions and 315-925 MHz applicators for superficial tumours. The goal of treatment was to maintain an intratumour temperature of at least 43°C for 45 min.	**US** **±RT± CT:** USMT, 1 or 2 MHz US applicator used for both superficial and eccentric lesions. The goal of treatment was to maintain an intratumour temperature of at least 43°C for 45 min.	Adverse events
(Estes *et al.* 1986)	Non-randomised study	Colorectal cancer	**MT+CT:** Whole body MT, 434 MHz 40°C ± 0.5°C for 1 hour on the 2nd and 5th day of the infusion period CT, 5FU 800 mg/m2 infusion per day for 7 days + Mitomycin C 10 mg/m2 given as a slow intra-arterial bolus at the completion of the infusion period (7th day)	**CT:** 5FU 800 mg/m2 infusion per day for 7 days + Mitomycin C 10 mg/m2 given as a slow intra-arterial bolus at the completion of the infusion period (7th day)	Adverse events
(Fujiwara *et al.* 1987)	Non-randomised study	Gynaecological cancers	**MT+CT** **±Surgery** **±RT:** MT, 2450 MHz microwave 42°C – 43°C + CT, Bleomycin or Peplomycin 5mg intravenous infusion on 7 consecutive days and mitomycin C 10 mg on the 8th day. This schedule was repeated 1-5 times with one week intervals	**CT** **±Surgery** **±RT:** CT, Bleomycin or Peplomycin 5mg intravenous infusion on 7 consecutive days and mitomycin C 10 mg on the 8th day. This schedule was repeated 1-5 times with one week intervals	Adverse events
(Kapp *et al.* 1988)	Non-randomised Phase-I study	Various cancers	**MT±RT±CT:** MWMT, 95 MHz, 310-915MHz and 100MHz.	**US±RT±CT:** USMT, 365 KHz, 0.7-3.5 MHz	Adverse events
(Lindholm *et al.* 1990)	see Lindholm 1987, 1988 in Table 28 for detail				

Citation	Study type	Population	Intervention	Comparator	Outcomes
(Nishimura *et al.* 1992)	Non-randomised study	Primarily unresectable and recurrent colorectal cancer	MT+RT: MT, 430 MHz microwave system. Treatment applied directly after radiotherapy for 30-60 min for a total of 2-14 sessions RT, 1.6-2.1 Gy per day, 5 days week, to a total dose of 40-70 Gy	RT: RT, 1.6-2.1 Gy per day, 5 days week, to a total dose of 40-70 Gy	Adverse events
Intervention Level IV evidence					
(DuBois *et al.* 1990)	Case series	Chest wall recurrences of breast cancer	**MT±CT±RT:** MT, 2450 MHz microwave 41.5°C – 42.5°C maintained for 45 minutes CT, 50mg/m2 doxorubicin + 500mg/m2 cyclophosphamide + 500mg/m2 5FU. Administered on the same day and repeated every 3 weeks depending on tolerance RT, 2 x 450cGy or 3 x 350cGy/week	–	Adverse events
(Gaboriaud *et al.* 1982)	Non-randomised phase I/II study	Various cancers	**MT:** 434 MHz. 45 min sessions, 43°C-45°C-plateau temp. Six sessions in 3 weeks, 2 sessions per week with 52 hr of interval time between sessions	–	Adverse events
(Gardner *et al.* 2002)	Non-randomised phase I study	Breast cancer	**MT:** Planned thermal dose equivalent to 60 min at 43°C	–	Adverse events
(Holt and Nelson 1976)	Case series	Report of AEs limited to 3 male cancer patients	**MT:** 434MHz microwave therapy	–	Adverse events
(Holt 1979)	Case studies	Report of AEs limited to 2 male cancer patients. One with lung cancer the other with rectal cancer	**MT:** 434MHz microwave therapy. 34 sec of MT in patient 1; 63 sec of MT in patient 2	–	Adverse events

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Citation	Study type	Population	Intervention	Comparator	Outcomes
(Holt 1975)	Case study	Report of AE in one female child with glioma in the left posterior parietal region infiltrating medially and into the occipital regions	**MT:** 433.92 MHz microwave therapy	–	Adverse events
(Luk *et al.* 1979)	see Luk, 1981 in Table 28 for detail				
(Luk *et al.* 1983)	Case series / patient registry	Superficial lesions	**MT±RT:** MT, 434, 915 and 2450 MHz for the most part. A minium of three heat treatments was required RT, External radiation therapy using photon or electron beams with dose fraction 200-700 Cgy	–	Adverse events
(Mendecki *et al.* 1978)	Case series	Various cancers	**MT+Various:** MT, 915-2450 MHz microwave radiation.	–	Adverse events
(Sannazzari *et al.* 1986)	Case series	Various cancers	**MT±RT±CT:** MT, 2450, 915, and 434 MHz. 27 MHz used in one patient. 43.5°C – 45°C for 30 min, bi-weekly, for 3-5 weeks immediately following radiation. RT, 4 Gy/fraction	–	Adverse events
(Van Vulpen *et al.* 2003)	Non-randomised study	Prostate cancer	**MT+RT:** MT, One treatment per week for 75 min. All patients completed 5 microwave therapy treatments RT, 66-70 Gy fractions in 2 Gy fractions (5 fractions per week) delivered to the prostate and seminal vesicles. The seminal vesicles were excluded from the irradiation field after 50 Gy when they were not invaded by tumours	**RT:** RT, 66-70 Gy fractions in 2 Gy fractions (5 fractions per week) delivered to the prostate and seminal vesicles. The seminal vesicles were excluded from the irradiation field after 50 Gy when they were not invaded by tumours	Adverse events
(Vargas *et al.* 2004)	Uncontrolled, prospective, multicentre, non-randomised dose escalation study	Early stage breast cancer	**MT:** 915 MHz microwave 80-100 cumulative equivalent minutes thermal dose	–	Adverse events

Citation	Study type	Population	Intervention	Comparator	Outcomes
(Yerushalmi 1988)	Non-randomised study	Prostate carcinoma	**MT±RT:** MT, was applied twice per week, 1-2 hours post irradiation RT, 30 Gy delivered over 3 weeks in 5 daily fractions per week of 2 Gy each. After 3-4 week rest period, further irradiation doses to the pelvis were administered to a total of 50 Gy without further MT treatment. A boost to the prostate of 10 Gy was then given in week 1 (five fractions)	**RT:** RT, 30 Gy delivered over 3 weeks in 5 daily fractions per week of 2 Gy each. After 3-4 week rest period, further irradiation doses to the pelvis were administered to a total of 50 Gy without further MT treatment. A boost to the prostate of 10 Gy was then given in week 1 (five fractions)	Adverse events

Abbreviations: AEs, adverse events; MT, microwave therapy; MW, microwave; MHz, megahertz; RT, radiotherapy; US, ultrasound.

Mortality

The deaths of five patients were recorded in the included studies. These studies report the use of microwave therapy in more than 1000 patients.

One child with glioma in the left posterior parietal region infiltrating medially and into the occipital regions was treated in Western Australia with microwave therapy on six occasions over four weeks. She was intolerant of the sensation of warmth in her head, but was reported to respond remarkably. One month later the clinician decided to give the child further microwave treatment. One short microwave session produced headache, pain in the eyes and vomiting in the child. The child was admitted to Princess Margaret's Hospital for Children for a sudden increase in intracranial pressure and died seventy-two hours after admission (Holt 1975).

Two male patients died after having less than two minutes of microwave therapy in Western Australia (Holt 1979). Both patients were terminally ill, one with widespread lung cancer the other with rectal cancer. The patient with lung cancer was treated with microwave therapy for less than one minute before collapsing in the harness. He was examined and found to be pulseless and was given oxygen and external cardiac massage for five minutes without effect. His temperature was 36.8˚C at that time. The patient with rectal cancer stopped breathing one minute after microwave therapy was initiated. The patient could not be resuscitated and seven minutes later his rectal temperature was measured at 38.1˚C (Holt 1979).

In another study a patient died from a carotid artery rupture two months after treatment with microwave therapy combined with radiation therapy (Valdagni *et al.* 1988; Valdagni and Amichetti 1994).

In a further study, one patient died from blood loss after suffering from post–therapeutic necrosis and rupture of the common coronary artery (Lindholm *et al.* 1987; Lindholm *et al.* 1988; Lindholm *et al.* 1990).

Mortality associated with microwave therapy should be considered in the context of the disease prognosis and the mortality associated with other treatment options.

Morbidity

Table 37 shows the adverse events reported in the included studies. The quality, methods and rates of adverse event recording and reporting were highly variable. More often than not, adverse events were not systematically recorded and, in general, the standard of reporting was very poor (see first column of **Table 37**). Furthermore, adverse events were not always clearly reported in the results section of the publications, so information was often obtained from the discussion.

Some studies reported the adverse events per patient, some per field and some per lesion. Other reported adverse events are narratives only, with no quantification of the relevant denominator. Therefore, it was not possible to quantitatively summarise the frequency at which adverse events occur with microwave therapy.

Some of the more common adverse events associated with microwave therapy appear to be pain, erythema, fibrosis, necrosis, ulcerations, blisters and thermal burns. Third degree burns, arterial rupture and development of fistulae have been reported on occasions.

Table 37 Adverse events reported

Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
Level II							
(Overgaard *et al.* 1996; Overgaard *et al.* 1995) No	Melanoma		RT + MT (% fields)	RT (% fields)	Researchers state: "Complications were acceptable with the exception of a few heat–induced burns or ulcerations, there was no difference between areas treated with RT + MT and RT alone." No pain or discomfort = 73% of treatments. Slight pain = 13% of treatments. Moderate pain = 8% of treatments. Pain severe enough to interrupt or stop treatment = 6% of treatments. Only 9% of heat treatments were in accordance with the protocol requirements	nr	Not possible
		Acute radiation reaction in skin:					
		None/slight	42%	51%			
		Moderate/severe	58%	49%			
		Late radiation reaction in skin:					
		None/slight	63%	72%			
		Moderate/severe	37%	28%			
(Perez *et al.* 1991; Perez *et al.* 1989) Yes	Superficial		RT + MT (na/N pts)	RT (na/N pts)			
		Acute:					
		Erythema	36/119 (30%)	36/117 (31%)		nr	ns
		Dry desquamation	8/119 (7%)	21/117 (18%)		nr	P = 0.009
		Moist desquamation	2/119 (2%)	9/117 (8%)		nr	P = 0.03
		Ulceration	14/119 (12%)	19/117 (16%)		nr	ns
		Necrosis	11/119 (9%)	4/117 (3%)		nr	P = 0.07
		Thermal blister	36/119 (30%)	0/119 (0%)		nr	P < 0.0001
		Long term:					
		Minimal depigmentation/ fibrosis	15/119 (13%)	43/117 (37%)		nr	P < 0.0001
		Loss of sweating/ telangiectasis	8/119 (7%)	8/117 (7%)		nr	ns
		Persistent ulceration	0/119 (0%)	18/117 (15%)		nr	P < 0.0001
		Skin/ subcutaneous necrosis	24/119 (20%)	0/117 (0%)		nr	P < 0.0001

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Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
(Trotter *et al.* 1996) No, selected AEs only	Colorectal		RT + MT (n/N pts)	RT (n/N pts)	No sign. difference between treatment arms for any specified toxic effects were found No record of burns or ulceration rates Patients treated with microwave therapy + external beam radiotherapy reached significantly lower pelvic pain levels during treatment (P= 0.03). However, at the commencement of treatment slightly more pain was present in patients in the radiotherapy alone arm, but this difference was not significant (P=0.74)	ns (Two-tailed Mann-Whitney U–test)	–
		Toxicity – leucocyte					
		Grade 0 =	19/36 (53%)	25/37 (69%)			
		Grade 1 =	8/36 (22%)	10/37 (27%)			
		Grade 2 =	6/36 (17%)	2/37 (5%)			
		Grade 3 =	1/36 (3%)	0/37 (0%)			
		Unknown =	2/36 (6%)	0/37 (0%)			
		Toxicity – Platelets					
		Grade 0 =	32/36 (89%)	36/37 (97%)			
		Grade 1 =	1/36 (3%)	0/37 (0%)			
		Grade 2 =	0/36 (0%)	1/37 (3%)			
		Grade 3 =	1/36 (3%)	0/37 (0%)			
		Unknown =	2/36 (6%)	0/37 (0%)			
		Toxicity – Nausea and vomiting					
		Grade 0 =	12/36 (33%)	16/37 (43%)			
		Grade 1 =	5/36 (14%)	8/37 (22%)			
		Grade 2 =	7/36 (19%)	8/37 (22%)			
		Grade 3 =	7/36 (19%)	2/37 (5%)			
		Grade 4 =	5/36 (14%)	3/37 (8%)			
		Toxicity – Diarrhoea					
		Grade 0 =	20/36 (56%)	19/37 (51%)			
		Grade 1 =	5/36 (14%)	10/37 (27%)			
		Grade 2 =	6/36 (17%)	2/37 (5%)			
		Grade 3 =	3/36 (8%)	5/37 (14%)			
		Grade 4 =	0/36 (0%)	1/37 (3%)			
		Unknown =	2/36 (6%)	0/37 (0%)			

Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
			RT + MT	RT			
(Valdagni and Amichetti 1994; Valdagni *et al.* 1988; Valdagni 1988) No	Head & neck	Skin burn Acute toxicity: Fowler modified score Acute toxicity: WHO modified score Late toxicity: RTOG/EORTC score	1 pt Range = 1–9 Average = 3.15 Range = 0–3 Average = 1 Range = 0–4 Average = 1.52	nr Range = 1–8 Average = 3.2 Range = 0–3 Average = 1 Range = 0–3 Average = 1.04	Researchers concluded that MT does not increase acute toxicity and does not significantly affect late toxicity. One patient died 2 months after treatment from a carotid artery rupture. Two grade 4 side effects (bone necrosis) were noted in the combined treatment arm. Both cases occurred with nodes fixed to the mandibular bone. In 15% of heat sessions the power was adjusted due to pain experienced during treatment. 3 pts required no more than 1 administration of non-narcotic drug at the end of their microwave therapy treatment.	nr	–
			RT + MT (n/N pts)	RT (n/N pts)			
(Vernon *et al.* 1996; Sherar *et al.* 1997) Yes	Breast	Erythema (mild/ moderate) Erythema (severe/ desquamation) Blister Ulceration Necrosis Fibrosis Telangiectasia Pigmentation	82/163 (50%) 37/163 (23%) 19/166 (11%) 11/166 (7%) 12/166 (7%) 59/114(52%) [b] 29/97 (30%) [b c] 52/114 (46%) [b]	65/122 (53%) 29/122 (24%) 2/122 (2%) 3/122 (2%) 1/122 (1%) 37/83 (45%)[b] 18/67(27%)[b c] 36/83 (43%)[b]	A small number of patients had their microwave therapy treatment terminated early because of pain. In addition, two patients had their microwave therapy treatment halted because of the discovery of pleural effusions that made it impossible for them to lie flat. Researchers state: "In general, the acute effects of microwave therapy treatment tended to occur in areas of reduced sensitivity and healed with conservative treatment, with little impact on patient well–being." Several late reactions occurred: one each of bone necrosis, bone fracture, and brachial plexus lesion all in the combined arm of the ESHO trial. 'Hyperthermia, as delivered in these trials, was well tolerated and did not significantly add to clinically relevant or long–term toxicity over irradiation, even in those patients who had received prior radical radiotherapy'.	nr nr nr nr nr nr nr nr	ns ns P = 0.001 ns P = 0.009 ns ns ns

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Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
Level III-2							
(Arcangeli *et al.* 1980; Arcangeli *et al.* 1987; Arcangeli *et al.* 1985) No	Head & neck	Blisters	RT + MT (n/N nodes) 8/38 (21%)	RT nr	Researchers state: "At the beginning of the study, a flat heating applicator was used even for irregular skin surfaces. Since the first and the second patient developed a small vesicle at the edge of the thermal field, where the skin was sledge- shaped or concave, efforts were made to develop other applicators fitting the irregular surface … No unusual skin reactions were seen thereafter and treatment was never discontinued or interrupted. Some patients experienced only an occasional warm sensation at the beginning of heating." Researchers state: "No abnormal reactions were seen in areas that were treated with the combined treatment, except reactions typical of areas that were treated with irradiation alone." Researchers state: "The addition of heat did not result in any enhancement of early or late radiation effects on normal skin and subcutaneous tissue." Researchers state: "The percentage of acute skin reactions and of late fibrosis was approximately similar in both treatment arms (MT and no MT). However, thermal damage (blisters) was seen in eight patients, as a consequence of power leakage and overheating of applicators used in this study."	nr	Not possible

Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
(Ben Yosef and Kapp 1995) Yes	Various	Acute toxicities: None Pain in field Referred pain Blister/ ulceration Positional discomfort Other Subacute toxicities: None Pain Blister/ ulceration Oedema/ induration	RT + MT (n/N treatments) 59/118 (50%) 50/118 (42%) 2/118 (2%) 2/118 (2%) 3/118 (3%) 2/118 (2%) 114/118 (97%) 1/118 (1%) 3/118 (3%) 0/118 (0%)	US MT+ RT (n/N treatments) 19/79 (24%) 44/79 (56%) 16/79 (20%) 0/79 (0%) 0/79 (0%) 0/79 (0%) 73/79 (92%) 1/79 (1%) 3/79 (4%) 2/79 (3%)	Pain related treatment was the most common side effect	P = 0.0005 (toxicity vs. no toxicity) P = 0.32 (toxicity vs. no toxicity)	P = 0.0003 P = 0.0665 P < 0.0001 ns ns ns ns ns ns ns
(Dunlop *et al.* 1986) No	Superficial	–	RT + MT	RT –	On eight occasions treatment was prematurely stopped due to either pain or general discomfort. Researchers state: "Superficial blistering that healed satisfactorily developed occasionally at points corresponding to where skin temperatures in excess of 45°C had been sustained." Minor superficial burns were recorded. In all these instances, the skin changes healed without excess scarring after a day of some local discomfort	–	–
(Estes *et al.* 1986) No	Rectal	–	MT + Intra-arterial CT	Intra-arterial CT	Only 4 patients received microwave therapy treatment Researchers state: "No catheter, chemotherapy, or microwave therapy complications have occurred"	nr	Not possible

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Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
			MT + CT (n/N pts)	CT alone (n/N pts)			
(Fujiwara *et al.* 1987) Yes	Vaginal	General fatigue	36/42 (86%)	27/27 (100%)		nr	P = 0.04
		Nausea / vomiting	32/42 (76%)	27/27 (100%)		ns	P = 0.006
		Fever	10/42 (24%)	21/27 (78%)		ns	P < 0.0001
		Alopecia	11/42 (26%)	10/27 (36%)		ns	P = ns
		Aphtha	2/42 (5%)	2/27 (7%)		ns	P = ns
		Acrocyanosis	2/42 (5%)	2/27(7%)		ns	P = ns
		Exanthema	2/42 (5%)	0/27 (0%)		sig (p nr)	P = ns
		Lung fibrosis	2/42 (5%)	6/27 (22%)		ns	P =0.05
		RBC <300 x 104/mm^3 or Hb < 10g/dl	4/42 (10%)	11/27 (41%)		ns	P = 0.006
		WBC < 3000/ mm^3	6/42 (48%)	13/27 (48%)		ns	P = 0.002
		PLT < 1 x 105/ mm^3	0/42 (0%)	2/27 (7%)		ns	P = ns
		GOT > 40U or GPT > 40U	6/42 (14%)	4/27 (15%)		ns	P = ns
			RT + MT (n/N lesions)	RT (n/N lesions)			
(Howard and Bleehen 1988) No, selected AEs only	Superficial	Low grade skin reaction (grade 0–3)	12/20 (60%)	20/21 (95%)	Researchers state: "The acute toxicity of the procedure, though limiting the success of the treatment in virtually every case, was short lived. We have not noted any excessive late toxicity, although this is difficult to assess in such a heavily treated group of patients."	nr	P = 0.006
		High grade skin reaction (grade 4–7)	8/20 (40%)	1/21 (5%)		nr	P = 0.009

Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
			RT + MT (n/N lesions)	RT (n/N lesions)			
(Howard *et al.* 1987) No selected AEs only	Superficial	No visible reaction	1/20 (5%)	5/21 (24%)	Three cases of fibrosis were seen all of which occurred at the site of lesions which had received microwave therapy treatments	nr	ns
		Slight but definite erythema	6/20 (30%)	6/21 (29%)		nr	ns
		Moderate erythema	3/20 (15%)	6/21 (29%)		nr	ns
		Severe erythema (deep red or pink)	1/20 (5%)	3/21 (14%)		nr	ns
		First sign of breakdown	1/20 (5%)	1/21 (5%)		nr	ns
		Moist desquamation over less than half the field	4/20 (20%)	0/21 (0%)		nr	P = 0.05
		Moist desquamation over more than half the field	3/20 (15%)	0/21 (0%)		nr	ns
		Complete breakdown of the field	0/20 (0%)	0/21 (0%)		nr	ns
			RT + MT (n/N treatments)	US MT ± RT (n/N treatments)			
(Kapp *et al.* 1988) Yes	Various	Acute toxicities:					
		Pain	335/730 (46%)	172/236 (73%)		nr	P < 0.0001
		Neurological	1/730 (0%)	1/236 (0%)		nr	P = 0.06
		Referred pain	6/730 (1%)	17/236 (7%)		nr	P < 0.0001
		Other	3/730 (0%)	4/236 (2%)		nr	P = 0.06
		Subacute toxicities:					
		Pain	6/730 (1%)	10/236 (4%)		nr	P = 0.0004
		Referred pain	1/730 (0%)	1/236 (0%)		nr	P = 0.06
		Blister	26/730 (4%)	10/236 (4%)		nr	ns
		Oedema	1/730 (0%)	0/236 (0%)		nr	ns
		Fever	3/730 (0%)	3/236 (1%)		nr	ns
		Nausea	1/730 (0%)	0/236 (0%)		nr	ns
		Other	35/730 (5%)	0/236 (0%)		nr	P < 0.0001

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Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
(Scott *et al*. 1983) No	Melanoma	–	RT + MT	RT	Researchers state: "At the conclusion of treatment there were occasional demonstrations of skin reactions which were more severe than would be expected from the radiation therapy dose which was given. However, when patients presented with paired lesions, only in one instance did the area being treated with microwave therapy show a notably more severe reaction over that resulting from radiotherapy. At follow–up all such reactions had healed."	–	–
(Scott *et al*. 1984) No	Superficial		RT + MT	RT	Researchers state: "Toxicity of the treatment, both at the end of therapy and in continued follow–up was limited to that resulting from radiotherapy. The heated field, with the exception of occasional slight increased hypopigmentation was essentially indistinguishable from the surrounding radiotherapy field which always overlapped it"	na	na

Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm		No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
			MT+RT 2450MHz no water bag	MT+RT 915 MHz with water bag	RT			
(Lindholm *et al*. 1987; Lindholm *et al*. 1988; Lindholm *et al*. 1990) No, selected AEs only	Superficial	Sev/mod pain	26/38 pts (68%)	nr	nr	A case of post–therapeutic necrosis of the coronary artery occurred in one patient. A rupture of 10mm was seen in the common carotid artery. The patient died from blood loss from the carotid artery. One of the grade 4b reactions in normal skin did not heal. 7 months after end of treatment there was still a large necrosis with suppuration. Brisk arterial bleeding occurred from the bottom of the ulceration. The bleeding was stopped by resection of the necrotic area. Some patients felt pain for several hours after treatment Referred pain to the left arm was recorded in one patient treated with 915MHz microwave therapy in connection with the brachial nerve plexus. The pain vanished when the microwaves were switched off. Due to an unacceptably high rate of undesirable local side effects, 2450MHz microwave therapy without skin cooling could not be recommended.	nr	–
		Severe pain	11/33 regions (33%)	2/24 regions (8%)	nr			
		Moderate pain	15/33 regions (46%)	8/24 regions (33%)	nr			
		Skin reactions:						
		Grade 1						
		(a) No visible reactions	–	–	nr			
		(b) Minimal erythema	9/33 regions (27%)	17/24 regions (71%)	nr			
		(c) Marked erythema	7/33 regions (21%)	3/24 regions (12.5%)	nr			
		Grade 2						
		(a) Erythema with slight desquamation	2/33 regions (6%)	–	nr			
		(b) Dry desquamation	–	1/24 regions (4%)	nr			
		Grade 3						
		(a) Desquamation with blisters	7/33 regions (21%)	1/24 regions (4%)	nr			
		(b) Moist desquamation	–	–	nr			
		Grade 4						
		(a) Small necrosis or ulceration	3/33 regions (9%)	1/24 regions (4%)	nr			
		(b) Massive ulceration	5/33 regions (15%)	1/24 regions (4%)	nr			
		Subcutaneous fat tissue necrosis	3/33 regions (9%)	1/24 regions (4%)	nr			

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Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
(Nishimura *et al.* 1992) No	Colorectal	Blisters	RT + MT (n/N tumours) 1/5 (20%)	RT (n/N tumours) 0/30 (0%)	Radiofrequency (8MHz) and microwave (430 MHz) heating performed. Only 5 pts received MW therapy, therefore, AEs presented for microwave heating only. Local infection or abscess was mainly caused by contamination via the catheters inserted into the tumour .	nr	ns
(Scott *et al.* 1983) No	Melanoma	–	RT + MT	RT	Researchers state: "At the conclusion of treatment there were occasional demonstrations of skin reactions which were more severe than would be expected from the radiation therapy dose which was given. However, when patients presented with paired lesions, only in one instance did the area being treated with microwave therapy show a notably more severe reaction over that resulting from radiotherapy. At follow–up all such reactions had healed."	–	–
(Scott *et al.* 1984) No	Superficial		RT + MT	RT	Researchers state: "Toxicity of the treatment, both at the end of therapy and in continued follow–up was limited to that resulting from radiotherapy. The heated field, with the exception of occasional slight increased hypopigmentation was essentially indistinguishable from the surrounding radiotherapy field which always overlapped it"	na	na
Level III-3							
(de Graaf-Strukowska *et al.* 1999) No	Meso-thelioma	 Malaise Oesophagus Upper GI Skin	RT + MT (n/N pts) 2/18 (11%) 3/18 (17%) 1/18 (6%) 5/18 (28%)	RT (n/N pts) 4/24 (17%) 0/24 (0%) 4/24 (17%) 3/24 (13%)		 nr nr nr nr	 ns P = 0.07 ns ns

Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
(Holt 1988; Holt 1977; Holt 1979; Holt 1982; Nelson and Holt 1977; Nelson and Holt 1978) No	Head & Neck	–	RT + MT and/ or radioactive gold grain implant)	RT+ hypobaric oxygen; Supervoltage therapy alone –	Safety data poorly reported Researchers state: "Headaches and eye pain have been noted, but can be avoided by acetazolamide" "Three patients have had skin burns" "No distressing effects or evidences of damage by microwave therapy occurred in this series of patients"	None	Not possible
(Hornback *et al.* 1986) No	Cervical		RT + MT	RT	The only difference in symptoms between the patients treated with 25 MeV alone or 25 MeV + heat was a significant increase in generalised weakness immediately following the microwave therapy treatments. There was no difference in acute radiation skin reactions or other symptoms (ie. nausea, vomiting or diarrhoea) between patients treated with 25 MeV alone or 25 MeV + heat. Patients who received their external therapy with cobalt–60 have been excluded from this summary.	nr	Not possible
(Masunaga *et al.* 1990) No	Breast	Second degree burns Moist desquamation Ulcer	RT + MT ± CT (n/N tumours) 10/30 (33%) 8/30 (27%) 1/30 (3%)	RT nr nr nr	The trial employed a mixture of heating devices that included: 8, 13.56, 430 and 2450 MHz equipment. AEs were not reported separately for each of these frequencies therefore all AEs are presented Almost all patients complained of pain during heat treatment. Pain was the limiting factor to power elevation. No fat necrosis was observed	nr nr nr	Not possible Not possible Not possible

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Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
(Ohizumi *et al.* 2000) Yes	Head & Neck		MT + re- RT (n/N pts)	Re– RT (n/N pts)			
		Acute complications:					
		Thermal blisters	2/12 (17%)	0/12 (0%)		nr	ns
		Ulcers	2/12 (17%)	0/12 (0%)		nr	ns
		Necrosis	1/12 (8%)	0/12 (0%)		nr	ns
		Late complications:					
		Persistent ulcer	1/12 (8%)	0/12 (0%)		nr	ns
		Syncope	0/12 (0%)	1/12 (8%)		nr	ns
		Myelitis	0/12 (0%)	1/12 (8%)		nr	ns
		Laryngeal oedema	0/12 (0%)	1/12(8%)		nr	ns
(Perez *et al.* 1986) No	Breast		RT + MT (n/N pts)	RT (n/N pts)	Dry or moist desquamation had a comparable incidence in both groups. Dysphagia = 7 pts[a], this data was considered to be irrelevant due to differences in treatments between the two groups		
		Superficial ulceration	12/48 (25%)a	9/116 (8%)[a]		nr	P=0.003
		Thermal burns	4/48 (8%)[a]	nr		nr	Not possible
(Yamada *et al.* 1992) No	Pancreatic	Severe subcutaneous fatty burns	MT + intraoperative RT (n/N pts) 1/14 (7%)	Intra-operative RT nr		None	Not possible
Level IV							
(DuBois *et al.* 1990) No	Breast		MT alone	–	NB. AEs not reported by arm (n/N pts)	–	–
		Phlyctenae (blister) (grade 3)			5/42 (12%)		
		Dry erythematous epidermitis showing no desquamation (grade 1C)			4/42 (10%) No late skin reaction was observed in patients surviving beyond 18 months		

Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
(Gaboriaud *et al.* 1982) No	Various		MT alone		NB. AEs not reported by treatment arm. For cervical nodes a burn sensation is reported when the temperature reaches 42–43 degrees at 0.5cm depth. For pts with mammary disease/ axillary node there is no specific sensation even at 45 degrees Researchers state: "Although the implantation of thermocouples is traumatic, it is necessary to control the tumour temperature."	None	Not possible
(Gabriele *et al.* 1990) No	Various	Skin burns Blisters with moist desquamation Local infection	MT 2/60 lesions (3.3%) 6/56 pts (10%) 8/60 lesions (13%)	– – –	Researchers state: "Side effects and complications of the treatment were tolerable." A cutaneous necrosis required a surgical excision	na	na
(Gabriele *et al.* 1989) No	Various	–	MT ± CT ± RT	–	Researchers state: "In general, no systemic ill effects are experienced by patients treated with microwave–induced hyperthermia." "… erythema and desquamation of the skin were observed in proportion similar to that noted with irradiation alone. A thermal burn was noted in two cases only; they both healed spontaneously"	nr	Not possible
(Gardner *et al.* 2002) No	Breast	Limited flap necrosis Blister	MT (n/N pts) 3/10 (30%) 1/10 (10%)		Limited flap necrosis occurred in the first three breast cancer patients treated A small blister (approx 1cm in diameter) occurred in 1 patient. It healed completely with no treatment required and presented no special considerations during surgery	nr	na
(Holt 1982) No	Breast (stage 1-4 pts)[d]		MT		Researchers state: "No complications or sequelae have been revealed" in 26 patients with stage 1 to 4 cancer	None	Not possible

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Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
(Luk *et al.* 1981; Luk *et al.* 1979) No	Superficial	Blisters Burns	MT ± RT (n/N treatments) 1/11 (9%) (tumour temp < 42.5°C) 18/28 (64%) (tumour temp 42.6–43.9°C) 3/9 (33%) (tumour temp >44.0°C) 5/9 (56%) (tumour temp >44.0°C)		Blisters usually healed spontaneously within ten days. Burns required careful daily nursing care, cleansing with hydrogen peroxide and many required up to one month for healing. One patient developed a cellulitis, which was treated successfully with oral antibiotics. Two patients had massive tumour necrosis, leaving large open ulcers that required a long time to heal		
(Luk *et al.* 1983)	Superficial		MT		**NB**. AEs not reported by treatment arm. Report was limited to patients that received microwave therapy therapy with microwaves in sessions scheduled 48–96 hours apart 31% of the treated lesions and adjacent normal tissues showed either no reaction or transient or light erythema 27% experienced desquamation 24% showed reversible moderate or marked erythema 25% experienced blistering or ulceration Total minutes of heat and worst skin reaction score were correlated	nr	Not possible
(Mendecki *et al.* 1978) No	Various	nr	RT + MT Depigmented area in one patient	RT nr	–	None	Not possible

Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
(Sannazzari *et al.* 1986) No	Various	–	MT ± RT ± CT	–	Researchers state: "In general, no systemic ill effects are experienced by patients treated with microwave–induced hyperthermia." "… erythema and desquamation of the skin were observed in a proportion similar to that noted with irradiation alone. Only one patient suffered from a thermal burn."	–	–
(Van Vulpen *et al.* 2003) No	Prostate	–	MT (regional or interstitial) + RT	RT nr	NB. AEs not reported whether interstitial or regional MT. Researchers state: "No toxicities above grade 2 were seen" "Local pain presented in 66%, mostly at the pubic bone, but also at the hips, the sacrum and the testicles. In ten patients this pain was treatment limiting" Systemic stress, presenting only as general discomfort, was never treatment limiting	–	–
(Vargas *et al.* 2004) Yes	Breast	Short–lived erythema Mild pain Pain Severe pain (treatment limiting) 1st degree burns 3rd degree burns Oedema of breast/areola	MT (n/N patients) 9/25 (36%) 2/25 (8%) 7/25 (28%) 1/25 (4%) 2/25 (8%) 1/25 (4%) 5/25 (20%)		The third–degree burn occurred over a small area enclosing the focusing probe entry point which was within the microwave field in proximity to one of the microwave applicators	na	na

Citation Systematic recording and reporting of all AEs?	Cancer type	AE description	MT arm	No MT arm	Description / notes	Statistical comparison reported in publication	Post–hoc statistical comparison performed by reviewer
(Yerushalmi 1988) No	Prostate	–	MT	–	None of the treated patients experienced thermal damage or burns. No reactions of the rectal mucosa, such as erythema, oedema or ulceration, were observed. The combined treatment was generally well tolerated, and the addition of microwave therapy to radiotherapy made no impact on the complications caused by radiotherapy alone	nr	Not possible
Level unknown							
(Holt and Nelson 1976) No	Various		MT ± unknown	–	Safety data poorly reported (in discussion). 'Survey reveals no evidence of damage by UHF radiation to normal tissues, except aspermia discovered in 3 male cancer patients'	None	Not possible
(Holt 1979) No	1 lung cancer 1 rectal cancer		MT ± unknown		Safety data poorly reported 2 male patients died after having less than 65 seconds of UHF therapy	None	Not possible
(Holt 1975) No	Glioma	–	MT	–	Safety data poorly reported Microwave produced a sudden increase in intracranial pressure and finally death in one child with glioma in the left posterior parietal region infiltrating medially and into the occipital regions. Microwave produced headaches, pain in the eyes, and vomiting.	None	Not possible

Abbreviations: AE, adverse events; ESHO, European Society of Hyperthermic Oncology; GI, gastrointestinal; MT, microwave therapy; na, not applicable; ns, not statistically significant; NSR, not systematically reported; nr, not reported; pts, patients; QoL, quality of life; sr, systematically reported; WHO, World Health Organization

[a] Numerator calculated post hoc from percentages reported
[b] Many of the trial sites confined their reports to patients that had a minimum of one year of follow–up
[c] One trial site (Princess Margaret Hospital/ Ontario Cancer Institute, Toronto Canada) did not report the rate of telangiectasia
[d] Series of stage 1-4 patients ie., not the historically controlled group of patients included in efficacy section

In addition to adverse events related to microwave therapy per se, there is also significant morbidity linked to the invasive thermometry that is typically undertaken at the time of treatment for the measurement of intra-tumour temperature[22]. As a result, there is ongoing debate regarding the requirement for routine invasive thermometry. Invasive thermometry tends to be expensive, unpleasant and is associated with increased patient morbidity (Wust *et al.* 1998).

A study of patients with colorectal cancer reported that a number of participants developed local abscesses and infections after undergoing microwave therapy treatment. The researchers stated that the majority of these infections were caused by contamination introduced via catheters inserted into the tumours (Nishimura *et al.* 1992). This was also the case in a study of microwave therapy in patients with bladder, cervical and rectal cancer, where a number of patients developed infections after the introduction of intra-tumour thermometry catheters. Furthermore, the researchers noted that participants found the introduction of the thermometry probes to be particularly unpleasant (Van Der Zee *et al.* 2000).

In a comprehensive investigation into the use of invasive thermometry for regional microwave therapy treatment in pelvic tumours the researchers found that the local morbidity associated with invasive thermometry was significantly linked to catheter dwell times (Wust *et al.* 1998). In this study, patients that had invasive catheters removed up to 4 days after implantation had a low rate of complications. However, the majority of these patients found the procedure to be unpleasant (with minor pain occurring in 10–20% of patients). In contrast, patients that had catheters implanted for >4 days had a high level of complications. These complications included: superficial infection (27%), abscess formation (9%), exacerbation of tumour-related pain (6%), tumour cell seeding in the catheter track (3%), disruption of the catheter (3%), catheter migration outside the body (3%) and catheter obstruction (3%).

Wust *et al.*, (1998) concluded that for many patients with primary rectal, cervical, prostate, bladder and anal cancers, invasive thermometry gave no more information to improve power deposition patterns than tumour-related endoluminal temperature measurements. Therefore, invasive thermometry could be dispensed with in these patients. In the cases where invasive temperature measurement is required, the dwell times of the catheters should be minimised and consideration should be given to performing invasive thermometry only during the first few heat treatments.

Van der Zee (1992) reports an isolated case of tumour growth along the thermometry catheter trace. Seven months following treatment with concurrent thermometry, tumour growth was visible at the insertion site of one of the thermometry catheters.

Safety summary

In general, the safety of microwave therapy has been poorly investigated. More often than not, adverse events were not systematically recorded and, in general, the standard of reporting was very poor.

There have been several reports of death associated with microwave therapy, often related to inadvertent heating of blood vessels. Other adverse events associated with microwave therapy are pain, erythema, fibrosis, necrosis, ulcerations, blisters and thermal burns. Third degree burns, arterial rupture and development of fistulae have been reported on occasions.

[22] Intra-tumour temperature is not measured at the Western Australia facility

In addition to adverse events related to microwave therapy per se, there is also significant morbidity linked to the invasive thermometry required to confirm adequate intra-tumour temperature. As a result, there is ongoing debate regarding the requirement for routine invasive thermometry.

The safety concerns surrounding microwave therapy that elicits localised hyperthermia are not insignificant and should be clearly articulated to patients. Nevertheless, the nature, severity and rate of adverse events associated with microwave therapy should be considered relative to the adverse events associated with standard cancer treatments such as radiotherapy and chemotherapy. It is also necessary to consider the possible adverse events relative to the possible benefit of microwave therapy - the evidence for which remains unconvincing at present.

Microwave therapy that is of insufficient power or localisation to elicit significant hyperthermia (as practised in Western Australia) is likely to result in fewer heat-related adverse events. However, it is not possible to determine the safety of this method at present. Safety information currently provided to patients by Dr Holt appears in **Appendix 8**.

SYSTEMATIC LITERATURE REVIEW: CONCLUSIONS

1) Microwave therapy in combination with radiotherapy

At present there is minimal evidence to support the routine use of microwave therapy in addition to radiotherapy for the treatment of cancer. Whilst a considerable volume of clinical reports and related information exists, the content is generally inadequate for assessment of treatment efficacy. Furthermore the efficacy results are inconsistent, with the possible exception of head and neck cancer where, on balance, there is suggestion of a benefit.

It is not currently possible to determine whether the lack of convincing and consistent evidence is due to a) a lack of effect of microwave therapy per se; b) a failure in the practice of microwave therapy due to inability to adequately reach or heat the tumour; or c) weak research methodology, including possible selection bias. The last of these certainly applies, but may not be the only reason.

2) Microwave alone or with "glucose-blocking agents"

Evidence that relates to the use of microwave therapy with concurrent radiotherapy should *not* be extrapolated to the use of microwave therapy alone, or microwave therapy with non-cytotoxic compounds such as glucose blocking agents. There is currently *no* published evidence available to determine the benefit of such practices relative to conventional cancer treatments.

Safety concerns are not insignificant and should be clearly articulated to patients. This is particularly the case when microwave therapy is used to elicit localised heating. Nevertheless, the nature, severity and rate of adverse events associated with microwave therapy should be considered relative to the adverse events associated with standard cancer treatments such as radiotherapy and chemotherapy. It is also necessary to consider the possible adverse events relative to the possible benefit of microwave therapy - although the evidence for the latter remains unconvincing at present.

PART 2: INDIVIDUAL PATIENT DATA FROM PATIENTS, CARERS OR MEDICAL PRACTITIONERS

In excess of 10,000 patients have received microwave therapy in Australia over the past three decades (Holt 2004b; Holt 2004a). Therefore, information relating to the efficacy and safety of microwave therapy was also sought directly through submissions from Australian patients, their carers and medical practitioners.

Clinical data obtained by this method represents low level evidence that is difficult to interpret in a meaningful way for the following reasons:

- Individual patient information solicited in this way results in data for a highly selected patient group, rather than a dataset that includes all the patients who have received the treatment. Firstly, the call for submissions is more likely to reach patients who had a favourable outcome and are still in contact with the clinician and/or support group. Secondly, a submission containing clinical information is more likely to be received from patients who a) are alive at the time submissions are called, and b) who had a favourable outcome from the treatment.
- Communication between patients and doctors is not always perfect, particularly because many of the terms used to describe cancer, its treatment and prognosis are hard to convey in lay terms. A diagnosis of cancer is still viewed with fear and anticipation of an unfavourable outcome, and this has the potential to influence the information that the patient takes on board and remembers. Anecdotal patient reports are therefore subject to misinterpretation of the conversations held with the treating medical professionals and by failure to record significant treatments.
- An individual patient provides only one data point, and therefore it is difficult to consider the individual's response to a novel therapy relative to the group response to the standard therapy. For example, cancer survival data is usually quoted as median survival, both in the medical literature and by doctors to their patients at the time of their diagnoses. Whilst median survival represents a measure of the 'average' response (ie., in the case of median, that of the middle person when all are ranked), it is important to recognise that the range of survival is usually very broad indeed. Patients considered as outliers (those whose response lies a long way from the 'average' response) are also present amongst those receiving best supportive care alone and those receiving conventional treatments such as radiotherapy and cytotoxic therapy.
- It is not possible to express the number of responding patients as a percentage of all patients who have received the treatment, as the total number (denominator) is not known. Therefore, comparison of the percentage of responders with standard therapy is not valid.
- Anecdotal reports by patients and their carers typically contain little information regarding the extent ('staging') of disease at the time of diagnosis or treatment. Few patient submissions to the current review contained staging information. The stage of a patient's cancer has a profound effect upon their prognosis, and when comparing treatments it is absolutely critical that patients are matched for the stage of their disease.
- Patients diagnosed with cancer as a result of a proactive screening programme may present for treatment at an earlier stage of disease than those who are diagnosed after a symptomatic presentation. Patients diagnosed earlier than is usual may have a considerably better prognosis.

- Anecdotal reports by patients and their carers contain limited information regarding the exact nature of the treatment they had received. In the case of the current review, relevant information would have included that relating not only to the patient's microwave therapy, but also any preceding or subsequent surgery, radiotherapy or chemotherapy.
- Because anecdotal reports have not been independently verified or followed up for further information, the presumed diagnosis may be incorrect. It is not uncommon for cancers to be misclassified. Therefore, a presumed diagnosis of malignancy may occasionally be incorrect.
- Furthermore, whether or not microwave therapy was administered with concurrent radiotherapy was not always clear in the submissions made to the current review.
- Anecdotal reports by patients and their carers usually contained outcome information that is incomplete or difficult to interpret. Patients often do not have access to imaging reports or other clinical information that provides an objective measure of tumour response.
- Outcomes such as tumour response measured in normal clinical practice (as distinct from in a clinical trial) are not measured in a blinded fashion[23] and therefore are subject to potential bias.
- Many patients have received more than one type of treatment concurrently or in close succession. In these cases it is not possible to differentiate the response due to microwave therapy from that due to other treatments the patients have received.
- Without ongoing follow-up and monitoring, the patient providing a submission may not be aware of local progression of disease or the presence of distant metastases. In a clinical trial setting, these changes are more likely to be detected due to scheduled and more comprehensive follow-up that is dictated by the study protocol.

Nevertheless, the experiences of individual patients treated with microwave therapy warrant consideration. Whilst difficult to interpret in isolation, and subject to all the caveats outlined above, such information may suggest a treatment effect that then warrants further investigation using research methodology where biases are eliminated.

Seventy-four of the 293 submissions received contained individual patient data relating to the efficacy and safety of microwave therapy[24]. A summary of the submissions providing patient data is presented below[25].

[23] A blinded assessment is where the assessor is unaware of treatment, and therefore has no preconceived expectation of the result

[24] Patient and clinician submissions that did not contain outcome data relating to microwave therapy are not included here.

[25] It should be noted that there are less histories than submissions as in some cases multiple submissions described the same case.

INDIVIDUAL PATIENT DATA RECEIVED FROM MEDICAL PRACTITIONERS

Three submissions containing individual patient data were received from medical practitioners. These submissions provided clinical data relating to eight different patients.

Five of the patients had brain cancer (four glioblastoma multiforme and one grade II astrocytoma), one had breast cancer, one had bladder cancer and one had lung cancer. Minimal treatment information was provided regarding the patient with lung cancer who had died approximately five years ago. The remaining seven patients had all received microwave therapy with glucose blocking agents in Western Australia between 1995 and 2002. Several of the patients also received radiotherapy around the time of their microwave therapy.

Of the patients with brain cancer, the patient with grade II astrocytoma was known to be alive three years after treatment. The five year survival rate of this cancer with conventional surgical and radiotherapy treatment is as high as 70% (Boyages and Tiver 1986) and therefore this result is not unexpected. One of the patients with glioblastoma multiforme was known to have died 19 months after treatment, whilst the status of the other three patients was not known.

The patient with breast cancer had received surgery (lumpectomy), followed by microwave therapy and glucose blocking agents four years ago. This patient is currently alive with no indication of recurrence. It is difficult to interpret this result as no information was provided with regard to the stage of her disease at diagnosis or at the time of treatment.

The patient with bladder cancer was treated with microwave therapy and glucose blocking agents for a recurrence of bladder cancer in 1995. This treatment was unsuccessful, with bone metastases apparent in 1999. The patient was re-treated with microwave treatment and glucose blocking agents again in 1999 and 2002, and is currently alive. According to the submission, bone scans show stable disease without progression.

INDIVIDUAL PATIENT DATA RECEIVED FROM PATIENTS OR THEIR CARERS

Submissions were received from 71 patients, or carers of patients, who had received microwave treatment for a wide variety of cancers. The majority of the submissions received from patients or carers expressed support for Dr Holt or his treatment. The Review Committee could not consider the anecdotal support for Dr Holt treatment as constituting scientific evidence. **Table 38** summarises the nature of the cancers reported by patients or their carers where outcomes were available[26]. It was not possible to measure care outcome in ten submissions received from patients who had only recently received microwave treatment and who are still awaiting results.

[26] Few patients reported symptomatic outcomes, most referring to reported tumour response or survival. Only survival data is discussed here, due to the variable reporting of other outcomes. However, submissions were considered in full by the Review Committee.

Table 38 Nature of cancers reported in submissions that contained clinical outcome data

Cancer type	Number of patients	Percentage of patients	Range of treatment dates[a]
Sarcoma	6	8.5	1976–2004
Breast	14	19.7	1974–2004
Head and neck	4	5.6	1975–2003
Bladder	4	5.6	1989–2003
Colorectal	3	4.2	~1995–2004
Prostate	6	8.5	1989–2004
Lymphoma	5	7.0	1978–2003
Brain/CNS	7	9.9	1987–2004
Lung	5	7.0	1990–2004
Melanoma	1	1.4	1974
Basal cell carcinoma	1	1.4	post 1998
Stomach	3	4.2	2004
Mesothelioma	8	11.3	1991–2002
Thyroid	1	1.4	2002
Sweat gland	1	1.4	~2003
Liver (secondary)[b]	1	1.4	~1992
Type not reported	1	1.4	
Total	**71**	**100**	

[a] Date of treatment not reported in all submissions
[b] Nature of primary cancer not reported

Interpretation of the clinical information provided in the submissions from patients and carers is difficult. With only a few exceptions, little or no information was provided regarding the stage of disease at diagnosis or at the time of microwave treatment and details of concurrent treatment was limited. Furthermore, a large proportion of the patients treated prior to 1991 had received microwave therapy in conjunction with conventional radiotherapy. In these cases it is not possible to determine the effect of microwave treatment as distinct from that due to the radiotherapy treatment. Furthermore, there is generally insufficient data relating to outcomes such as tumour response, disease progression and the current status of the patient.

In all 24 cases where the date of diagnosis and the date of death were both provided[27], these were well within the range of life expectancies[28] observed for patients treated with conventional surgical, chemotherapy and radiotherapy - albeit without sufficient information to determine the severity of disease at the time of diagnosis.

Of the 42 patients who were reported in the submissions to be alive at the present time, the majority had only recently received microwave treatment (7 from 1999–2002 and 21 from 2003–2004). When considering the nature of cancer in these patients and the recency of their microwave treatment[29], it is not yet possible to assess whether the treatment has been successful in these patients

[27] Date of diagnosis or current status was not reported for five patients.
[28] Refers to range of survival, rather than median survival
[29] And the fact that in the case of three patients, the patient had received either surgery, chemotherapy or radiotherapy **subsequent** to their last bout of microwave therapy

Submissions were received from, or on behalf of 14 patients who were known to be alive at present and who had received their last microwave treatment prior to 1999. However, it was reported that seven of these patients had received microwave therapy with concurrent or subsequent surgery, chemotherapy or radiotherapy that could entirely explain the observed survival[30].

The submissions of the remaining seven patients were also considered in detail by the Review Committee. It was noted in all cases that the information contained within the submission did not provide sufficient detail to determine whether or not these patients had experienced extraordinary clinical responses, relative to how they may have responded to conventional therapies such as surgery, radiotherapy or chemotherapy. Interpretation of these data is further complicated by the fact that these patients represent a heterogenous group, both with respect to the nature of their cancer and the nature of the microwave therapy they had received. Some of these patients may have received concurrent radiotherapy whilst some had received concurrent 'glucose blocking agents'. The Review Committee also had the opportunity to meet with some of these patients at a meeting at the Western Australia clinic in Perth in January 2005. The issues for discussion and minutes of that meeting are presented in **Appendices 10** and **11**, respectively.

SUMMARY

Interpretation of the clinical information provided in the submissions from patients and carers is difficult. With only a few exceptions, little or no information was provided regarding the stage of disease at diagnosis or at the time of microwave treatment, details of concurrent treatment and tumour response. Furthermore, a large proportion of the patients treated prior to 1991 had received microwave therapy in conjunction with conventional radiotherapy. For all of these reasons, it was not possible for the Review Committee to reliably determine on the basis of the submissions whether or not these patients had experienced extraordinary clinical responses - relative to how they may have responded to conventional therapies such as surgery, radiotherapy or chemotherapy.

In order to consider more reliable individual patient data, the NHMRC has undertaken to review in detail the medical records of the following series of Dr Holt's patients:

a) a consecutive series of 100 patients who have been treated with the currently-available treatment regimen of microwave therapy and 'glucose blocking agents';

b) a consecutive series of 100 patients who were treated with the previous treatment regimen of microwave therapy with radiotherapy;

c) a selection of patients with the best clinical outcomes as identified by Dr Holt; and

d) a series of 39 cases with advanced bladder cancer who were treated with radiotherapy and microwave therapy.

Examination of these patient records is subject to ethical and privacy considerations, and to the availability of this information.

[30] One patient who reported receiving a new therapy from Dr Holt in 1975 is assumed to have received MT + RT, as he also remembers being told he had radiotherapy.

CHAPTER 5: AUDIT OF PATIENT MEDICAL RECORDS

INTRODUCTION

A recommendation from the Review Committee's interim report to the NHMRC was that consecutive patients treated with microwave cancer therapy (with and without radiation) be independently reviewed, specifically to address the second of the terms of reference *to assess the therapeutic effectiveness of microwave (UHF) cancer therapy.*

Following discussion with Dr Holt in April 2005, the Review Committee proposed to assess the medical records of the following case series:

- 30 patients with bladder cancer treated with radiation therapy (RT) alone, with combined ultra high frequency radiation (UHF) and RT or with UHF and glucose blocking agents (UHF + GBA);
- 100 consecutive patients with any cancer treated with UHF and RT or UHF + GBA and
- 10 patients identified by Dr Holt as representing the best clinical outcomes.

In consultation with Dr Holt, bladder carcinoma was chosen because it is often localised, treated with radiotherapy rather than chemotherapy or radical cystectomy and often managed with repeat cystoscopy and biopsy to assess response. Also, this tumour was nominated by Dr Holt as one tumour that is particularly sensitive to treatment with RT + UHF and, perhaps to a lesser extent, treatment with UHF + GBA. In a previously published report by Dr Holt, 31 of 31 patients (100%) treated with Stage T1 (confined to mucosa) or Stage T2 (involving bladder wall muscle) bladder cancer had complete resolution of their primary tumours. Five subsequently died from metastases but none had a local recurrence. Twenty-six (84%) remained clinically clear of disease up to two years after treatment. Stage T3 (extra-vesical spread) lesions had a control rate of 80%.[31]

Records were obtained from three locations: the Perth Radiation Oncology Centre (PROC – the private centre where Dr Holt was a partner up to 1989); Sir Charles Gairdner Hospital (SCGH) in Perth; and the Microwave Therapy Centre in Perth (Dr Holt's private rooms). Due to difficulties in locating medical records, particularly arising from the culling of the records of some deceased patients, it was necessary to amend the case series. Following discussions with Dr Holt in June 2005, the final agreed case series were:

- Group A: 34 bladder cancer patients treated with RT alone between 1973 and 1992;
- Group B: 12 bladder cancer patients treated with combined UHF and RT between 1974 and 1991;
- Group C: 18 bladder cancer patients treated with combined GBA and UHF between 1992 and 2005;
- Group D: 56 consecutive cancer patients treated with UHF and RT between 1980 and 1990;
- Group E: 49 consecutive cancer patients treated with GBA and UHF between 2001 and 2003 and
- Group F: 10 patients representing the best clinical outcomes identified by Dr Holt.

[31] "Microwaves are not hyperthermia" The Radiographer 1988; 35(4): 151-161.

These patient groups were analysed for demographics, tumour characteristics, treatment modality, treatment toxicity, symptom control, and tumour response. Given the small numbers of patients in each group and the lack of follow-up data, survival evaluation was not undertaken. To ascertain survival analysis, electronic records from the PROC, were matched to the Western Australian Cancer Register. This was possible for patients treated after 1985, when PROC introduced an electronic data base. Treatment modality was determined by linkage to billing records. Analysis was restricted to 1701 patients treated within 12 months of diagnosis with the six most common cancer types as well as for patients with invasive bladder cancer, given specific interest in this tumour type. The analysis included calculation of mean age, and 5- and 10-year survival rates by disease site and treatment modality.

METHODS

The project involved the following stages:

Formation of the team and completion of confidentiality agreements

The sub-committee included members with expertise in data and clinical trials management; medical biostatistics; radiation and medical oncology and retrospective data audit experience. Support was provided from a scientific editor and the NHMRC secretariat.

Review of ethical issues

Required patient records were stored at three different locations: PROC, Dr Holt's consulting rooms and SCGH. Approval to proceed was sought from and granted by the Managing Partner of PROC, the chair of the Ethics Committee of SCGH and by Dr Holt. Because the project was an audit, involving the use of de-identified data, the Audit sub-committee was advised that formal Ethics Committee approval was not required.

Contact with data custodians

The Chair of the Sub-Committee notified the Managing Partner of PROC of the review and assessed any potential constraints prior to formal contact by the NHMRC. Contact was also made with staff from Dr Holt's office to facilitate access to records of patients treated by UHF + GBA. The data manager and project coordinator liaised with the data custodians to ensure access to historical records, and space to undertake the data extraction.

Establishment of minimum data set

A minimum data set (MDS) was developed by the Sub-Committee, with advice from appropriate consultants (e.g. bladder cancer specialists, specialists in symptom control). The data set was established with the primary aims of assessing the effectiveness and safety of microwave cancer treatments and thus, key data items that were collected included: patient demographics, tumour characteristics, treatment characteristics, treatment toxicity, evidence of symptom control, and treatment outcome. Detailed data definitions were developed, tested and refined before a data form was designed. Wherever possible, existing published data definitions were used (see **Appendix 6**).

Data form development—pilot and final

The final paper data form was designed on the basis of the MDS (**Appendix 5**). Further to the MDS, detailed descriptive, precedent-informed guidelines for data entry were established to ensure consistency of data extraction. These Guidelines were updated and refined throughout the process of data collection to document any new precedents or address any unanticipated problems (**Appendix 6**).

Obtaining patient records

The process of identifying appropriate patient lists and accessing relevant records was different at each location.

- Groups A, B and D

  These records were obtained from PROC. Patients in these groups had treatment with RT with or without UHF. Files were kept in crates in a storage facility. The contents of each crate were sorted manually to obtain the relevant documents.

  Since the early 1990s, the records of many patients at PROC had been culled. This process involved destroying the file of any patient who had died over 10 years previously. Files were destroyed by alphabetical order of surname, from the letter A through to the beginning of letter R, after which the process had been suspended temporarily because of staffing changes and, therefore, the records of all patients with surnames beginning with the letters R to Z remained intact.

  To minimize the potential bias caused by this culling process it was decided to utilize only the files from the R–Z patients for Group D. Restricting Groups A and B to the R–Z section of the alphabet resulted in too great a reduction in sample size and, therefore, it was decided to utilize all records, regardless of surname.

- **Groups C, E and F**

  These files were obtained from Dr Holt's rooms. Eligible patients were identified from the database by Dr Holt's staff, the relevant records were photocopied and copies were provided to the audit sub-committee. A review of a previously published group of 31 bladder cancer patients treated by Dr Holt with RT and UHF in the 1970s was intended[32]. In this review Dr Holt described a 100% complete response rate, however, no record of the patients' names remained.

Pilot testing of the data collection form

The two data managers completed three cases independently. The completed forms and de-identified source documents were verified and validated by the medical reviewers and any variation in data interpretation were clarified. Some minor changes to the data form were made following this process and guidelines for data form completion were updated. The data guidelines were based on established criteria and were also precedent-based following discussion and agreement with the team.

Data extraction and recording

The two data managers examined the patient records and extracted the data using the final data form. The form had detailed notes for the verifiers and included an audit trail and various quality assurance data items. Unclear responses or equivocal data were noted in a 'comments' section for later discussion with medical reviewers.

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[32] "Microwaves are not hyperthermia" The Radiographer 1988; 35(4): 151-161.

Data verification process

Verification documents for particular data elements were copied for review by the medical reviewers. These elements were: evidence of the initial diagnosis (biopsy report), evidence of tumour response and status at the last follow-up visit. All data forms were verified by the medical reviewers to assess for omissions, errors and problems in interpretation of the data. Where there were difficulties with interpretation of data, (e.g. in the assessment of response, stage of disease, date of recurrence) the case was discussed by the data manager and audit team members. The verification process took place over four working days with meetings with the data managers in Perth and Sydney.

Data coding and keyboard entry

A coding system was developed and tested for the responses on the data form. A Microsoft Excel spreadsheet was developed and tested by the data entry staff in consultation with the Chairman of the Data Audit Sub-committee, the medical statistician and the scientific editor. The data from each collection form were keyed into a password-protected file by experienced data entry staff. All queries were referred to the data managers, and if necessary the medical experts, for resolution, and the spreadsheet was amended as necessary.

Data quality control checks

The first five case records keyed in by each of the two data entry staff were checked against the paper data forms by the scientific editor and the chairman. Subsequently, all electronic entries by each operator were checked by the other operator against the record form and when necessary (less than 10 entries for the entire data set) the electronic file was amended. Other quality checks included sorting data and identifying outliers. Completed data forms were deidentified and stored in locked cabinets and will be archived by the NHMRC.

Data analysis

Frequency distributions were prepared on all data fields where appropriate, and outlier checks were performed. Any missing or inconsistent data was then double checked with the source records and data forms. Numeric fields had minimum, maximum, median and mean calculations. The overall response rate to treatment, toxicity, symptom control, and also disease status at last follow-up or death were calculated. All tables were pre-defined by the audit sub-committee and completed by the medical biostatistician.

Western Australian Cancer Registry analysis

The number of patients obtained through the data audit was too small to make any meaningful comparison between the effect of treatment (RT versus RT + UHF versus GBA + UHF) and survival, and assessment was further complicated by the medical record culling process that had occurred. It was considered, however, that such a comparison might be possible by comparing outcomes of the total number of patients treated by Dr Holt and others at PROC by different treatment modalities with or without UHF. To ascertain survival analysis, electronic records from PROC were matched to the Western Australian Cancer Register. This was possible for patients treated from 1985, when PROC introduced an electronic data base. Treatment modality was determined by linkage to billing records. A data file containing 5789 records was supplied by PROC (see **Table 39**).

The file contained information useful for data linkage, including names, sex, birth date and address, and diagnostic information of varying levels of specificity in three separate data fields. It also contained dates and summary treatment information—RT, UHF and the use of glucose analogues.

A probabilistic record linkage computer program was used to rank potential "matches" for each of the data file records, with clerical review and decision-making assisted by on-screen review of demographics from both Cancer Registry and the data file, the data file diagnosis data, and the Cancer Registry pathology data.

The matching programme was operated by the Director of the Registry, who has medical training and ten years of experience in the development and use of the program with the Cancer Registry data. Because most of the data file cancer cases would have been recorded on the Cancer Register, matches that were incomplete were accepted on the basis of matching address and diagnosis information despite birth date differences, as is standard practice in such projects within the Registry.

Cases in which the cancer types were not the same, or persons with more than one invasive malignant Cancer Registry tumour type recorded, or any case in which it could not be judged confidently that the tumour being treated was the one on the Cancer Registry records, were excluded from the final data file. Cases of in situ neoplasm, primary skin squamous cell or basal cell carcinoma were excluded, unless the person was known to have died from the skin cancer.

The final data file of 3788 individuals included a 3-character cancer type code based on the Cancer Registry, years of diagnosis and treatment/s, 5-year age group at the time of diagnosis and at the time of each initial treatment, if applicable; cause of death if any; and survival times in days from diagnosis and from each relevant treatment date, to death or a 31 December 2004 censoring date. For the purposes of the current analyses, the data file was restricted to cases matched to Cancer Registry cases with a WA-diagnosed invasive malignancy ("cancer") (excluding primary SCC/BCC of the skin), and provided to the audit sub-committee in a de-identified format.

The number treated by RT without UHF was 3143, by UHF without RT 53, and by UHF and RT 592. 2780 (73%) of the patients were first treated within one year of diagnosis, and of these 2468 (89%) were first treated within 6 months of first diagnosis. The analysis was restricted to those first treated within 12 months of diagnosis since the remainder were a heterogeneous group that presumably would have contained a greater number of patients presenting with local recurrence or metastasis. Analysis was also restricted to the comparison of RT with RT + UHF, since there were clearly too few treated with UHF without RT.

Table 39 Determination of sample size

Reason for exclusion	RT	RT + UHF	UHF	Number excluded	Total
Total from PROC					5789
Unable to match[1]					2001
Able to be matched	3143	592	53		3788
Greater than 12 months between diagnosis and treatment	781	196	31	1008	
Treated within 12 months of diagnosis	2362	396	22		2780
Treated in 1992	282	0	0	282	
Other sites with insufficient numbers fo analysis [2]	670	105	13	788	
Tumour site one of seven main sites (breast, lung, lymphoma, prostate, head and neck, colorectal and bladder)	1410	291	9		1710
Excluded (UHF alone)[3]	0	0	9	9	
Final Sample Size	**1410**	**291**	**0**		**1701**

[1] Cancer type not the same, the patient had more than one invasive malignant tumour type.
[2] A site was only included if in total there were at least 150 cases and at least 25 of these had been treated with UHF + RT. The exception was bladder cancer which was accepted with only 148 cases included 19 UHF + RT because of the audit's particular emphasis on this site.
[3] Excluded because too few numbers
PROC – Perth Radiation Oncology Centre

The year of treatment ranged between 1985 and 1992 although the year of diagnosis ranged between 1972 and 1992. All of the cases treated in 1992 were in the RT treatment group, and to avoid bias when comparing the treatment groups these patients were excluded from the analysis.

Tumour site-specific analysis was performed for 1701 patients with the six most common cancer sites treated at PROC (breast, colo-rectal, head & neck, lung, prostate and lymphoma) as well as for patients with invasive bladder cancer, given specific interest in this tumour type. The analysis included calculation of mean age, and 5- and 10-year survival rates by disease site and treatment modality.

For four of the seven cancer sites the RT group was on average at least two years younger than the RT + UHF group, for one site the difference was in the other direction, whilst for the other two sites the average difference was less than one year. Differences in the mean ages between the treatment groups were taken account of in the analysis by fitting a proportional hazards model with allowance for age at diagnosis in five categories (<45, 45-54, 55-64, 65-74, 75+ years).

Year of diagnosis (taken as a continuous variable) was also included in the model and allowed for in the treatment comparison, as was sex for the five sites with both male and female patients. A graphical check, plotting the logarithm of cumulative hazard against the logarithm of time, was carried out to confirm that it was reasonable to assume a proportional hazards model. A formal diagnostic test of the proportional-hazards assumption was carried out by adding a time-dependent variable with value equal to the logarithm of survival time for the RT + UHF group and zero for the RT group. For none of the seven sites was this term statistically significant ($p > 0.3$ for all sites).

There was a statistically significant effect (at the 5% level) of year of diagnosis for two sites; for breast cancer there was an improvement in survival during the period 1984 to 1991, whilst for colorectal cancer those diagnosed in 1991 had a longer survival than those diagnosed earlier. The improvement probably reflected changes in stage due to earlier diagnosis and the increased use of adjuvant chemotherapy in this era. There was an effect of sex on survival for head and neck cancer. Year of diagnosis and sex were allowed for in the treatment comparison irrespective of their significance in the fitted model. Since the effect of year of diagnosis for colorectal cancer was mainly a higher survival for those diagnosed in 1991, rather than a trend over the whole period, the colorectal cancer group was re-analysed with year of diagnosis in two categories, 1984-90 and 1991.

The measure of treatment difference in the proportional hazards model is the hazard ratio. This takes the value of 1 if the two treatments do not differ after allowance for age, year of diagnosis and sex, greater than 1 if the RT + UHF have a higher mortality rate than the RT group, and less than 1 if the RT + UHF has a lower mortality rate than the RT group.

Based on the fitted proportional hazards model, survival percentages at 5 and 10 years with 95% confidence intervals were calculated standardizing to the proportions in the age categories, the mean year of diagnosis, and to the proportion of males and females.

RESULTS

Overview

In general, patient records, whilst adequate for clinical purposes, did not meet today's rigorous standards required for clinical research. Nevertheless, the records were well structured and in latter years involved typed entries for the patient history and follow-up notes. Toxicity and symptom control during treatment were documented though not systematically, and long-term toxicity and measures of quality of life were generally missing as patients were usually followed up elsewhere.

Patients' demographics (Table 40)

The median age at diagnosis ranged from 54 to 62 years, depending upon the particular patient group. Patients who received RT as part of their treatment were predominantly residents of Western Australia (58%–94%) whereas patients who received UHF + GBA were less likely to be residents of Western Australia (6%–43%). The source of referral was predominantly from a specialist for group A (bladder RT alone; 97%) and mainly by self-referral for Group E (any invasive cancer—GBA + UHF; 78%).

- **Bladder carcinoma**

  The majority of patients with invasive bladder carcinoma (groups A–C) were male, consistent with the natural history and presentation of this disease. Patients with invasive bladder carcinoma treated with RT alone were more likely to be newly diagnosed whereas patients treated by RT + UHF or UHF + GBA were more likely to have recurrent disease, making comparisons difficult. The proportions 'recurrent' or 'metastatic' for Groups A–C were 18%, 75% and 73%.

- **Any invasive carcinoma**

  For the 'Any invasive' carcinoma group, 55% was male and 45% female for Group D and 57% male and 43% female for Group E. The proportions with 'recurrent' or 'metastatic' disease in for Groups D and E were 36% and 61% respectively.

- **Best 10**

  For Group F, the majority of patients (60%) were female and 30% had recurrent or metastatic disease.

Table 40. Patients' demographics—number and proportion (%) of patients by tumour site, treatment modality and period of first treatment

Demographic	Tumour site					
	Bladder			Any invasive		Any – 10 best
	RT alone (A)*	RT + UHF (B)	UHF + GBA (C)	RT + UHF (D)	UHF + GBA (E)	UHF + GBA ± RT (F)
	1973–1992	1974–1991	1992–2005	1980–1990	2001–2003	1974–2000
	N=34	N=12	N=18	N=56	N=49	N=10
Gender						
Male	29 (85%)	9 (75%)	16 (89%)	31 (55%)	28 (57%)	4 (40%)
Female	5 (15%)	3 (25%)	2 (11%)	25 (45%)	21 (43%)	6 (60)%
State of residence						
WA	32 (94%)	7 (58%)	1 (6%)	46 (82%)	21 (43%)	6 (60%)
Other	2 (6%)	5 (42%)	17 (94%)	10 (18%)	28 (57%)	4 (40%)
Source of referral						
Specialist	33 (97%)	6 (50%)	3 (17%)	40 (71%)	0%	2 (20%)
General practitioner	0%	5 (42%)	10 (56%)	8 (14%)	11 (22%)	6 (60%)
Self	0%	0%	5 (28%)	7 (12%)	38 (78%)	1 (10%)
Unknown	1 (3%)	1 (8%)	0%	1 (2%)	0%	1 (10%)
Patient status						
New	10 (29%)	1 (8%)	3 (17%)	17 (30%)	14 (29%)	3 (30%)
New post-chemo-therapy	1 (3%)	1 (8%)	0 (0%)	1 (2%)	1 (2%)	0%
New post-operative	17 (50%)	1 (8%)	2 (11%)	18 (32%)	3 (6%)	4 (40%)
Recurrent	6 (18%)	8 (67%)	10 (56%)	7 (13%)	9 (18%)	2 (20%)
Metastatic	0 (0%)	1 (8%)	3 (17%)	13 (23%)	21 (43)%	1 (10%)
Other	0%	0%	0%	0%	1 (2%)	0%
Patient status (combined)						
Any new	28 (82%)	3 (25%)	5 (28%)	36 (64%)	18 (37%)	7 (70%)
Recurrent/metastatic	6 (18%)	9 (75%)	13 (72%)	20 (36%)	30 (61%)	3 (30%)

* Median age (and range) at first treatment, years: Bladder/RT alone, 62(39–77); Bladder/RT + UHF, 54(3–78); Bladder/UHF + GBA, 59(53–81); Any invasive/RT + UHF, 57(27–69); Any invasive/UHF + GBA, 54(11–79); Any—10 best/UHF + GBA±RT, 54(20–64).

Patients' tumour characteristics

The referrals often contained information from the urologist or other specialist about the histology but for many patients the actual pathology report was not available ranging from 30% for group F (Any–10 best) to 57% for Group D (Any invasive, RT + UHF) (see **Table 41**).

- **Bladder carcinoma**

  For patients in Group A (RT alone) treated for invasive bladder carcinoma 89% had disease localised to the bladder or invading into the adjacent tissue compared to 92% for group B (RT + UHF) and 72% for Group C (UHF + GBA).

- **Any invasive carcinoma**

  The mix of primary cancer sites differed between patients treated in Group D (Any invasive, RT + UHF) and Group E (Any invasive, UHF + GBA). For Group D, the most common site was cancer of the breast (38%) compared to carcinoma of the digestive tract (16%) for Group E. Most patients had regional or metastatic disease making treatment comparisons difficult because of the different disease extent.

- **Best 10**

  For Group F, 6 patients had carcinoma and one patient had a non-invasive DCIS of the breast. Six patients had localised disease at presentation.

Table 41. Patients' tumour characteristics—number and proportion (%) of patients by tumour site and treatment modality

Characteristic	Tumour site					
	Bladder			Any invasive		Any – 10 best
	RT alone (A)	RT + UHF (B)	UHF + GBA (C)	RT + UHF (D)	UHF + GBA (E)	UHF + GBA ± RT (F)
	N=34	N=12	N=18	N=56	N=49	N=10*
Pathology report						
None	12 (35%)	5 (42%)	8 (44)%	32 (57%)	24 (49)%	3 (30%)
Initial only	17 (50%)	0 (0%)	2 (11%)	19 (34%)	14 (29%)	4 (40%)
Subsequent only	3 (8%)	7 (58%)	3 (17%)	4 (7%)	5 (10%)	3 (30%)
Both	2 (6%)	0 (0%)	5 (28%)	1 (2%)	6 (12%)	0 (0%)
Primary site of cancer (ICD code)						
Breast				21 (38%)	6 (12%)	1 (10%)
Lung				6 (11%)	6 (12%)	1 (10%)
Prostate				6 (11%)	2 (4%)	
Digestive)				3 (5%)	8 (16%)	
Melanoma & skin cancer				3 (5%)	7 (14%)	
Bladder	34 (100%)	12 (100%)	18 (100%)			2 (20%)
Other				17 (30%)	20 (41%)	6 (60%)

Continued over page ➤

Characteristic	Tumour site					
	Bladder			Any invasive		Any – 10 best
	RT alone (A)	RT + UHF (B)	UHF + GBA (C)	RT + UHF (D)	UHF + GBA (E)	UHF + GBA ± RT (F)
	N=34	N=12	N=18	N=56	N=49	N=10*
Histology						
Carcinoma	34 (100%)	11 (92%)	17 (94%)	48 (86%)	41 (84%)	6 (60%)
Sarcoma		1 (8%)	1 (6%)	2 (4%)	2 (4%)	2 (20%)
Melanoma					4 (8%)	
Seminoma & non- seminoma				1 (2)%		
Lymphoma				3 (5%)	1 (2%)	1 (10%)
Other*						
Not known				2 (4%)	1 (2%)	1 (10%)
Histological grade						
Low	0%	2 (17%)	1 (6%)	5 (9%)	1 (2%)	0%
Intermediate	1 (3%)	2 (17%)	1 (6%)	6 (11%)	5 (10%)	0%
High	29 (85%)	5 (42%)	11 (61%)	12 (21%)	9 (18%)	3 (30%)
Not known	4 (12%)	3 (25%)	5 (28%)	33 (59%)	34 (69%)	7 (70%)
Degree of spread						
Localised	25 (74%)	8 (67%)	13 (72%)	21 (37%)	12 (24%)	6 (60%)
Invasion of adjacent tissue or organ	5 (15%)	3 (25%)	0 (0%)	5 (9%)	4 (8%)	0%
Regional nodes	2 (6%)	0 (0%)	2 (11%)	15 (27%)	7 (14%)	2 (20%)
Distant metastases	1 (3%)	1 (8%)	3 (17%)	15 (27%)	26 (53%)	2 (20%)
Not known	1 (3%)	0%	0%	0%	0%	0%
Tumour status prior to treatment start						
None or microscopic	11 (32%)	1 (8%)	2 (11%)	14 (25%)	1 (2%)	3 (30%)
Macroscopic	23 (68%)	11 (92%)	15 (83%)	40 (71%)	47 (96%)	6 (60%)
Not known	0%	0%	1 (6%)	2 (4%)	1 (2%)	1 (10%)

*1 patient with DCIS of the breast

Patients' treatment characteristics

The treatment groups differed making comparisons difficult. For example, patients treated with RT alone were less likely to have had chemotherapy (6%) compared to all other groups (27%-56%). The median dose and fractionation of RT was 60Gy (range 45-65 Gy) in 32 fractions for patients treated with curative intent by RT alone (n=32). Patients treated with RT + UHF with curative intent had a lower median dose (51Gy, range, 24-55Gy)(n=8) in a median of 35 fractions (see **Table 42**).

- **Bladder carcinoma**

  For patients with bladder cancers, treatment intent was curative for 94% of Group A (RT alone), 92% for group B (RT + UHF) and 78% for group C (UHF + GBA). In order to understand the 'tumour volume' prior to therapy, the extent of residual macroscopic disease was extracted from the records. Residual macroscopic disease was present in 56%, 33% and 22% of patients with invasive bladder carcinomas treated by RT alone (Group A), RT + UHF (Group B) or UHF + GBA (Group C) respectively.

- Any invasive carcinoma

  The treatment intent was curative in 61% for group D (RT + UHF), but only 18% for Group E (UHF + GBA). Residual macroscopic disease was present in 11% for group D and 16% for group E.

- Best 10

  For Group F the treatment intent was curative for 50% of patients and residual macroscopic disease was present in 10% at presentation. In this group 30% had received previous RT and 40% had received prior chemotherapy.

Table 42. Patients' treatment characteristics—number and proportion (%) of patients by tumour site and treatment modality

Characteristic	Tumour site					
	Bladder			Any invasive		Any – 10 best
	RT alone (A)	RT + UHF (B)	UHF + GBA (C)	RT + UHF (D)	UHF + GBA (E)	UHF + GBA ± RT (F)
	N=34	N=12	N=18	N=56	N=49	N=10
Treatment intent						
Curative	32 (94%)	11 (92%)	14 (78%)	34 (61%)	9 (18%)	5 (50%)
Non-curative	2 (6%)	1 (8%)	3 (17%)	22 (39%)	40 (82%)	4 (40%)
Unknown			1			1 (10%)
Prior surgery to index site						
No surgery	4 (12%)	3 (25%)	8 (44%)	29 (52%)	27 (55%)	4 (40%)
Resection (no residual macroscopic)	10 (29%)	5 (42%)	5 (28%)	21 (38%)	13 (27%)	4 (40%)
Resection (residual macroscopic)	19 (56%)	4 (33%)	4 (22%)	6 (11%)	8 (16%)	1 (10%)
Unknown/other	1 (3%)	0%	1 (6%)	0%	1 (2%)	1 (10%)
Radiotherapy to index site						
None	0%	0%	11 (61%)	0%	32 (65%)	7 (70%)
Study therapy only	34 (100%)	8 (67%)	0%	32 (57%)	0%	%
Other courses only	0%	0%	7 (39%)	0%	17 (35%)	2 (20%)
Study therapy & other courses	0%	4 (33%)	0%	24 (43%)	0%	1 (10%)
Chemotherapy						
No	32 (94%)	6 (50%)	8 (44%)	45 (71%)	36 (73%)	6 (60%)
Yes	2 (6%)	6 (50%)	10 (56%)	11 (29%)	13 (27%)	4 (40%)
UHF						
No	34 (100)%	0%	0%	0%	0%	0%
Yes, without GBA*	0%	10 (83%)	0%	44 (79%)	0%	0%
Yes, with GBA	0%	0%	18 (100%)	12 (21%)	49 (100%)	9 (90%)
Unknown	0%	2 (17%)	0%	0%	0%	1 (10%)
Mean total dose (and range), kW	0	128 (72 – 176)	94 (54–144)	108 (3–272)	108 (72–202)	98 (67–160)
Mean no. of fractions (and range)	0	13.9 (4–22)	14.1 (10–15)	15.4 (2–33)	15.0 (10–28)	13.6 (6–15)

*GBA, Glucose blocking agents

Treatment toxicity and disease symptom control

Table 43 shows outcomes related to treatment toxicity and disease symptom control at last follow-up. Patients treated by RT + UHF appeared to have a higher incidence of moderate or severe toxicity or toxicity requiring hospitalisation (see **Table 43**).

- **Bladder carcinoma**

  For patients in Group A (RT alone), 41% had moderate or severe toxicity compared to 75% in Group B (UHF + RT). Of patients in Group C (UHF + GBA) 37% had moderate or severe toxicity. One patient had toxicity requiring hospitalisation in the RT alone group.

  Symptom control was measured only for patients with documented symptoms at presentation. Symptom control was higher for patients who received radiotherapy—83% for RT alone, 71% for RT + UHF and 57% for UHF + GBA.

- **Any invasive carcinoma**

  For patients in Group D (RT + UHF), 64% had moderate or severe toxicity compared to 47% for patients in Group E (UHF + GBA). For group D, 4 other patients (7%) had toxicity requiring hospitalisation or termination of treatment.

  Symptom control was higher for patients who received radiotherapy—74% for RT + UHF and 50% for UHF + GBA.

- **Best 10**

  Seven patients in this group had no or mild toxicity and one patient's treatment was terminated because of toxicity. Symptom control was achieved in the three patients who had symptoms.

Table 43. Treatment toxicity and symptom control—number and proportion (%) of patients by tumour site and treatment modality

Attribute	Tumour site					
	Bladder			Any invasive		Any – 10 best
	RT alone (A)	RT + UHF (B)	UHF + GBA (C)	RT + UHF (D)	UHF + GBA (E)	UHF + GBA ± RT (F)
	N=34	N=12	N=18	N=56	N=49	N=10
Patient assessed for toxicity						
Yes	34 (100%)	12 (100%)	16 (89%)	56 (100%)	49 (100%)	10 (100%)
No	0%	0%	2 (11%)	0%	0%	0%
Number of toxicities						
0	3 (9%)	0%	5 (31%)	7 (12%)	17 (35%)	3 (30%)
1	9 (26%)	2 (17%)	5 (31%)	15 (27%)	8 (16%)	5 (50%)
2	10 (29%)	3 (25%)	4 (25%)	9 (16%)	13 (27%)	1 (10%)
3	6 (18%)	2 (17%)	0%	7 (12%)	6 (12%)	0%
4 or more	6 (18%)	5 (42%)	2 (12%)	18 (32%)	5 (10%)	1 (10%)
Maximum degree of toxicity						
None	3 (9%)	0%	5 (31%)	7 (12%)	17 (35%)	3 (30%)
Mild	16 (47%)	3 (25%)	5 (31%)	9 (16%)	9 (18%)	4 (40%)
Moderate	10 (29%)	6 (50%)	5 (31%)	35 (62%)	22 (45%)	2 (20%)

Attribute	Tumour site					
	Bladder			Any invasive		Any – 10 best
	RT alone (A)	RT + UHF (B)	UHF + GBA (C)	RT + UHF (D)	UHF + GBA (E)	UHF + GBA ± RT (F)
	N=34	N=12	N=18	N=56	N=49	N=10
Maximum degree of toxicity						
Severe	4 (12%)	3 (25%)	1 (6%)	1 (2%)	1 (2%)	0%
Requiring hospitalisation	1 (3%)	0%	0%	1 (2%)	0%	0%
Requiring termination of treatment	0%	0%	0%	3 (5%)	0%	1 (10%)
Resolution or relief of symptoms						
No. with symptoms	6 (18%)	7 (58%)	14 (78%)	34 (61%)	28 (57%)	3 (30%)
Yes	5 (83%)	5 (71%)	8 (57%)	25 (74%)	14 (50%)	3 (100%)
No	0%	1 (14%)	2 (14%)	7 (21%)	11 (39%)	0%
Not known	1 (17%)	1 (14%)	4 (29%)	2 (6%)	3 (11%)	0%

Treatment outcome

Table 44 shows tumour response and follow-up outcomes following treatment for all groups. Of note, assessment for tumour response was limited. Most patients did not re-attend for follow-up, and contact was often made by telephone call or letter. The median follow-up time in months for patients with bladder carcinoma was as follows: Bladder/RT alone, 5 months; Bladder/RT + UHF, 6 months; Bladder/UHF + GBA, 11 months; Any invasive/RT + UHF, 9 months; Any invasive/UHF + GBA, 7 months; Any—10 best/UHF + GBA±RT, 114 months. An accurate assessment of long-term response rates for all groups was therefore impossible. However, for many patients an assessment of response could be made towards the end of therapy or at their first follow-up visit or from a letter from their referring urologist.

- **Bladder carcinoma**

  For the invasive bladder cases, the complete remission (CR) rate after initial treatment was 44%, 17% and 11% for patients treated by RT alone, RT + UHF or UHF + GBA respectively. The overall response rate (complete remission (CR) and partial remission (PR)) for the invasive bladder cancers was 50%, 34% and 17% for the RT alone, RT + UHF and UHF + GBA groups respectively. Treatment after recurrence was also documented. For the bladder cases, 15% of the RT-alone group, 17% of the RT + UHF and 28% of the patients treated by UHF + GBA had subsequent surgery which was usually a total cystectomy.

  Following initial and all known subsequent treatments, the complete remission rate at last follow-up or death was 41% for patients with bladder cancer treated by RT, 17% for bladder cancer treated by RT + UHF and 11% for patients treated by UHF + GBA.

- **Any invasive carcinoma**

  For the 'Any Invasive' groups, the CR rate was 45% for Group D (RT + UHF) and 4% for Group E (UHF + GBA). The overall response rate (CR+PR) was 70% for the RT + UHF group and 10% for UHF + GBA.

  Following initial and all known subsequent treatments, the complete remission rates at last follow-up or death was 38% and 8% for RT + UHF or UHF + GBA respectively.

- Best 10

  In the best ten patient series, one patient had non-invasive ductal carcinoma in-situ (DCIS), and therefore results regarding this patient should not be considered to reflect results for treatment of patients with invasive cancer. This patient also had a salvage mastectomy showing DCIS after UHF therapy. Of the nine remaining patients, eight patients had complete remission or stable disease within three months of initial treatment. However, four subsequently had disease progression. Following study treatment, seven patients received subsequent treatment, including RT alone, UHF + RT, UHF +GBA and/or surgery. Nine patients had complete remission or stable disease at last follow up.

Table 44. Treatment outcome—number and proportion (%) of patients by tumour site and treatment modality

Outcome	Tumour site					
	Bladder			Any invasive		Any – 10 best
	RT alone (A)	RT + UHF (B)	UHF + GBA (C)	RT + UHF (D)	UHF + GBA (E)	UHF + GBA ± RT (F)
	N=34	N=12	N=18	N=56	N=49	N=10
Tumour response within 3 months of treatment						
Complete remission (CR)	15 (44%)	2 (17%)	2 (11%)	25 (45%)	2 (4%)	6 (60%)
Partial remission (PR)	2 (6%)	2 (17%)	1 (6%)	14 (25%)	3 (6%)	0%
Stable disease (SD)	4 (12%)	2 (17%)	1 (6%)	6 (11%)	24 (49%)	2 (20%)
Progressive disease (PD)	1 (3%)	3 (25%)	8 (44%)	3 (5%)	10 (20%)	0%
Not applicable/not known	12 (35%)	3 (25%)	6 (33%)	8 (14%)	10 (20%)	2 (20%)
Disease progression after CR, PR or SD						
Yes	5 (24%)	5 (83%)	3 (75%)	19 (42%)	14 (48%)	4 (50%)
No	8 (38%)	1 (17%)	1 (25%)	18 (40%	12 (41%)	4 (50%)
Not known	8 (38%)	0%	0%	8 (18%)	3 (10%)	0%
Post study treatment*						
None	9 (26)%	2 (17%)	4 (22%)	20 (36%)	14 (29%)	3 (30%)
UHF + RT	0%	1 (8%)	1 (6%)	12 (21%)	1 (2%)	1 (10%)
UHF + GBA	0%	0%	5 (28%)	12 (21%)	22 (45%)	6 (60%)
RT alone	1 (3%)	1 (8%)	1 (6%)	6 (11%)	4 (8%)	2 (20%)
Chemotherapy	1 (3%)	2 (17%)	1 (6%)	5 (9%)	0%	0%
Surgery	5 (15%)	2 (17%)	5 (28%)	6 (11%)	1 (2%)	2 (20%)
Other	0%	1 (9%)	0%	4 (7%)	6 (12%)	0%
Unknown	19 (56%)	6 (50%)	5 (28%)	10 (18%)	7 (14%)	0%
Follow-up of five years or longer†	3 (9%)	3 (25%)	8 (44%)	5 (9%)	0%	9 (90%)

Outcome	Tumour site					
	Bladder			Any invasive		Any – 10 best
	RT alone (A)	RT + UHF (B)	UHF + GBA (C)	RT + UHF (D)	UHF + GBA (E)	UHF + GBA ± RT (F)
	N=34	N=12	N=18	N=56	N=49	N=10
Disease status at last follow-up or death						
Complete remission (CR)	14 (41%)	2 (17%)	2 (11%)	21 (38%)	4 (8%)	6 (60%)
Partial remission (PR)	1 (3%)	1 (8%)	0%	7 (12%)	3 (6%)	0%
Stable disease (SD)	4 (12%)	2 (17%)	1 (6%)	4 (7%)	7 (14%)	3 (30%)
Progressive disease (PD)	5 (15%)	4 (33%)	10 (56%)	19 (34%)	28 (57%)	1 (10%)
Not known	10 (29%)	3 (25%)	5 (28%)	5 (9%)	7 (14%)	0%
Patient status at last follow-up						
Alive	33 (97%)	11 (92%)	11 (61%)	54 (96%)	28 (57%)	10 (100%)
Dead, cancer related	1 (3%)	1 (8%)	5 (28%)	2 (4%)	18 (37%)	0%
Dead, non-cancer related	0%	0%	0%	0%	1 (2%)	0%
Dead, cause unknown	0%	0%	2 (11%)	0%	0%	0%
Not known	0%	0%	0%	0%	2 (4%)	0%

* Note that the percentages add to > 100% because some have more than one treatmen

"Best ten"

Table 45 shows a summary of Dr Holt's selected best ten cases. These comprised a mixed cohort. Of note, one patient had an atypical meningioma and a further patient had ductal carcinoma in situ of the breast (non-invasive), one patient had a non-Hodgkin's lymphoma and one patient has a localised pleural mesothelioma. Six patients had received prior chemotherapy or radiotherapy and seven had undergone previous surgery. Four patients had received no prior chemotherapy or radiotherapy. Of these four patients, one had non-invasive DCIS of the breast and underwent a salvage mastectomy post UHF treatment. A second patient had an "atypical malignant meningioma" which was also treated surgically prior to UHF therapy. Of the other two patients, one had a non-small cell carcinoma of the lung who achieved a complete remission after surgery followed by adjuvant UHF + GBA. One patient had a myxoid liposarcoma of the leg is alive but has progressive disease. All patients are alive, 5-17 years after treatment.

Western Australia Cancer Registry Analysis

The numbers and mean ages are given in **Table 46** for the seven disease sites of sufficient sample to compare RT with RT +UHF. The status of all patients at 5 and 10 years is given in **Table 47**. For those who were alive at 31/12/2004 their survival was at least 13 years from diagnosis. Survival at five years, less likely to be influenced by competing causes of death than survival at 10 years, was higher for the RT group for all disease sites. For invasive bladder carcinoma, the five-year survival was 22% for RT and 15% for RT + UHF.

The estimates of the hazard ratio, with 95% confidence intervals, and levels of significance are given in **Table 48**. For four of the disease sites (breast, lung, lymphoma and prostate) there was a statistically significant difference in survival between RT and UHF +RT. In all cases the survival advantage favoured the RT group (p=0.002–0.048).

Survivals adjusted for age at diagnosis, year of diagnosis and sex, are given in **Table 49**. The directions of the differences correspond to the hazard ratio estimates in **Table 48**, with statistically significantly longer survival for RT for cancer of the breast, lung, lymphomas and prostate, and non-significantly for colorectal cancer. There were no significant survival differences for cancers of the bladder, and head and neck..

Table 45. 'Best ten' of all UHF-treated patients (nominated by Dr Holt)

Case record	Referred by	Primary site	Histology report	Histological diagnosis	Degree of spread	Surgery*
G07	GP	Lung (C34)	Yes	Carcinoma	Regional	(Pre) Resected
G09	Specialist	Connective/soft tissue (C49)	Yes	Sarcoma	Localised	(Pre) Resected
G21	GP	Brain (C70)	Yes	Atypical malignant meningioma	Localised	(Pre) Resected
G05	GP	Pleura (C38.4)	Yes	Mesothelioma	Localised	No
G27	Specialist	Bladder (C67)	Yes	Carcinoma	Localised	(Pre) Resected
G25	GP	Breast (C50)	Yes	Non-invasive DCIS	Localised	(Post) Resected
G13	Not known	Lymphoma (C85.9)	Yes	NHL	Regional	No
G01	GP	Bone (C40)	No	Sarcoma	Metastatic	Incomplete resection
G17	GP	Bladder (C67)	No	Carcinoma	Localised	No
G03	Self	Pleura (C38.4)	No	Carcinoma	Distant metastases	Yes (status post surgery NK)

Case record	Radio-therapy	Chemo-therapy	GBA	Status	Age at diagnosis	FU time (years)
G07	No	No	Yes	Alive/CR	54	10
G09	No	No	Yes	Alive/PD	38	12
G21	No	No	Yes	Alive/CR	58	7
G05	No	Yes	Yes	Alive/CR	49	13
G27	Yes	Yes	Yes	Alive/CR	54	10
G25	No	No	Yes	Alive/CR	55	7
G13	Yes	No	NK	Alive/CR	48	17
G01	No	Yes	Yes	Alive/SD	19	7
G17	Yes	No	Yes	Alive/SD	62	11
G03	No	Yes	Yes	Alive/SD	52	5

DCIS, Non-invasive ductal carcinoma in situ; **GBA**, Glucose blocking agent; **NK**, Not known (to the audit team); **NHL**, non-Hodgkin's lymphoma; **CR**, complete remission; **SD**, stable disease; **PD**, progressive disease
* Surgery prior to (Pre) or after (Post) UHF + GBA treatment

Table 46. Cancer sites in the WA Cancer Registry analysis—number of patients and mean age at diagnosis by treatment modality

Site	Number		Mean age at diagnosis, years	
	RT	RT + UHF	RT	RT + UHF
Bladder	95	13	68.6	73.7
Breast (female)	387	49	54.4	56.9
Colorectal	113	54	59.8	60.3
Head & neck	119	22	61.4	58.6
Lung	325	103	64.8	65.4
Lymphomas	150	15	50.1	56.8
Prostate	221	35	68.7	71.4

Table 47. Cancer outcome for seven cancer types in the WA Cancer Registry analysis—number and proportion (%) of deaths and survivals for 5 and 10 years after diagnosis by treatment modality

Site	Death		Survival for 5 years		Survival for 10 years	
	RT	RT + UHF	RT	RT + UHF	RT	RT + UHF
Bladder	87 (92%)	11 (85%)	21 (22%)	2 (15%)	11 (12%)	2 (15%)
Breast	182 (47%)	39 (80%)	270 (70%)	26 (53%)	233 (60%)	15 (31%)
Colorectal	96 (85%)	54 (100%)	23 (20%)	4 (7%)	18 (16%)	1 (2%)
Head & neck	101 (85%)	18 (82%)	45 (38%)	6 (27%)	29 (24%)	6 (27%)
Lung	319 (98%)	103 (100%)	14 (4%)	2 (2%)	10 (3%)	0 (0%)
Lymphomas	75 (50%)	12 (80%)	93 (62%)	5 (33%)	82 (55%)	4 (27%)
Prostate	180 (81%)	33 (94%)	125 (57%)	9 (26%)	61 (28%)	3 (9%)

Table 48. Hazard ratios for seven cancer types in the WA Cancer Registry analysis for RT + UHF compared with RT, with adjustment for age at diagnosis, year of treatment and sex

Site	Hazard ratio(95% CI)	Significance (P)
Bladder	0.78 (0.38–1.57)	0.48
Breast	1.75 (1.22–2.50)	0.002
Colorectal	1.33 (0.92–1.93)	0.12
Head & neck	0.84 (0.48–1.48)	0.55
Lung	1.34 (1.06–1.70)	0.013
Lymphomas	2.09 (1.01–4.35)	0.048
Prostate	1.81 (1.23–2.66)	0.003

Table 49. Adjusted survival at 5 and 10 years after diagnosis for seven cancer types in the WA Cancer Registry analysis, with adjustment for age at diagnosis and year of treatment and sex, as necessary

Site	Per cent (and 95%CI) surviving 5 years*		Per cent (and 95%CI) surviving 10 years*	
	RT	RT + UHF	RT	RT + UHF
Bladder	20% (13–30)	28% (12–66)	10% (5–18)	17% (5–54)
Breast	72% (68–76)	56% (46–69)	61% (56–66)	42% (31–56)
Colorectal	17% (11–25)	9% (4–19)	11% (6–18)	5% (2–13)
Head & neck	36% (28–46)	42% (27–67)	23% (16–32)	29% (15–55)
Lung	4.4% (2.7–7.2)	1.5% (0.6–3.9)	2.7% (1.5–5.1)	0.8% (0.2–2.5)
Lymphomas	72% (64–81)	50% (31–83)	62% (53–72)	37% (18–75)
Prostate	56% (50–62)	34% (23–51)	26% (21–33)	9% (4–22)

* Note that since the standardization is to the proportions in each age category, and the relationship between survival and the linear predictor in the proportional hazards analysis is non-linear, the adjusted survivals do not correspond exactly to the crude survivals in Table 47.

DISCUSSION

This study involved two parts—firstly, a detailed review of 179 case notes of patients treated with RT alone or RT + UHF or UHF + GBA for a series of patients with bladder and other cancers and, secondly, a detailed matching study with the Western Australian Central Cancer Registry which compared the survival outcome of 1701 patients with seven different cancer sites treated with RT or RT + UHF.

In consultation with Dr Holt, bladder carcinoma was chosen because it is often localised, treated with radiotherapy rather than chemotherapy or radical cystectomy and often managed with repeat cystoscopy and biopsy to assess response. Also, this tumour was nominated by Dr Holt as one tumour that he regards as being particularly sensitive to treatment with RT + UHF and, perhaps to a lesser extent, to treatment with UHF + GBA. In a previous published report by Dr Holt, 31 of 31 patients (100%) treated with Stage T1 (confined to mucosa) or Stage T2 (involving bladder wall muscle) bladder cancer had complete resolution of their primary cancers following treatment with RT and UHF. Stage T3 (extra-vesical spread) lesions had a control rate of 80%.[33]

Despite the small sub-groups, some trends were evident in this audit. Firstly, the complete remission rates were not high in any group. The study did not confirm Dr Holt's previous reports of a 100% response rate for bladder tumours (Holt, 1988). Of note, 28% of patients with bladder cancer treated by UHF + GBA underwent salvage surgery after treatment. The initial response rate (CR+PR) was 50% for Group A (RT alone), 34% for Group B (RT + UHF) and 17% for Group C (UHF + GBA). Following salvage surgery, the overall response rate (CR+PR) was higher for patients treated with RT alone (44%) compared to RT + UHF (25%) and 11% for UHF + GBA.

Long-term toxicity was not well recorded but in general toxicity during treatment was recorded with weekly reviews. Patients treated with UHF + GBA appeared to have the lowest toxicity—37% of patients with invasive bladder carcinoma treated in this way had moderate or severe toxicity. This toxicity rate was similar to patients with invasive bladder cancer treated by RT alone (41% moderate or severe) whereas patients treated

[33] "Microwaves are not hyperthermia" The Radiographer 1988: 35(4): 151-161.

with UHF + RT had the highest toxicity (75% moderate or severe), possibly consistent with a radiosensitising effect from UHF. Despite the higher toxicity, patients with invasive bladder cancer treated by RT + UHF had lower disease symptom control rates than patients treated with RT.

The ten best cases comprised a mixed cohort of often rare diagnoses and interpretation of the role of UHF was frequently problematic because numerous other therapies were employed in their management—six patients had previously received either chemotherapy or radiotherapy and seven had prior surgery. Four patients received no chemotherapy or radiotherapy. Of these four patients, one had non-invasive DCIS of the breast and underwent a salvage mastectomy post UHF treatment; a second had an "atypical malignant meningioma" which was also treated surgically prior to UHF therapy. The other two patients had a non-small cell carcinoma of the lung and a myxoid liposarcoma of the leg who achieved a complete remission after surgery followed by adjuvant UHF + GBA. All patients are alive, 5-17 years after treatment , however, it is unclear whether other treatment modalities (previous or subsequent surgery, chemotherapy, radiotherapy) may at least be partly responsible for these patients' favourable outcomes. Also favourable responses are sometimes observed (thought infrequently) in many types of human cancers without any treatment (known as "spontaneous remission")[34].

One of the strengths of the study was the meticulous audit process undertaken by experienced data management and clinical staff with expertise in clinical trial design. Prior to the implementation of data extraction, data definitions were developed using, wherever possible, existing State or National definitions. All responses were verified by an experienced medical audit team who examined key aspects of the records and pathology reports detailing disease status at presentation, initial referral letters, and pathology and x-ray reports.

The limitations of the study were difficulties in sourcing consecutive records, the short follow-up time after treatment and the lack of long-term survival data. Also the retrospective nature of the review led to problems with drawing definitive conclusions from the data, particularly regarding tumour response. The intention of the audit had been to apply standard RECIST response criteria (**Appendix 16**) to assess efficacy of treatment. However, in practice, the application of these parameters to retrospective data was problematic. In general, documentation of baseline disease status did not meet the strict standards required and post-treatment evaluations to assess response were either absent or inadequately documented for audit purposes. This highlights the difference between clinically adequate practice and the more exhaustive demands of medical research. Nevertheless, it is important to remember that UHF treatment was and still is investigational in nature and therefore requires a more rigorous and systematic degree of monitoring than standard clinical practice.

In the audit, the classification of response into the standard categories—Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD)—was, as far as possible, based on objective evidence. However, in some situations the evidence required interpretation, particularly to distinguish between PR and SD. In such cases, the determination was made following discussion between the data managers (both experienced oncology nurses) and data verifiers (both experienced oncologists). Thus, whilst an attempt was made to apply objective and standardized scientific response criteria, this was often very difficult and ultimately a 'clinically based' decision had to be sufficient.

[34] Nathanson, L. Spontaneous regression of malignant melanoma: a review of the literature on incidence, clinical features, and possible mechanisms. Natl Cancer Inst Monogr, 44: 67-76, 1976.

In view of these difficulties, a separate data matching study was performed involving residents of Western Australia diagnosed with invasive cancer and treated at the Perth Radiation Oncology Centre. The analysis focussed upon a comparison of patients treated with either radiation therapy alone (RT) or radiation therapy in combination with UHF treatment. The analysis showed a survival disadvantage for patients treated with RT + UHF for four of the seven cancer sites (breast, lung, lymphoma and prostate) and no significant difference between RT and RT + UHF for patients with head & neck cancer, colorectal cancer and bladder cancer. Although it is likely that the groups were not strictly comparable in view of stage at presentation, patients were excluded from this analysis if the date of diagnosis and date of treatment varied by more than 12 months. Of note, 89% of patients in this group had treatment within six months of diagnosis, which is an appropriate time period for recovery from surgery or the completion of initial chemotherapy.

It is unclear whether this survival disadvantage for patients with breast, lung, and prostate cancer or lymphoma treated by RT + UHF was simply due to more advanced disease or because sub-optimal doses of radiation therapy were prescribed. The median dose for patients with bladder carcinoma who received RT was 60Gy in 32 fractions, whereas for patients who received RT + UHF the median dose was 51Gy in 34 fractions, and the dose per fraction was lower.

In summary, a meticulous audit of historical patient records did not find any advantage for the addition of UHF with RT in terms of tumour response or symptomatic control. Moderate or severe toxicity was higher for patients who received UHF in addition to RT. Further, a comprehensive data matching of 1701 patients treated by RT alone or by RT + UHF found no benefit from the addition of UHF to RT. Further, in four sub-groups of patients (breast, lung, lymphoma and prostate) accounting for over 1200 patients, survival was significantly inferior for patients treated by RT + UHF compared to RT alone.

CHAPTER 6: GAPS IN CURRENT RESEARCH KNOWLEDGE

Scientific knowledge development is based upon a sequenced series of studies that demonstrate the theoretical foundation of an area of investigation (animal and human testing), the feasibility and safety of conducting an intervention study, and the testing of a hypothesis to determine if there is preliminary data to support an expensive randomised controlled trial (RCT). If the findings from these studies demonstrate scientific merit and do not appear to result in greater harm to the patient than would be the case with standard treatment, then a RCT is appropriate.

This systematic review did not provide evidence for use of UHF for the treatment of patients with cancer and raised some concerns about safety. Subsequent examination of the clinical data and data matching study did not provide evidence of improved survival and symptom control, and in fact showed poorer survival for breast cancer, lung cancer, lymphoma or prostate cancer. Therefore, there appears to be no justification for further research at present on the use of UHF for the treatment of patients with cancer.

The Review Committee has, however, identified the following gaps in research knowledge aimed at improving the communication and interpretation of information about medical treatments:

- Understanding how to improve communications to patients with cancer, and their families and carers about the risks and benefits of potential treatments;
- Understanding how patients obtain, interpret and apply medical information about health and disease to themselves and others; and
- Understand how to assess the quality and scientific validity of medical information.

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APPENDIX 1: NHMRC PROCESS REPORT

On 3 September 2004 the Minister wrote to Professor Alan Pettigrew, CEO of NHMRC, asking the NHMRC to undertake an assessment of the therapeutic effectiveness of microwave cancer therapy as practiced by Dr John Holt. The NHMRC accepted the reference from the Minister under Section 9 of the *National Health and Medical Research Council Act 1992*. At the NHMRC 154th Session on 16-17 September 2004, the Council considered the review and agreed on the terms of reference, process and composition of the Review Committee on Microwave Cancer Therapy.

The Terms of Reference of the NHMRC Review Committee on Microwave Cancer Therapy are provided in **Appendix 2**. The membership of the Review Committee is provided at **Appendix 3**.

The Review Committee, in consultation with relevant individuals and organisations, was requested to undertake an analysis of all available, relevant scientific evidence, including patient records and prepare a detailed report for the Minister.

In September 2004, the NHMRC commissioned Health Technology Analysts to:

- Undertake a systematic review of the relevant scientific evidence, addressing the scientific basis, effectiveness and safety of microwave cancer therapies including the microwave cancer therapy used in Western Australia.
- Prepare a draft report that includes an evaluation of the scientific literature for the level, quality, relevance and strength of evidence.

The studies included in the literature review are listed in the References, above, and a full list of excluded literature and the justification for exclusion is provided in **Volume 2** of this report. At its meeting in December 2004, the Review Committee finalised the report on the literature review.

In October 2004, the NHMRC called for public submissions, including personal testimonies from patients, their carers, relatives, and treating practitioners. Public notices were placed in The Weekend Australian and all major metropolitan newspapers on Saturday 2 October 2004. A notice was placed on the NHMRC website and letters sent to known stakeholders and other interested parties (see **Appendix 4** for a copy of the public notice calling for submissions and **Appendix 5** for a list of organisations and individuals who were invited by letter to make a submission). At the close of the consultation period on 26 November 2004, 252 submissions were received. A further 41 submissions were received and considered following the close of the consultation. A full list of submissions is provided at **Appendix 6**.

The initial 254 submissions were considered by the Review Committee in December 2004, with the additional 41 submissions considered in February 2005.

Dr Helen Zorbas, Dr Michael Jefford, Professor John Boyages, Mr John Drew and Mr Phil Callan from the Review Committee met with Dr John Holt, Dr Michael Holt, Mr Robert Fleay, Mr William Macham, Ms Nikki Hillman, Ms Dawn Hillman, and Ms Jenny Pickworth at the Radiowave Therapy Centre in Perth on Saturday 8 January 2005. The purpose of the meeting was to discuss the review, to clarify a number of issues raised in Dr Holt's submission, and to seek agreement to gain access to the medical records of patients treated by Dr Holt. The minutes from the meeting are provided at **Appendix 11**.

At the meeting, Dr Holt agreed to an audit of the medical records of the following series of patients.

- A consecutive series of 100 of Dr Holt's current patients from 2001-2002, using the current treatment regimen of glucose blocking agents combined with 434 MHz radiowave (microwave) therapy;
- A consecutive series of 100 of Dr Holt's past patients, treated with radiotherapy combined with 434 MHz radiowave (microwave) therapy;
- A selection of the best clinical outcomes achieved by Dr Holt; and
- A series of 39 bladder cancer patients.

It was intended that the series of patients would be measured against historical results from conventional cancer therapies. The timing of the audit would depend on appropriate Ethics Committee clearance, consideration of privacy issues and the ability to locate old medical records.

The Review Committee met in February 2005 to finalise the report to the Minister. Prior to the Report being considered by the NHMRC, Dr Holt was given an opportunity to provide comments on the report. The report was sent to Dr Holt on Monday 28 February 2005.

The Review Committee considered it was important to provide an interim report to the Minister at this time, noting that a final formal report would be provided later in 2005. The final report was to incorporate a detailed assessment of the audit of medical records of Dr Holt's patients, as requested by the Minister.

The National Health and Medical Research Council considered the draft interim report, the comments from Dr Holt, and the Review Committee response to Dr Holt's comments at its 156th Session on Wednesday 9 March 2005. The report was revised by the Review Committee based on comments from the NHMRC and submitted to the Minister for Health and Ageing in early April 2005.

The interim report was not made publicly available.

Professor Boyages and Mr Phil Callan met with Dr John Holt, Dr Michael Holt and Ms Jenny Pickworth at the Radiowave Therapy Centre in Perth on Thursday 7 April 2005 to discuss the audit of patient medical records. The minutes of the meeting are provided at **Appendix 14**. Professor Boyages and Mr Callan also met with Dr Chris Harper at the Perth Radiation Oncology Centre to discuss the audit of patient medical records.

The patient record audit and an associated data matching study commenced in May 2005 and the data collection and data analysis process was completed by early August 2005. The process for undertaking the audit is described in Chapter 5 and the data audit form and audit completion guidelines are provided at Appendix 14 and Appendix 15 respectively. During August 2005, the Patient Audit Sub-Committee finalised the report.

On 2 September 2005, the Review Committee agreed to the final report being provided to the NHMRC for consideration at its 158th Session on 8-9 September 2005.

APPENDIX 2: TERMS OF REFERENCE OF THE REVIEW COMMITTEE ON MICROWAVE CANCER THERAPY

The Terms of Reference for the 2004-2005 Review Committee on Microwave Cancer Therapy were as follows:

The NHMRC has established the Review Committee on Microwave Cancer Therapy (UHF radiowaves in the range 300 MHz to 300 GHz)[35] which will, having regard to the best available evidence and following consultation with relevant individuals and organisations:

1. Establish and describe the scientific basis of microwave therapy in the treatment of cancer;
2. Assess the effectiveness and safety of microwave cancer treatments including the use of the Tronado machine; and
3. Identify gaps in research knowledge.

[35] Hereafter referred to as 'microwave cancer therapy', 'microwave therapy' or 'MT'

APPENDIX 3: MEMBERSHIP OF REVIEW COMMITTEE ON MICROWAVE CANCER THERAPY

The Review Committee comprised:

Name	Area of expertise
Dr Helen Zorbas (Chair)	Evidence based medicine; Breast cancer
Dr Julia Nicholls	Consumer perspectives
Dr Peter Greenberg	General physician
Professor Richard Kefford	Oncology
Associate Professor John Boyages	Radiation Oncology
Professor Anthony McMichael	Epidemiology
Professor Linda Kristjanson	Nursing
Dr Michael Jefford	Medical Oncology
Dr Guy van Hazel (resigned Jan 2005)	Radiation Oncology
Dr Brendon Kearney	Public Health
Mr John Drew	Radiation oncology; Medical physics
Mr Phil Callan (Secretary)	

The Patient Audit Sub-committee comprised:

Name	Area of expertise
Associate Professor John Boyages (Chair)	Radiation Oncology
Dr Helen Zorbas	Evidence based medicine; Breast cancer
Dr Michael Jefford	Medical Oncology
Professor Geoffrey Berry	Biostatistics
Ms Ruth Dunleavey	Data collection/management
Ms Marlene Kolybaba	Data collection
Dr Greg Heard	Technical editing
Mr Phil Callan (Secretary)	

APPENDIX 4: CALL FOR PUBLIC SUBMISSIONS

Australian Government

National Health and Medical Research Council

INVITATION TO MAKE A SUBMISSION
REVIEW OF MICROWAVE CANCER THERAPY

Under Section 9 of the *National Health and Medical Research Council Act (1992)*, the Minister for Health and Ageing has asked the NHMRC to examine the therapeutic effectiveness of microwave cancer therapy in Australia, including the Tronado machine used in Western Australia. The NHMRC has established a committee to review available evidence, consult with relevant individuals and organisations, and prepare a report for the NHMRC by early December 2004. The Terms of Reference for this review are to:

1. Establish and describe the scientific basis of microwave therapy in the treatment of cancer;
2. Assess the effectiveness and safety of microwave cancer treatments including the use of the Tronado machine; and
3. Identify gaps in research knowledge.

As part of this review, you are invited to make a submission to the NHMRC about microwave cancer therapy. Ideally, submissions should address the terms of reference, be evidence-based, and any references cited should be enclosed with the submission.

Past and current patients, their carers, relatives and treating practitioners are also welcome to make a submission. Personal testimonies should include as much detail as possible about the condition treated and the outcome. Where appropriate please include the name and contact details of any medical practitioners you would be happy for us to contact who have been involved in your treatment.

How to make a submission

Please make your submission in writing or on audiotape, and include your name and address or phone number at which we can contact you.

Please post or e-mail your submissions to:

Microwave Review Project Officer
Health Advisory Section (MDP 24)
National Health and Medical Research Council
GPO Box 9848
CANBERRA ACT 2601

E-mail: microwave.review@nhmrc.gov.au

Closing Date

The closing date for submissions is 5 November 2004.

Other consultations

As well as this invitation for submissions, the NHMRC will write to individuals and organisations with a known interest in the field.

For further information, please contact the project officer at the email address above, or by telephone on (02) 6289 9105.

If you would like your submission to be treated as confidential, please indicate this clearly (for example, by marking your written submission 'CONFIDENTIAL'). Submissions may be subject to release under the *Freedom of Information Act 1982.*

APPENDIX 5: LIST OF ORGANISATIONS AND INDIVIDUALS INVITED BY LETTER TO MAKE A SUBMISSION

Name	Title	Affiliation
Dr Greg Stewart	Chief Health Officer	NSW Department of Health
Ms Helen Hopkins	Executive Director	Consumers Health Forum of Australia
Dr Jill Sewell	President	Royal Australasian College of Physicians
Ms Lyn Swinburne	Chief Executive Officer	Breast Cancer Network Australia
Mr Harvey Cuthill	Chair	The Cancer Council of Tasmania
Dr John Loy	CEO	Australian Radiation Protection and Nuclear Safety Agency
Dr Terry Slater	National Manager	TGA
Dr Steven Blamey	Chair	Medical Services Advisory Committee
Ms Michele Kosky		Health Consumers' Council WA
	Director	Sydney Cancer Centre
	Director	Sydney Cancer Foundation
	Director	Queensland Cancer Fund
	Director	National Breast Cancer Centre
	Director	Australian Cancer Network
	Director	Cancer Institute NSW
Professor Bob Baxter	Director	Kolling Institute of Medical Research
	Director	National Breast Cancer Foundation
Ms Olga Kovacev	Senior Operations Manager	Trans-Tasman Radiation Oncology Group Inc (TROG)
	Director	Clinical Oncology Society of Australia
Professor Mark Elwood	Director	National Cancer Council Initiative
	Chief Executive Officer	Alfred Hospital
	Director	The Cancer Council ACT
Professor Alan Coates AM	Chief Executive Officer	The Cancer Council Australia
Mrs Deborah Page	Chair	The Cancer Council NSW
Ms Helen Smith	Director	The Cancer Council of Northern Territory
Professor David Hill	Director	Cancer Council of Victoria
Ms Susan Fitzpatrick	Executive Officer	Cancer Council of Victoria
	Director	Victorian Cooperative Oncology Group Centre for Clinical Cancer Research
Professor Carol Gaston	Chair	Cancer Council of South Australia
	Director	The Cancer Council of Western Australia
	Director	Ashford Cancer Centre
	Director	Austin & Repatriation Medical Centre
Professor Mark Hogarth	Director	Austin Research Institute
	Director	Australian Cancer Research Foundation
Professor Garry Jennings	Director	Baker Medical Research Institute
Associate Professor Joe McKendrick	Director of Oncology	Box Hill Hospital

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APPENDIX 5: LIST OF ORGANISATIONS AND INDIVIDUALS INVITED BY LETTER TO MAKE A SUBMISSION

Name	Title	Affiliation
	Director	Centenary Institute of Cancer Medicine
Associate Professor Mark Rosenthal	CEO	Cancer Trials Australia
Professor M.A Burton	Researcher	Charles Sturt University Rural Biomedical Research Group
Professor Ursula Kees	Head of Leukaemia and Cancer Research Division	Child Health Research Institute
Professor Michelle Haber	Executive Director	Children's Cancer Institute Australia
	Director	Children's Medical Research Institute
Dr Stephen Ackland	President	Clinical Oncology Society of Australia
Professor John Shine	Executive Director	Garvan Institute of Medical Research
Professor Howard Morris	Director	Hanson Centre for Cancer Research
Professor Tony Burgess	Director	Ludwig Institute for Cancer Research
Professor Derek Hart	Director	Mater Medical Research Institiute
Mr Craig Bennett	CEO	Peter MacCallum Cancer Centre
	Director	Prince Henry's Institute of Medical
Dr Michael Good	Director	Queensland Institute of Medical Research
Professor Lester Peters	Dean of Radiation Oncology	Royal Australian and New Zealand College of Radiologists
	Director	Skin & Cancer Foundation
Professor Thomas Kay	Director	St. Vincent's Institute of Medical Research
Associate Professor Lorraine Holley		University of Technology Sydney Department of Health Sciences
Professor Judith Whitworth	Director	John Curtin School of Medical Research
Professor Nick Nicola	Division Head of Cancer and Haematology	The Walter & Eliza Hall Institute of Medical Research
Professor Peter Klinken	Director of the Laboratory for Cancer Medicine	Western Australian Institute for Medical Research
Professor Tony Cunningham	Director	The Westmead Millennium Institute
Dr David Boadle	Chief Health Officer	Department of Health and Human Services
Dr Steven Guthridge	Director, Health Gains Planning	Department of Health and Community Services
Dr Paul Dugdale	Chief Health Officer	ACT Department of Health and Community Care
Dr Gerry FitzGerald	Chief Health Officer	Queensland Health
Dr Robert Hall	Director of Public Health and Chief Health Officer	Department of Human Services
Professor Brendon Kearney	Executive Director, Clinical Systems	Department of Human Services
Dr Brian Lloyd	Deputy Director General, Acute Services	Department of Health
Dr John Horvath	Chief Medical Officer	Department of Health and Aged Care
A/Professor Peter Sainsbury	Director of Population Health	Central Sydney Area Health Service
Professor Ian Olver	Chairman	Medical Oncology Group of Australia
Dr Paul Craft	Director Medical Oncology	Canberra Hospital
Dr Alison Davis	Medical Oncology Unit	Canberra Hospital
Dr David Leong		John James Medical Centre

Name	Title	Affiliation
Assoc Professor Robin Stuart-Harris		Medical Oncology Unit The Canberra Hospital
Dr Desmond Yip	Staff Specialist	Medical Oncology Unit The Canberra Hospital
Dr Fiona Abell		Medical Oncology Newcastle Mater Misericordiae Hospital
A/Prof Ehtesham Abdi		Department of Medical Oncology Northern Rivers Area Health Services
Dr Stephen Ackland	Director	Dept of Medical Oncology Newcastle Mater Misericordiae Hospital
Dr Rod Aroney	Staff Specialist	Cancer Care Centre Gosford Hospital
Dr Philip Beale	Staff Specialist	Dept of Medical Oncology Royal Prince Alfred
Dr Stephen Begbie		
Dr Jane Beith		Medical Oncology Royal Prince Alfred Hospital
Dr David Bell		Dept of Clinical Oncology Royal North Shore Hospital
Professor Jim Bishop	Director	Sydney Cancer Service
Dr Tony Bonaventura	Senior Staff	Specialist Dept of Medical Oncology Mater Misericordiae Hospital
Dr Adam Boyce		Cancer Care Unit Lismore
Dr Frances Boyle	Staff Specialist Dept of Medical Oncology	Royal North Shore Hospital
Clinical Associate Professor Michael Boyer	Head	Dept of Medical Oncology Royal Prince Alfred Hospital
Dr Joseph Bucci	Staff Specialist	Cancer Care Centre St George Hospital
Dr Stephen Clarke	Staff Specialist	Medical Oncology Royal Prince Alfred Hospital
Dr Philip Clingan	Director	Cancer Services Illawarra Area Health Service
Professor Alan Coates	CEO	The Cancer Council Australia
Dr Catherine Crombie	Senior Staff Specialist	Med. Oncology Nepean Hospital
Dr Barry Dale		Baxter Healthcare
Dr David Dalley	Director	Medical Oncology St Vincents Hospital,
Dr Stephen Della-Fiorentina	Clinical Director	Macarthur Cancer Therapy Centre Campbelltown Hospital
Assoc Professor Michael Friedlander		Dept of Medical Oncology Prince of Wales Hospital
Dr Amanda Glasgow	Staff Specialist	Medical Oncology Illawarra Cancer Care Centre
Dr David Goldstein	Senior Staff Specialist	Dept of Medical Oncology, Institute of Oncology Prince of Wales Hospital

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APPENDIX 5: LIST OF ORGANISATIONS AND INDIVIDUALS INVITED BY LETTER TO MAKE A SUBMISSION

Name	Title	Affiliation
Assoc Professor John Grygiel		Dept of Medical Oncology St Vincents Hospital
Dr Howard Gurney		Medical Oncology Westmead Hospital
Dr Anne Hamilton	Medical Oncologist	Sydney Cancer Centre Royal Prince Alfred Hospital
Assoc Professor Paul Harnett	Director of Cancer Services	Dept. Medical Oncology Westmead & Nepean Hospitals
Conjoint Professor Peter Hersey		Oncology & Immunology Unit, Newcastle Mater Misericordiae Hospital
Dr Jane Hill	Medical Oncologist	Riverina Cancer Care Centre
Dr Elizabeth Hovey	Staff Specialist	Cancer Therapy Centre Medical Oncology Liverpool Hospital
Dr Rina Hui	Staff Specialist	Medical Oncology Westmead Hospital
Professor Richard Kefford		Department of Medicine Westmead Hospital
Dr Fred Kirsten	Director of Clinical Oncology	Oncology Unit, Bankstown - Lidcombe
Professor John Levi	Director	Dept of Clinical Oncology Royal North Shore Hospital
Dr Craig Lewis	Senior Staff Specialist	Dept of Medical Oncology Prince of Wales Hospital
Professor J. Norelle Lickiss	Senior Staff Specialist	Sydney Institute of Palliative Medicine Royal Prince Alfred Hospital
Dr Matthew Links		Cancer Care Centre St George Hospital
Dr Gavin Marx	Medical Oncologist	Sydney Haematology & Oncology Clinic
Dr Michael Millward	Head of Clinical Research	Sydney Cancer Centre Royal Prince Alfred Hospital
Dr Marianne Morgan	Consultant Medical Oncologist & Haematologist	
Dr Eugene Moylan	Director	Medical Oncology & Palliative Care Department of Medical Oncology Liverpool Hospital
Dr Jonathan Page	Medical Oncologist	Royal North Shore Hospital
Dr Nick Pavlakis	Staff Medical Oncologist	Department of Medical Oncology Royal North Shore Hospital
Professor Ronald Penny	Director Centre for Immunology	St Vincents Clinic
Dr Kiran Phadke	Director of Medical Oncology	St George Hospital
Dr Joseph Rutovitz	Medical Oncologist	Sydney Haematology & Oncology Clinics
Dr Eva Segelov	Dept of Medical Oncology	Haematology and Oncology Ambulatory Care Centre St Vincents Hospital
Professor Robert Simes	Director	NHMRC Clinical Trials Centre
Dr Jennifer Shannon	Medical Oncologist	Nepean Cancer Centre
Dr John Stewart		Dept of Medical Oncology, Newcastle Mater Hospital

Name	Title	Affiliation
Dr Craig Underhill		Border Medical Oncology
Dr Robyn Ward	Staff Specialist	Department of Medical Oncology St Vincents Hospital
Dr Helen Wheeler	Medical Oncologist	Royal North Shore Hospital
Dr Nicholas Wilcken	Staff Specialist	Medical Oncology Westmead Hospital
Dr Sudarshan Selva-Nayagam		Royal Darwin Hospital
Dr Rick Abraham	Medical Oncologist	St. Andrew's Hospital
Dr Geoffrey Beadle	Medical Oncologist	Wesley Medical Centre
Dr Ian Bunce		Wesley Medical Centre
Dr Boris Chern	District Director	Oncology Department Redcliffe Hospital
Dr Poh See Choo	Medical Oncologist	Mater Hospital
Dr Melissa Eastgate		Department of Medical Oncology Royal Brisbane Hospital
Dr Paul Eliadis	Director	Haematology & Oncology Wesley Medical Centre
Dr Terence Frost	Clinical Haematologist	
Dr Bahram Forouzesh	Director of Medical Oncology	Townsville Cancer Centre
Dr Geoffrey Hawson	Staff Oncologist	Nambour General Hospital
Dr Robert Hitchins		Pacific Private Clinic
Dr Keith Horwood	Medical Oncologist	Gold Coast Oncology Pacific Private Clinic
Dr Pretoria Irwin		Redcliffe Hospital
Dr Sybil Kellner	Senior Specialist Haematology & Oncology	Cotton Tree Specialist Centre
Dr Jason Lickliter	Medical Oncologist	Royal Brisbane Hospital
Dr Paul Mainwaring	Head of Cancer Service	Mater Adult Hospital
Dr Michelle Nottage	Medical Oncologist	Royal Brisbane Hospital
Dr John Reardon	Clinical Director	Sunshine Coast Haematology & Oncology Cliniic
Dr Catherine Shannon	Staff Specialist	Medical Oncology Mater Adult Hospital
Dr Michael Slancar		
Dr Bruce Stafford		Department of Oncology & Palliative Care Redcliffe Hospital
Associate Professor Damien Thomson	Director Oncology	Sth Brisbane Oncology Research Unit Princess Alexandra Hospital
Dr Euan Walpole	Senior Specialist	Medical Oncology Princess Alexandra Hospital
Dr Natasha Woodward		Princess Alexandra Hospital
Dr David Wyld	Director of Med. Oncology	Royal Brisbane Hospital
Dr Carolyn Bampton	Ashford Cancer Centre	
Dr James Dickson	Consultant Medical Oncologist	Flinders Medical Centre
Dr Tabitha Healey	Consultant Medical Oncologist	Calvary Cancer Centre

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APPENDIX 5: LIST OF ORGANISATIONS AND INDIVIDUALS INVITED BY LETTER TO MAKE A SUBMISSION

Name	Title	Affiliation
Dr Christos Karapetis	Consultant Medical Oncologist	Flinders Medical Centre
Dr Dorothy Keefe	Snr. Consultant	Cancer Centre Royal Adelaide Hospital
Dr Bogda Koczwara	Head Dept. of Oncology	Flinders Medical Centre
Dr Dusan Kotasek		Ashford Cancer Centre
Dr Trevor Malden		St Andrew's Medical Centre
Dr Tony Michele		Department of Medical Oncology Royal Adelaide Hospital
Professor Ian Olver	Clinical Director	RAH Cancer Centre Royal Adelaide Hospital
Dr Francis Parnis		Ashford Cancer Centre
Dr Kenneth Pittman	Head Cancer Services	The Queen Elizabeth Hospital
Dr Timothy Price	Senior Consulting Medical Oncologist	Queen Elizabeth Hospital
Dr Alistair Robertson	Senior Visiting Physician	Royal Adelaide Hospital
Dr Ram Seshadri	Clinical Head Haematology/ Oncology Unit	Flinders Medical Centre
Dr Brian Stein		Ashford Cancer Centre
Dr Anne Taylor	Staff Specialist Medical Oncology	Royal Adelaide Hospital
Dr Nicolas Wickham		Ashford Cancer Centre
Dr Tonya Wright	Medical Oncologist	Ashford Cancer Centre
Dr Ian Byard	Medical Oncologist	Holman Clinic Launceston General Hospital
Professor Ray Lowenthal	Director Haematology & Oncology Unit	Royal Hobart Hospital
Dr Robert McIntosh		Medical Oncology Department Royal Hobart Hospital
Dr Rosemary Young	Senior Lecturer	Dicipline of Medicine University of Tasmania
Dr Yoland Antill		Peter MacCallum Cancer Centre
Dr Richard Bell	Associate Professor	Andrew Love Cancer Centre The Geelong Hospital
Dr Rodney Bond		Ballarat Oncology & Haematology Services
Dr Benjamin Brady		Cabrini Hospital
Dr Peter Briggs	Director Medical Oncology	Monash Medical Centre
Dr Graeme Brodie		
Dr Ivon Burns		Dept of Oncology St Vincents Hospital
Dr Philip Campbell	Clinical Haematologist	Andrew Love Cancer Centre Geelong Hospital
Assoc Prof Jonathan Cebon		Ludwig Institute, Oncology Unit Austin & Repatriation Med Centre
Dr Mitchell Chipman		Warringal Private Hospital
Dr Jacquie Chirgwin	Medical Oncologist	Box Hill Hospital, Maronndah Hospital
Dr Kerrie Clarke	Oncologist	Border Medical Oncology

Name	Title	Affiliation
Dr Maria Coperchini ,	Director of Palliative Care Services	Palliative Care Western Health
Dr Walter Cosolo	Medical Oncologist	John Fawkner Oncology
A/Prof Ian Davis		Ludwig Institute Oncology Unit Austin & Repatriation Medical Centre
Dr Richard de Boer		Department of Medical Oncology Royal Melbourne Hospital
Dr Rowan Doig		The Epworth Centre
Dr Anthony Dowling	Medical Oncologist	St Vincents Melbourne
Dr Prudence Francis	Medical Oncology	Peter MacCallum Cancer Centre
Dr Vinod Ganju	Medical Oncologist	Dept. of Medical Oncology, Frankston Hospital
Dr Peter Gibbs		Oncology Department Royal Melbourne Hospital
Dr Geraldine Goss	Medical Oncology	
A/Prof Michael Green		Royal Melbourne Hospital
Dr Michael Jefford	Consultant Medical Oncologist	Peter McCallum Cancer Institute
Dr George Kannourakis	Medical Oncologist	
Dr Katherine Hamilton		Internal Medicine Service Ballarat Health Services
Dr Andrew Haydon	Medical Oncologist	Alfred Hospital
Dr Romayne Holmes	Medical Oncologist	Cabrini Medical Centre
Dr Michael Leyden	Oncologist/Haematologist	Maroondah Hospital
Dr Graham Lieschke		Ludwig Institute for Cancer Research
A/Prof Geoffrey Lindeman	Medical Oncologist and Head RMH	Familial Cancer Centre Royal Melbourne Hospital
Dr Lara Lipton		Family Cancer Clinic
Dr Grant McArthur	Consultant Medical Oncology	Peter McCallum Cancer Institute
Dr Sue-Anne McLachlan	Medical Oncologist	St Vincents Hospital
Dr Michael Michael	Consultant Medical Oncologist	Peter MacCallum Cancer Institute
Dr Linda Mileshkin	Medical Oncologist	Dept of Haematology/Oncology Peter MacCallum Cancer Institute
Dr Paul Mitchell	Director of Cancer Services	Austin & Repatriation Medical Centre
Dr Sujoy Mitra		Garden Consulting Rooms
Dr Kam Narayan		
Dr Phillip Parente		Box Hill Hospital, Maronndah Hospital
Dr Gary Richardson	Director	Cabrini Oncology Cabrini Hospital
Prof Danny Rischin	Div of Haematology/Medical Oncology	Peter MacCallum Cancer Institute
Assoc Professor Mark Rosenthal	Dept of Medical Oncology	
Dr John Scarlett	Med. Oncologist	Latrobe Regional Hospital

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APPENDIX 5: LIST OF ORGANISATIONS AND INDIVIDUALS INVITED BY LETTER TO MAKE A SUBMISSION

Name	Title	Affiliation
Assoc Professor Max Schwarz	Head Medical Oncology Unit	Alfred Hospital
Dr John Seymour		Peter McCallum Cancer Institute
Dr Sanjeev Sewak	Staff Specialist	Medical Oncology Andrew Love Cancer Centre
Dr Jeremy Shapiro	Medical Oncologist	Cabrini Medical Centre
Dr Raymond Snyder	Oncologist	St Vincents Hosiptal
Dr Christopher Steer	Border Medical Oncology	Murray Valley Private Hospital
Dr Gregory Stefanou	Oncologist	John Fawkner Private Hospital
Dr Andrew Strickland	Dept. Medical Oncology	Monash Medical Centre
Dr John Sullivan		Freemasons Day Procedure Centre
Dr Jeffrey Szer	Head Bone Marrow Transplant Service	Royal Melbourne Hospital
Dr Niall Tebbutt	Medical Oncologist	Cancer Services Austin & Repatriation Medical Centre
Dr Jacquelyn Thomson	Medical Oncologist	Department of Medical Oncology Frankston Hospital
Dr Karin Tiedemann	Head BMT Programme	Dept Clinical Haematology/Oncology Royal Childrens Hospital
A/Prof Guy Toner	Director	Department of Medical Oncology Peter MacCallum Cancer Institute
Dr Keith Waters		Clinical Haematology & Oncology Royal Childrens Hospital
Dr Shane White	Consultant Medical Oncologist	Austin & Repatriation Medical Centre
Dr Shirley Wong	Consultant Medical Oncologist	Western Hospital
Dr Roger Woodruff	Medical Oncologistt & Director of Palliative Care	Austin & Repatriation Medical Centre
Professor John Zalcberg	Director	Division of Haematology and Medical Oncology Peter MacCallum Cancer Institute
Dr Allan Zimet	Medical Oncologist	Oncology Specialists of Melbourne
Dr Evan Bayliss	Medical Oncologist	Dept of Medical Oncology Royal Perth Hospital
Dr Martin Buck	Medical Oncologist	Perth Oncology
Dr Michael Byrne	Head of Medical Oncology Department	Sir Charles Gairdner Hospital
Dr Arlene Chan	Consultant	Mount Hospital
Dr John Davidson	Consultant	Medical Oncology Fremantle Hospital
Dr Joanna Dewar	Consultant	Dept of Medical Oncology Sir Charles Gairdner Hospital
Dr Guy Van Hazel	Medical Oncologist	Perth Oncology

APPENDIX 6: SUBMISSIONS RECEIVED

Listed below are all the submissions received during the public consultation conduct in 2004. In many cases, it was not clear whether these submissions were made on behalf of the individual's affiliated organisation, or on behalf of the individual. For this reason, affiliations listed here do not necessarily imply that submissions have been made from the organisation.

Submissions received

Submission	Person/s making submission	Role/Affiliation/Organisation (if stated)
1	Sally Crossing	Cancer Voices NSW
2	Dr Bruce Kynaston	Radiologist
3	David Stevenson	
4	Geof Whyte	
5	Sue Fittel	
6	Cherie Bourne	
7	Frank Hurley	
8	Angela Romero	
9	Bec Gale	
10	Mrs AE Trew	
11	Rhonda Doye	
12	Garry Hodgson	
13	Alex McGavin	
14	Sancia Shawcross	
15	Professor Arthur Musk	Department of Respiratory Medicine, Sir Charles Gardiner Hospital; Clinical Professor of Medicine and Public Health, UWA
16	Harold Herft	
17	Dr Malcolm A Traill	
18	Anita Farrell	
19	Phillip Crosbie	
20	Mrs Loren Noble	
21	Dr Igor Tabrizian	Nutrition Review Service, WA
22	Mrs Ann McDermid	
23	Brian Bartlett	
24	Jillian Brenand-Coombs	
25	Synon and Deborah Toone	
26	Anne Hanson	
27	Mrs Valerie Stokes	
28	Phillip Schmall	The Cancer Council of WA
29	Dr David Nelson	General Practitioner, WA
30	Cleve McMillan	
31	Rae Harrison	
32	Dr Ian Haines	Medical Oncologist, Melbourne Oncology Group
33	Dr Alan Coates AM	The Cancer Council Australia
34	Lee Rieniets	Rener Health Centre (The Natural Path)

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Submission	Person/s making submission	Role/Affiliation/Organisation (if stated)
35	Jacqui Woodcock	
36	William Pierce	
37	Mrs M Jenkins	
38	Susan Case	
39	Michael Malaxos	
40	Patrick Fitzgerald	
41	Sue McKenna	
42	Meredith Hardy	
43	Dr Michael Tait	General Practitioner, Alternative Medicine Practitioner
44	Wafa Hijazeen	
45	Marie Bond	
46	Alexandra Medalha	
47	Susanna Piper	
48	Sue Turvey	
49	Mrs BL Thomas	
50	Mrs N Yuzguc	
51	Angela Ormonde	
52	Robert Fleay	Physicist
53	Mr John Stipanicev	
54	Andres Costa	
55	Alistair Drew	
56	David Coulston	
57	Janusz Rygielski	
58	Michael and Jill Minchin	
59	Peter Zeug	
60	Rodney Watters	
61	Mrs Moody	
62	Susan Edwards	
63	Mrs Christina E Bosdyk	
64	Corine Richards	
65	Rosemary Trudeau	
66	Jackie Creed	
67	Maxwell Ralphs	
68	Betty Andrews	
69	Gerard Vaughan	
70	Ian Chisholm	
71	Bernice Garratt	
72	Kery Love	
73	Louisa Raso	
74	Angela Kalatzakos	
75	Lenore Miller	
76	Karen Barnes	
77	Anon	

Submission	Person/s making submission	Role/Affiliation/Organisation (if stated)
78	Robin Hughes	
79	Maree Healey	
80	Mare Healey	
81	John Wickham	
82	Peter Reedy	
83	Michael King	
84	Ann Hamilton	
85	Dr GN Brodie	Individual doctor
86	Jennifer Robertson	
87	Rosalie O'Neill	
88	Joseph Borg	
89	Anon	
90	Hamish Wight	
91	Dr Gerard Goldman	
92	Cristina Saliadarre	
93	Dr Catherine Buccilli	General Practitioner, Victoria
94	Debra Chant	
95	Dr Jeff Dunn	Queensland Cancer Fund
96	Maree Healey	
97	Paul Healey	
98	Susan Vacic	
99	Frances Prosamo	
100	Ray Martin	Channel Nine
101	Chris Nazareth	
102	Gail Chancellor	
103	Fiona Pacey for Lester Peters	Dean, The Royal Australian and New Zealand College of Radiologists
104	Heather Sayer	
105	Cathy Tescher	
106	Lynne Miller	
107	John Steinke	
108	Dr Malcolm Traill	Pathologist
109	Peter and Judy Todd	
110	Jan Clarke	
111	Priscilla Shaw	
112	Claude John Riordon	
113	Janelle Titmarsh	
114	Maree McDonald-Pritchard	
115	Pam Quatermass	
116	John Gosper	
117	Sel Rowlings	
118	Jeanette Fugill	
119	Roy Weddell	
120	Mrs G Hodges	

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Submission	Person/s making submission	Role/Affiliation/Organisation (if stated)
121	Dr John Holt	Radiowave Therapy Centre, Perth, WA
122	Elvina Johnson	Dr Holt Support Group
123	Vicki Albrecht	
124	Ron Barnes	
125	Gilliam Berger	
126	Irene Bickford	
127	Genevieve J Bond	
128	Marie Brereton	
129	Elvina Brereton	
130	Robert Broertjes	
131	Peter Burr	
132	Mary Butler	
133	Brian Camp	
134	William Clissold	
135	Elsie Colgan	
136	Ken Collins	
137	Shirley Connor	
138	Ron Cooper	
139	Lesley Coppin	
140	Mrs G Coulter	
141	Jessie Dale	
142	June Darling	
143	Lynda Chamberlain	
144	Carol Darrington	
145	Margaret Davies	
146	Maggie Ellis	
147	Eric Farlow	
148	Daniela Fartais	
149	Mrs M Grady	
150	Neil Graham	
151	Rodney Grapes	
152	Karen Gravener	
153	Stephen Hamilton	
154	Peter Hickson	
155	Wayne Hillman	
156	Derek and Sandra Hughes	
157	Natalie Hunter	
158	Valmai Jolly	
159	Bernadette Johnson	
160	Rita Kennedy	
161	Paul Kleijn	
162	Herman Lamers	
163	Donna Mason	

Submission	Person/s making submission	Role/Affiliation/Organisation (if stated)
164	Robert Matheson	
165	Elwyn Meddings	
166	Annette Meldrum	
167	Dr Douglas R Mendoza	
168	Leonard Miller	
169	Fernanda Moffat	
170	Raymond McCarthy	
171	John McNabb	
172	Ms Dana Ng	
173	Olive C Ng	
174	Susan O'Loghlin	
175	Steven Philp	
176	Edward Pikor	
177	Mr TM Reeve	
178	Noreen Robinson	
179	Terry Samwell	
180	Mrs Joan Seymour	
181	John Schepsi	
182	Johanna Schreiter	
183	Maria Smereka	
184	Richard Smith	
185	Robert Taylor	
186	William Taylor	
187	Fatima Teixeira	
188	Penny Treadgold	
189	Dr Rachel Vahala	
190	Emma Van Herk	
191	Debbie Wilson	
192	Bruno Zappavigna	
193	Giovanni Zappia	
194	Mrs ME Rondello	
195	John Carr	
196	Dr Nicholas Chantler	Scientist
197	Dr John Andersen	Chemical Engineer
198	Gail Milner	Clinical and Aged Care Directorate, Department of Health, WA
199	Dr Hugh Tinsley, Dr Victor Thorne	National Satellite Services, Dublin
200	Dr Michael Holt	Orthopaedic surgeon
201	Dr Peter Daale	Cancer Support Association of WA
202	Professor James F Bishop	Cancer Institute of NSW
203	Christine Evans	
204	Justin Doneley	
205	Craig Bennett	Peter MacCallum Cancer Centre
206	Jenny Gillian	

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Submission	Person/s making submission	Role/Affiliation/Organisation (if stated)
207	David Hill	The Cancer Council Victoria
208	Janet Dobson	
209	Shelley	
210	Daphne Gosthoy	
211	Mr Farmer	
212	Catherine Howse	
213	JM Patterson	
214	Annette Arnold	
215	Valerie Becker	
216	Michael Abbott	
217	Janine Dayrit	
218	Susan Reynolds	
219	Genevieve Carrol	
220	Lyn Duproi	
221	Pam Sanders	
222	Loretta Polinelli	
223	Helen Minto	
224	Terry Slater	Therapeutic Goods Administration
225	Menaka Drew	
226	Christine Pacelli	
227	Suzana and Tiane Klaric	
228	Mr CT Forster	
229	Rose Strongylos	
230	Karina Edwards	
231	Mary Corley	
232	Tony Nobilo	
233	Ton Petrovski	
234	Margaret Keane	
235	Adam Kapps	
236	Dyson Devine	
237	Dr Eva Segelov, Dr David Dalley	Oncologists, St Vincent's Hospital, Sydney
238	Carroll Church	
239	Anon	
240	Cathy Trapani	
241	Matthew Hourn	
242	Bianka Sequenzia	
243	Paul Whitmore	
244	Maree Stevenson	
245	Dr Peter Main	Individual general practitioner
246	Anastasia Grammatikas	
247	Craig Glenroy Patterson	The Royal Australasian College of Physicians
248	Frank Sartor	NSW Government Minister for Science and Medical Research
249	Melissa Edwards	
250	Mrs Pamela Barnes	

Submission	Person/s making submission	Role/Affiliation/Organisation (if stated)
251	Doug Baker	
252	Glen	
253	Mary Meikle	
254	Noreen Dowd	Metropolitan Health and Aged Care Services, Victorian Government
255	Loretta Gray	
256	Peter Daniel	
257	Francesco Centofanti	
258	Vicki Erickson	
259	Luis Serrano	
260	Arthur W Thomson	
261	John K Gibling	
262	Eve Laing	
263	Paige Casonato	
264	Peter McCook	
265	Dr Michael Rice	Beaudesert Medical Centre
266	Judi Gibbs	HealthCare Division, WA Health
267	Noel Crymble	
268	Dianne Glennon	
269	Varee Smith	
270	John McPherson	
271	Sally Bonython	
272	Analia Siele	
273	Steven Wong	
274	Susan Meakins	
275	Ron Hills	
276	Jane Ellis	
277	Dianne Glennon	
278	Marie Bond	
279	Dr John Manton	
280	Alexia Mandadakis	
281	Andrew Fabrizio	
282	Michael Connor	
283	Pauline and Roy	
284	Jan Finkle	
285	Karyn Martin	
286	Neil Short	
287	Vince Bugge	
288	Kerry Dunbabin	Cancer Screening and Control Services, TAS
289	Alan Burgess	
290	Deanna Flemming	
291	Bob Luck	
292	Dr Peter Barratt	Department of Health, WA
293	Elizabeth Hristov	

APPENDIX 7: INVESTIGATORS OF MICROWAVE THERAPY INTERNATIONALLY

Following is a list of individuals or groups believed to have investigated or used microwave cancer therapy internationally. It is not intended to be a complete list.

List of microwave therapy investigators

Investigator	Location	Type	Equipment
John Holt	Australia (Perth)		434 MHz
Malcom Traill	Australia (Kew)		434 MHz and others
Michael Tait	Australia (Gold Coast)		
David Spall	Australia (Brisbane)		
Claude Bertrand	Belgium		
J Hunt	Toronto, Canada		
Li Rui-Ying	China	Superficial	915, 2450 MHz
Zhu Si-wei	China		
Da-Zhong Gu	China		
Overgaard	Denmark	Superficial	
Francois-Noel Gilly	France		
Jack Porcheron	France		
Dominique Elias	France		
Christian Letoublon	France		
Annie C Sayag	France		
E Dieter Hager	Germany		
Friedrich Douwes	Germany		
Friedrich Migeod	Germany		
B B Singh	India		
Bahram Goliaei	Iran		
Giuseppe Pigliucci	Italy		
Giorgio Arcangeli	Latina, Italy	Superficial	500 MHz
Paolo Pontiggia	Italy	Superficial/ regional/ whole body	RF Infra-red
Michele DeSimone	Italy		
Bruno Mondovi	Italy		
P Gabriele; V Tseroni	Turin, Italy (NB. late 1980s)	Superficial	434, 915 MHz
R Valdagni	Trento, Italy	Superficial	280-300 MHz
Shigeru Fujimoto	Japan	Superficial/ regional	Thermotron RF-8
S Egawa; T Inoue	Japan (NB. late 1980s)	Superficial	8, 13, 915, 2450 MHz
K Hayashi; H Komoriyama	Japan	Superficial	BSD 1000, TCA 434
S Masunaga; M Abe	Kyoto, Japan	Superficial	430 MHz
Y Ohizumi; T Akiba	Japan	Superficial	13 MHz, 2450 MHz
S Yamada	Japan	Superficial	

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Investigator	Location	Type	Equipment
de Graaf-Struckowska; Suresh Senan	Netherlands	Superficial	433 MHz
Gonzalez Gonzalez	Aarhus, Netherlands	Superficial	
J van der Zee	Rotterdam	Superficial	70-90 MHz
O Dahl	Norway	Superficial	
Jacek-Kaczmarkowski	Poland		
Sergej V Kosin	Russia		
Adolph A Wainson	Russia		
Samuel Yarmonenko	Russia	Superficial Deep Regional	YACHTA 3-915; YACHTA 4-433; YACHTA 5-40;
C Lindholm	Sweden	Superficial	915, 2450 MHz
Markus Notter	Switzerland	Superficial Regional	Siretherm Siemens BSD 2000
Oliver Huber	Switzerland		
Ashmet Cakmuk	Turkey		
Sukru Erkal	Turkey		
Meltem Serin	Turkey		
Sergej Osinski	Ukraine	Superficial	460 MHz
Igor Mikhalkin	Ukraine		
P Dunlop; S Field	UK (NB. 1980s)	Superficial	not specified
G Howard	UK (NB. late 1980s)	Superficial	650 MHz
C Vernon	UK	Superficial	434 MHz
Kenneth Alonso	United States (Atlanta, GA)		
Madhava Baikadi	United States (Scranton, PA)		
Haim I Bicher	United States (Los Angeles, CA)	Deep Superficial Superficial/ deep	Sonotherm 1000 (Labthermics Technology); Celsion System 100 (Cheung Labs); BSD 1000
Ivan Brezovich	United States (Birmingham, AL)		
Doug Coil	United States (Houston, TX)		
James C Conley	United States (South Portland, ME)		
Gregory W Cotter	United States (Mobile, AL)		
James Currier	United States (Anderson, IN)		
Victor Diamond	United States (Los Angeles, CA)		
Duke University Cancer Centre	United States (Durham, NC)		
Norman C Estes	United States (Kansas City, KS)		
Jeffrey Feinstein	United States (Hinsdale, IL)		
Reinhard A Gahbauer	United States (Columbus, OH)		
Mohamed Gaber	United States (San Francisco, CA)		
Irene M Gordon	United States (Lafayette, IN)		

Investigator	Location	Type	Equipment
Pierre J Greefe	United States (Tulsa, OK)		
David A Hornback	United States (South Bend, IN)	Superficial	CliniTherm
Ned B Hornback	United States (South Indianapolis, IN)	Superficial	Cheung Lab
Young D Kim	United States (Wadsworth, IL)		
Eric LeVeen	United States (Charleston, SC)		
K Luk	United States (CA)	Superficial	915, 2450 MHz
Roy Page	United States (Memphis, TN)	Superficial/ regional	Erbe-tag-med
C Perez	United States (St Louis, MI)	Superficial	915 MHz
Ian Robbins	United States (Madison, WI)	Whole body	Aquatherm Radian Heat Device
David P Schreiber	United States (Denver, CO)		
R Scott	United States (Buffalo, NY) (NB. 1980s)	Superficial	434, 915, 2450 MHz
Director. Centre for Neuro-oncology. West Penn Hospital	United States (Pittsburgh, PA)		
Gerald Sokol	United States (Hudson, FL)		
Arvil D Stephens	United States (Washington, DC)		
Jeanne Tumanjan	United States (Dana Point, CA)		
Raymond U	United States (Raleigh, NC)	External/ Interstitial Capacitive deep-seated hyperthermia	CliniTherm Mark VI; Thermotron RF-8
Ajmel Puthawala	United States (Long Beach, CA)	Interstitial/ superficial	BSD
Richard Steeves	United States (Madison, WI)	Superficial	BSD-1000
Roger Vertrees	United States (Galveston, TX)		
Robert Bradford	United States (Chula Vista, CA)		
William A Vivian	United States (La Jolla, CA)		
Washington University	United States (St Louis, MO)		

APPENDIX 8: PATIENT INFORMATION REGARDING TREATMENT AT WESTERN AUSTRALIA CLINIC

The following information is provided by Dr Holt for patients intending to visit the Western Australia clinic. The content does not necessarily reflect current scientific knowledge or the opinion of the Review Committee.

Source: http://www.drholtsupport.com/simple.asp. Accessed 22 February 2005

The Treatment Method

Intravenous injection of glucose blocking agents immediately before UHF are essential and have to be given quickly through a vein or an intravenous line. The blocking agents consist of cystine and oxidised glutathione and other similar forms of amino acids in their fully oxidised state. They carry a lot of oxygen with them, they look like glucose to the cancer cell and are therefore rapidly absorbed by them immediately the UHF radiation commences. The glucose is "burnt" by the blocking agent's oxygen and the cancer cell dies.

Large arm veins are the most suitable site for injection. The smaller veins of the hand are unsuitable. The injection is slightly irritant and is approximately 50 ml of fluid. Before treatment starts a PICC line (Per Intravenous Cutaneous Catheter) can be inserted if the patient has poor veins. The line is inserted by a radiologist using ultrasound placement into a deep vein in the upper arm and can only be done in Perth if the patient has private health insurance. At the end of treatment the PICC line can be easily removed.

Results have come from 15 treatments over three weeks, Monday to Friday - 15 working days (remember WA's public holidays!).

The infusion of the glucose blocking agent takes approximately fifteen minutes and is immediately followed by 20 to 25 minutes of UHF therapy using the radiowave machine to part or all of the body.

Complications of Treatment

434 MHz UHF creates resonance (it shakes cancer cells like a bell) and fluorescence (the cancer re-radiates different frequencies) and the energy does create some heat in the normal cells similar to sitting in front of a large electric fire. It must be emphasised that **this is not heat treatment and MUST NOT be called hyperthermia** where the body is deliberately raised to 41.8°C by non electrical methods. After treatment half an hour's rest on a relaxing chair/bed under a fan allows the patient to drive their car away if they wish.

Side Effects

Every patient has their haematology, biochemistry and proof of cancer levels etc estimated before and after treatment. The only **contraindication to treatment is a rare disease called thalassaemia** because the red blood corpuscles in this disease (there are a few lesser variants which also may cause trouble) are readily damaged by mild warming (body temperature never exceeds 39.5°C, upper limit of human tolerance is 41.8°C) and the patients become anaemic. This may need fairly urgent transfusion if it occurs.

Approximately 1% or 2% of patients slight symptoms of the brain being starved of glucose may occur. The cancer obtains its glucose supply using the amino acid cysteine but the brain extracts its glucose using the amino acid methionine. This rare complication can be completely avoided by eating 100 to 200 grams of cooked red meat five times a week. **If you are not willing to eat red meat during treatment there is 1 in 50 chance that you will experience these side effects and require admission to hospital. Patients must understand that if they do not eat red meat that treatment is at their own risk and that they must bear all consequences thereof.**

No patient will be treated who is taking any antioxidant other than that which is contained in a normal, simple diet. For example **large doses of Vitamin A, Vitamin C, Vitamin E, selenium and multiple other so-called anti-cancer antioxidants may result in ineffective treatment** simply because these substances destroy the glucose blocking agents before they reach the cancer cell.

General Features for Successful Treatment

A: The smaller the individual lesions the better the result because as cancer masses become bigger so the blood supply to the centre decreases and the drug cannot penetrate there.

Continued over page ➤

B: The total mass of cancer is important. Any estimated load in excess of 100 grams will probably require more than one session of treatment.

The Practical Regime

I treat every patient whom I consider have a chance of response with 15 days of treatment. Then wait six to eight weeks and reassess the situation. If there is significant improvement - decrease by 10-20% of the cancer mass - then retreatment should be carried out because cure is possible in such patients. The maximum number of treatment courses given was seven in a patient with mesothelioma treated twelve years ago who now is alive and well without evidence of the disease.

Specific Contraindications to Treatment

1. **A major contraindication to UHF therapy is having had any form of chemotherapy** (also called cytotoxics, or cytotoxic treatment). These drugs are non-specific cell poisons designed to act against the genetic material in the cell nucleus. They do not act specifically on the cause of cancer, which is damage in the cytoplasm or extra-nuclear part of the cell. Normal cells are designed and controlled perfection using genetic information. Cancer is caused by irreparable damage to the system which interprets our genetic "blueprint". It is pointless to destroy genes when their instructions are ignored by a defective system.

   Some cytotoxic drugs may make normal cells more conductive to electricity so that there is little electrical difference between cancer cells and normal cells and then UHF no longer only acts on cancer cells.
2. **Collections of fluid in the chest cavities, heart cavity or abdominal cavity must be drained and the cavities dry if satisfactory results are to be obtained in the underlying cancer.** As examples - cancer of the lung and breast can cause outpourings of fluid in the left or right pleural space (cavity surrounding the lung) and more rarely in the pericardial (heart) space. UHF radiation will not penetrate collections of fluid. They may become hot enough to increase the damage in the cavities.

   Fluid in the peritoneal cavity is called ascites. This is a common accompaniment of ovarian cancer and partial blockage to the lymphatics draining the abdominal cavity and occasionally due to obstruction in the liver from secondary cancer in that organ. Ascites may also get worse after UHF treatment and may prevent the underlying cancer receiving any effective UHF dosage. Ascites, pleural and/or pericardial collections of fluid are best treated by aspiration and installation of appropriate substances so that the surfaces of the space are inflamed and stick together thus obliterating the space. **The effusion must have been controlled completely by such measures before radiowave therapy is possible.**

   If patients arrive with collections of fluid and this minor operation has to be performed before or during treatment they will be referred for drainage by another doctor. Patients without private hospital insurance cover with this complication will be referred to a public hospital, if so requested.
3. **Smoking is absolutely contraindicated to the treatment. Treatment must not be commenced until at least several weeks after smoking has ceased.** The carbon monoxide in cigarette smoke may inactivate the oxygenating effect of the glucose blocking agent.

Further Information

Treatment is given only as out-patient attendance. Stretcher patients do not fit within the machine and wheel chair bound patients can only be treated if they are fairly mobile. Should any problem arise and a public hospital admission is essential, not only is Dr Holt unable to supervise you in such an institution but UHF therapy cannot be given whilst an in-patient in one.

All hospitals in WA require every interstate patient admitted to have a certificate from their local pathologist stating that they are free from MRSA (Methicillin Resistant Staphylococcus Aureus infection). To minimise cross infection in our own rooms the results of the MRSA test must be known to us before arriving for a course of therapy.

The treatment centre is in West Perth, an inner suburb with free bus travel to the city. Short term rental flats are available within a one to five kilometre radius. Your travel agent can arrange an hotel to start and then you can find your exact needs at leisure.

Costs

A three week course of treatment is a total of $6550 with a Medicare rebate (at 85% of the scheduled fee) of $2206.50 (as at 1 November 2003). The difference of $4343.50 must be paid during the first week of treatment.

Under the new Safety Net Medicare will now meet 80% of the out-of-pocket costs for medical services. Medicare may therefore give you a further rebate after the account for treatment has been processed by them.

Always make a claim from your State against your travel costs to WA (Patients' Assisted Travel Scheme/Patient Transport Assistance Scheme). These forms are available from your local hospital.

Please note that we do not have the facilities to accept eftpos or credit card transactions. Payment can be made via cash or cheque.

If you do not have a referral from your GP or a specialist Medicare will not pay their portion of your account. Please ensure you bring one with you.

J A G Holt
M.B., Ch.B., F.R.C.S., F.R.C.R., F.R.A.C.R, D.M.R.T., D.R.C.O.G.

CHECKLIST

In order for Dr Holt to accurately assess you on the day of your consultation, we require the following information:

1. A brief **summary** (not more than two pages) detailing your diagnosis and any secondaries you have, listing all treatments and surgery that you have had to date. Please include:
   - The dates of courses of chemotherapy undertaken including the drugs given.
   - The dates of courses of radiotherapy given and to which areas of the body.
   - The names of surgical procedures that have been undertaken, and the dates performed.
   - Any hormones taken including the daily dose.
   - Any antibiotics being taken.
   - If mistletoe extract or laetrile or similar substances are being taken.
   - If you are a smoker or non-smoker.
2. A **copy** of the biopsy report from the original diagnosis.
3. **Copies** of any surgical reports.
4. **Copies** of any recent blood tests **(These tests must be less than 4 weeks old)**.
5. **Copies** of any recent cancer antigen blood tests **(These tests must be less than 4 weeks old).**
6. X-rays, MRIs, CT scans, Bone scans, PET scans or any other scans you have had in the past four weeks. Bring both the scans and the report.
7. It is useful if you can also bring the scan/x-ray immediately prior to this most recent one for comparison.
8. A **referral** from your GP. Please note that if you do not have a referral Medical will not pay their portion of your account.

Please bring this information on the day of your consultation to:

2nd Floor, 31 Outram Street
WEST PERTH WA 6005

Source: Dr John Holt – provided to the Review Committee during meeting with Dr Holt on 8 January 2005.

APPENDIX 9: LITERATURE REVIEW - DATA EXTRACTION TABLES

Cervical cancer

Hornback, 1986					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-3 Retrospective chart review. Historical control. N=79 (46 subjects excluded - received non comparable radiotherapy [cobalt])	Women with primary Stage IIIB squamous cell carcinoma of the cervix, treated between November 1964 and January 1979. Women were excluded if they did not complete planned course of radiotherapy for reasons other than failure to tolerate or if seen in consultation only.	Hyperthermia + radiotherapy (external and internal) Hyperthermia *Frequency:* 434 MHz *Machine:* Not stated *Regimen:* 40-45 mins of heat beginning 10-15 min after external radiation *Temperature measurement:* Yes but problems early on so new method used later. Temperature between 39.5 and 41.5°C recorded within 20 min. Radiotherapy See Comparator	Radiotherapy alone (external and internal) From November 1964-June 1975 patients received cobalt radiotherapy. These patients (n=46) excluded. External radiation *Total dose:* 4000 cGy over 4.5-5 weeks *Fractions:* 150-200 cGy per day Intracavitary radiation Cervical and vaginal cesium insertions. 2 doses of 2000 rads delivered 2 weeks apart.	Response rate Acute and chronic complications Median survival Absolute survival	A. No. Historical control used. Intervention group treated from January 1977-January 1979. Controls treated between July 1975 and December 1976. B. No adjustments have been made for confounding. C. Probably. Retrospective chart review so none lost to follow-up. D. No. Subjective outcomes assessed by clinicians aware of treatment assignment. Quality rating: Poor.
Results summary:					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Head and neck cancer

Valdagni, 1994; Valdagni, 1988					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level II RCT Italy (1 site) N=44 lymph nodes (41 patients)	Patients with one of two diagnoses: (a) Histologically or cytologically proven nodal involvement of squamous cell carcinoma from a previous or concomitant T1-T3 head and neck primary or from an unknown primary (b) Fixed and inoperable n3 (TNM-UICC) cervical lymph nodes with maximum superficial diameter and maximum depth of 7 cm and 5 cm respectively. Karnofsky performance scale ≥ 60 and life expectancy ≥ 3 months. No prior irradiation of neck regions and/or previous chemotherapy.	Hyperthermia + radiotherapy Hyperthermia *Frequency:* 280-300 MHz *Machine:* Not stated but MA-150 applicator used (BSD Medical Corporation) *Regimen:* Twice-weekly, within 20-25 min of radiotherapy. *Temperature measurement:* Yes using Bowman thermal probes in a minimum of 5 intra and peri-tumoural locations and at least 3 skin sites. Aim to maintain lowest tumour temperature of 42.5°C for 30 min. Radiotherapy See Comparator	Radiotherapy alone *Total dose:* 64-70 Gy *Fractions:* Daily fractions of 2.0-2.5 Gy 5 times a week given to primary site and neck nodes. *Mode:* 6 or 12 MeV linear accelerators (electron or photon beam) or 60Co unit were used. *Mean dose* 67.05 Gy (67.85 for combined arm)	Tumour response (3 months after completion of therapy) Complete response: disappearance of all known nodal disease Partial response: a reduction in total nodal volume of > 50% No change: a reduction of < 50% or increase >25% Progressive disease: a >25% increase in tumour size	A. Probably. Described as randomised but no method stated. Patient characteristics similar with the exception of slightly different primary tumour site. B. Yes. Have stratified results according to factors they consider may be independent predictors. C. Probably. No loss to follow-up reported. Original paper provides results minus 4 pts who had not completed 3 month follow-up. Follow-up paper provides full analysis. Four nodes from 4 patients excluded from analysis. Will be included as non-responders in this analysis. D. Probably. Paper states that tumour size was clinically evaluated by two independent observers. Quality rating: Good/fair
Results summary: Following contains results as reported in the papers. For a full ITT analysis including patients excluded due to protocol violations (3 HT + RT and 1 RT only) see the report. Updated analysis from Valdagni et al. (1994) used as it includes 4 patients who had not been assessed in original paper. 3 months: complete response HT + RT (15/18) vs RT (9/22); partial response 1/18 vs 9/22 for overall response 16/18 and 18/22. 5 years: 68.6% vs 24.2% (p=0.015). Survival at 5 years: 53.3% vs 0%.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Ohizumi, 2000					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-3 Prospective non-randomised study with retrospectively selected controls N=24	Previously irradiated neck node metastases from squamous cell carcinoma from the head and neck Treated between Oct 84 and Sep 97 During same period 32 patients treated with re-irradiation alone. 12 selected to be controls based on anatomical diagnosis, recurrent nodal size and nodal site	Hyperthermia + radiotherapy Hyperthermia *Frequency:* 2443 (superficial tumours) or 13 (large nodes) MHz *Regimen:* Once or twice a week, immediately prior to radiotherapy for 2-7 treatments (mean 4) for 30-50 mins *Temperature measurement:* Yes. Aimed for core temperature > 42.5°C. Achieved >41°C in 83% and >42°C in 58%. Radiotherapy See Comparator	Radiotherapy alone Comparative study *Total dose:* Not stated *Fractions:* Not stated *Mode:* Not stated *Mean dose*: 57.7 ± 10.5 (vs 60.4 ± 9.49 for intervention group).	Tumour response Complete response Partial response (> 50% reduction in volume) No change (< 50% reduction in volume) Survival Progression free survival	A. No. No randomisation and control subjects selected from a group of eligible patients based on matching prognostic factors. B. No adjustments have been made for potential confounding although patients were matched based on potential prognostic factors. However, this may have the effect of underestimating the risk. C. Unclear. No loss to follow-up reported. Maximum follow-up 78 months (median 15 months). D. Unclear. No report of whether tumour volumes were assessed by independent reviewers. Quality rating: Poor. Note: Intervention patients received either 2433 or 13 MHz heating depending on tumour type (ie, superficial or large). Not reported separately so unclear how many received non-microwave therapy.
Results summary: Complete response HT + RT vs RT alone: 4/12 vs 5/12; Partial response: 6/12 vs 5/12; No change 2/12 vs 2/12. No diff in survival or progression free survival.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Holt, 1977					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-3 Non randomised study with historical controls 1) N=156 (104 relevant to review) 2) N=297	1) Patients with ear, nose or throat cancer: Late stage with tumours > 5 cm Earlier or recurrent stages with tumours < 5 cm Histologically positive nodes Fixed inoperable nodes Similar staging and site between treatment arms of interest 2) Head and neck – no further details	Hyperthermia + radiotherapy 1) Hyperthermia *Frequency:* 434 MHz *Regimen:* Once per week over 9 weeks *Temperature measurement:* Yes. Radiotherapy *Total dose:* 5400 rads *Fractions:* 200 rads 3 times per week *Mode:* megavoltage x-ray *Mean dose*: Not stated Note: radioactive implant to residual primary and/ or nodes n=2 2) Hyperthermia + radiation (no further details)	Radiotherapy alone 1) *Total dose:* 6000 rads *Fractions:* 30 x 200 rads over 6 weeks *Mode:* megavoltage x-ray *Mean dose*: Not stated Note: radioactive implant to residual primary and/ or nodes n=7 2) Radiotherapy – ionising radiation (no further details)	Patient response (free of cancer) Complete primary resolution Survival	A. No. 1) Selected case series used with historical control. Similar staging and site between treatment arms. Different RT regimens to intervention and control arms. 2) Unclear but appear to be continuation of case series. B. No. C. Unclear. No length of follow-up or loss to follow-up reported D. No. Assessor aware of treatment assignment. Quality rating: Poor. Note: Additional therapy (radioactive implant) given to 7 HT + RT patients compared with 2 RT only patients. Little information given regarding patients included in study. Analysis (2) appears to be a either a continuation of the initial series or a new case series. Unclear if comparison is historical or concurrent.
Results summary: Percent of patients without cancer (calculated from Figure) HT + RT vs RT: (1) After treatment – 94% v 36%; 1 year – 79% vs 21%; 2 year – 66% vs 15%; 3-year – 50% vs 8%. Crude 3-year survival – 54% vs 19%; Crude 8-year survival – 40% vs 11%. (2) Complete primary resolution – 92% vs 34%; Crude 3-year survival – 68% vs 17%.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Arcangeli, 1985; Arcangeli, 1980					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-3 Prospective non-randomised study with within patient controls N=81 nodes (38 patients)	Multiple N2-N3 neck node metastases from squamous cell carcinoma of the head and neck cancer. Not eligible if previously treated with radiotherapy.	Hyperthermia + radiotherapy Hyperthermia *Frequency:* 500 MHz *Machine:* Ailtech M125A *Regimen:* Days 1,3 and 5 each week, immediately after second daily fraction of RT, for 45 min, for a total of 7 treatments *Temperature measurement:* Yes. Measured using a single site (central base of tumour). Aimed for core temperature of 42.5°C Radiotherapy See Comparator	Radiotherapy alone Comparative study *Total dose:* 4000-7000 rads *Fractions:* 200 + 150 + 150/day, 4-5 hr interval between fractions, 5 days/week *Mode:* 5.7 MeV linear accelerator (photon)	According to Arcangeli 1980 Complete response: complete macroscopic disappearance of the lesion within the treatment period. Partial response ≥ 50% shrinkage within the treatment period. Assessed by two independent reviewers According to Arcangeli 1985 Tumour response (failure or success) with success defined as "total disappearance of lesion" Local control	A. No. No randomisation. Comparable lesions in the same patient treated with each of the treatments. B. No adjustments have been made for potential confounding although the effect of factors including tumour volume and termperature reached have been assessed. C. Unclear. No loss to follow-up stated. Maximum follow-up 28 months. D. Maybe. Earlier paper states that lesion size was determined by two independent reviewers. However, overall analysis does not. Quality rating: Poor. Note: 16 patients also given misonidazole but claim there was no difference in efficacy so have included all patients together. Arcangeli 1980 also include results for 4 patients with other cancer types receiving HT + RT. Not relevant to this report.
Results summary: Complete response HT + RT vs RT alone: 30/38 (79%) vs 18/43 (42). Local control at 2 years: 58% vs 14%.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Melanoma

Overgaard, 1996; Overgaard, 1995					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level II RCT EHSO Protocol 3-85 N=134 lesions (70 patients)	Advanced, recurrent or metastatic lesions of non-lentiginous malignant melanoma Candidates for radiotherapy Life expectancy > 3 months No concurrent cancer therapy Jan 86 – May 92	Hyperthermia + radiotherapy Hyperthermia *Frequency:* Not stated but mix of microwave and radiofrequency *Regimen:* Within 30 minutes after radiotherapy fractions *Temperature measurement:* Yes. Aimed for 43°C for 60 min Radiotherapy See Comparator	Radiotherapy alone *Total dose:* 24 or 27 Gy *Fractions:* 3 fractions in 8 days *Mode:* High voltage photons or electrons *Dose:* 31 got 24 Gy and 34 got 27 Gy (vs 29 got 24 Gy and 34 got 27 Gy for intervention group).	Complete response at 3 months Persistent local control	A. Probably. Study was randomised with randomisation arranged centrally. In subjects with > 1 tumour, treatments were assigned to pairs for tumours. Tumour characteristics similar between treatment groups. B. Yes. Other potential prognostic factors considered including tumour size, radiation dose, sex and others. C. Probably. Follow-up ranged from 3 to 73 months. No loss to follow-up reported. D. No. Primary outcome is subjective and treatments unblinded. No indication of whether outcome assessed independent of treatment status. Quality rating: Fair Notes: 6 lesions considered not evaluable however will be included in review (3 in each treatment arm). Mixture of microwave and radiofrequency hyperthermia. Proportion of each not reported and results not presented separately.
Results summary: As reported in paper: complete response at 3 months HT + RT vs RT: 62% vs 35% (p=0.003) RR 4.01 (1.77, 9.08); 2-year local control: RR 1.73 (1.07, 2.78).					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Shidnia, 1990					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-2 Non-randomised study with concurrent controls N=188 lesions (92 patients) Note: 181 lesions in 90 patients considered evaluable	Patients with malignant melanoma Jan 70 – Dec 87	Hyperthermia + radiotherapy Hyperthermia *Frequency:* 433, 915 or 2450 MHz *Regimen:* within 30 min after radiotherapy *Temperature measurement:* Yes Radiotherapy See Comparator	Radiotherapy alone Four regimens used: 200 cGy daily for 30 fractions in 6 weeks 600 cGy twice a week x 6 in 17 days 730 cGy once a week x 5 in 28 days 830 cGy x 4 in 20 days Using x-ray, cobalt 60 and electron beams (7 -28 MeV)	Tumour response	A. No. Patients selected for treatment based on tumour size; > 2 cm received HT + RT. B. No. Results stratified by radiation dose C. Unclear. Time of outcome assessment not stated. No details re loss to follow-up. D. No. Primary outcome is subjective and treatments unblinded. No indication of whether outcome assessed independent of treatment status. Quality rating: Poor
Results summary: Based on evaluable population: HT + RT vs RT alone (< 400 cGy): CR 70% vs 34%; OR 90% vs 62%. (> 400 cGy) CR 77% vs 63%; OR 100% vs 95%.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Arcangeli, 1987					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-3 Prospective non-randomised study with within patient controls N=38 lesions (17 patients) Note: also reports on head and neck series (see Head and Neck section)	Patients with cutaneous and nodal metastases from malignant melanoma Mar 77 – Jan 84	Hyperthermia + radiotherapy Hyperthermia *Frequency:* RF (27 MHz) and microwave (500, 2450 and 400 MHz) hyperthermia *Machine:* Various Schedule 1 *Regimen:* Following each radiation fraction at 42.5°C for 45 min for 8 treatments Schedule 2 *Regimen:* Following each radiation fraction at 45°C for 30 min for 5 treatments *Temperature measurement:* Yes. Measured using a single site (central base of tumour). Aimed for core temperature of 42.5°C Radiotherapy See Comparator	Radiotherapy alone Schedule 1 *Total dose:* 40 Gy *Fractions:* 2 weekly fractions of 5 Gy Schedule 2 *Total dose:* 30 Gy *Fractions:* 2 weekly fractions of 6 Gy *Mode:* 5.7 MeV linear accelerator (photon)	Tumour response Failure or success (ie, complete disappearance of lesion at end of treatment or soon after) Persistence of complete response	A. No. No randomisation. Comparable lesions in the same patient treated with each of the treatments. B. No adjustments have been made for potential confounding although the influence of tumour volume was assessed. C. Unclear. No loss to follow-up reported. Results note that some patients followed up to 24 months. D. Unclear. Open-label study with subjective outcome. No indication of independent outcome assessment. Quality rating: Poor.
Results summary: Complete response HT + RT vs RT alone: Schedule 1: 10/13 (77%) vs 5/9 (55%); Schedule 2: 6/8 (75%) vs 4/8 (50%). Persistence of complete response: 100% for all groups.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Scott, 1983					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-2 Prospective non-randomised study with within patient controls N=40 lesions (12 patients) Note: also reports on superficial tumour series (see Superficial tumours section)	Patients with extensive disease, limited survival, ≥ 3 superficial lesions and had failed all other therapy. All patients had advanced melanoma Mar 77 – Jan 84	Hyperthermia + radiotherapy Hyperthermia *Frequency:* 915 MHz *Machine:* Not stated *Regimen:* Following RT 3 treatments at 72 hour intervals Radiotherapy *Total dose:* 1500 rads *Fractions:* 3 x 500 rad at 72 hour intervals	Radiotherapy alone Three schedules of 3 treatments at 72 hour intervals: *Total dose:* 2100 rads *Fractions:* 700 rads *Total dose:* 2400 rads *Fractions:* 800 rads *Total dose:* 1800 rads *Fractions:* 600 rads	Tumour response at end of treatment and 3 month follow-up	A. No. No randomisation. Multiple lesions in the same patient assigned to each of the treatments. Unclear on what basis treatments were assigned. B. No adjustments have been made for potential confounding. C. Unclear. No loss to follow-up reported. D. Unclear. Open-label study with subjective outcome. No indication of independent outcome assessment. Quality rating: Poor.
Results summary: Complete response HT + RT vs RT alone (a), (b) and (c): Complete response at end of treatment: 2/12 vs 2/12, 1/12 and 0/12. Complete response at 3 months follow-up: 8/12 vs 2/12, 5/12, 0/12.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Superficial tumours (various types)

Egawa, 1989					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level II Open label RCT Multicentre (10 sites) Japan N=113 randomised (92 evaluable)	Superficially located tumours > 3 cm in diameter. Included any tumour type except extremely radiosensitive tumours (ie, malignant lymphoma and leukaemia), any site (mostly head and neck and breast), or status (ie, primary metastatic or recurrent) Of evaluable patients: 50% male ~ 60 years	Hyperthermia + radiotherapy Hyperthermia *Frequency:* RF 48% (8 and 13 MHz) and MW 52% (600-915 and 2450 MHz) *Regimen:* Once a week during radiotherapy *Temperature measurement:* Yes.Centre of tumour. Aimed for temp > 42.5°C for at least 40 min Radiotherapy See Comparator	Radiotherapy alone *Total dose:* 35-75 Gy *Fractions:* daily fractions 2 Gy; 5/week. *Mode:* Not stated *Dose:* Authors state that "radiation dose in Group B [comparator] seemed to be slightly larger than that in group A, but the differences was not statistically significant"	Tumour response (1 month after treatment)	A. No. Although study was randomised (using envelope method) 21 subjects were considered non-evaluable. A number of these cases were excluded due to hyperthermia-related side effects so selection bias cannot be ruled out. Similar baseline characteristics for evaluable patients. B. Yes. Prognostic factors including sex, site, radiation dose, tumour size, tumour type and age were examined in a multiple logistic regression. C. Outcome assessed at 1 month after treatment. Loss to follow-up not stated. D. Unclear. Subjective outcome and blinding of outcome assessment not reported. Quality rating: Poor Note: Substantial number of subjects considered non-evaluable due to heat side effects. ITT analysis could not be performed for this review as numbers excluded from each arm not stated.
Results summary: Complete response HT + RT vs RT: 20/44 (45%) vs 18/48 (38%). Partial response: 16/44 (36%)vs 12/48 (25%). Overall response (CR + PR): 36/44 (82%) vs 30/48 (63%).					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Perez, 1991; Perez, 1989					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level II Open label RCT N=307 randomised (250 with single tumours and of these 236 considered evaluable)	Superficial measurable malignant tumours of epithelial or mesenchymal origin < 5 cm in thickness. Of evaluable patients: Some differences between treatment groups: Male in HT + RT vs RT group: 8% difference Prior chemotherapy: 9% difference ~ 50% previously irradiated	Hyperthermia + radiotherapy Hyperthermia *Frequency:* Mostly 915 MHz *Regimen:* Within 15-30 min of RT, twice weekly *Temperature measurement:* Yes. Aimed for 42.5°C for 60 min Radiotherapy See Comparator	Radiotherapy alone *Total dose:* 32 Gy *Fractions:* 8 fractions of 4 Gy delivered twice weekly *Mode:* Mainly electrons but occasionally cobalt-60 or 4 MV photons *Dose:* < 30% overall (intervention and comparator arms) received < 90% of prescribed dose.	Initial tumour response Continuous control Treatment delivery	A. Unclear. Although study was randomised (centralised method) 14/250 subjects considered non-evaluable and numbers per arm not given. Some differences in baseline characteristics including sex and prior chemo. B. No adjustments made although results assessed according to tumour size and type. C. Unclear when initial tumour response was measured. No details on loss to follow-up. D. Unclear. Subjective outcome and blinding of outcome assessment not reported.. Quality rating: Poor Note: Fourteen patients considered non-evaluable, ITT analysis could not be performed for this review as numbers excluded from each arm not stated. 8 patients randomised to RT alone received heat and 5 patients randomised to heat received none. Kept in randomised arm for analysis.
Results summary: Complete response HT + RT vs RT: 38/119 (32%) vs 35/117 (30%). Non significant difference in tumours < 3 cm (52% vs 39%). No diff for bigger tumours. No diff in local control except for smaller tumours (p=0.02).					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Howard, 1987; Howard, 1988					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-2 Open label non-RCT N=41 lesions (16 patients)	Patients with one or more assessable superficial malignant lesions. Previously treated with radiotherapy.	Hyperthermia + radiotherapy Hyperthermia *Frequency:* 650 MHz *Regimen:* Within 30 min of RT *Temperature measurement:* Yes. 43°C for 60 min Radiotherapy See Comparator	Radiotherapy alone *Total dose:* 24 Gy *Fractions:* 6 twice-weekly fractions *Mode:* Mostly x-ray although sometimes electron or supervoltage *Dose:* 88% in both arms received full dose of RT	Tumour response: Assessed by caliper measurements in two orthogonal planes (or using photos). Based on area, not volume. Complete response – no evidence of residual tumour	A. No. Patients with one lesions received HT + RT. Patients with multiple lesions – most received RT alone or HT + RT on lesions considered ' suitable'. Potential for selection bias. B. No adjustments made although results assessed according to tumour size. C. Unclear Follow up between 4 and 31 weeks (mean 13 weeks). D. Unclear. Subjective outcome and blinding of outcome assessment not reported.. Quality rating: Poor Note: Study also included 9 lesions which were left untreated. Not included here.
Results summary: Complete response HT + RT vs RT: 9/20 vs 7/21. Large lesions: 1/20 vs 2/21. Small lesions: 8/20 vs 5/21.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Lindholm, 1988; Lindholm, 1987					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-2 Open label non-RCT N=98 lesions in 45 patients (85 lesions 38 patients considered evaluable) Note: also include analysis of 56 lesions in 28 patients who had multiple lesions treated with both modailities)	Superficial malignant tumours, refractory to established treatment modalities; ≥ 3 months life expectancy; ≤ 3 cm below skin; verified by fine needle aspiration or biopsy.	Hyperthermia + radiotherapy Hyperthermia *Frequency:* 915 or 2450 MHz *Regimen:* 30-90 min or 3-4 hours after RT 2 days/week for 2 weeks *Temperature measurement:* Yes. Aimed for as high as possible without causing discomfort (not > 45°C). Radiotherapy See Comparator	Radiotherapy alone *Total dose:* 30 Gy *Fractions:* 10 x 3 Gy during 2 weeks *Mode:* Electrons (48 tumours), X-rays (27 tumours) or photons (10 tumours) *Dose:* Not reported Note: 5 patients received greater doses due to no prior exposure to RT.	Tumour response (2 observations with continuing response at least one month apart required) Duration of response	A. No. Patients with single lesions received HT + RT while patients with multiple lesions received both. Largest received HT + RT and smallest received RT alone. No details provided on prior or concomitant therapies. B. No. C. Unclear. No loss to follow-up reported. D. Unclear. Subjective outcome and blinding of outcome assessment not reported.. Quality rating: Poor Note: Overall analysis and "comparative" analysis (patients with > 1 tumour) reported. Only overall analysis considered for this review.
Results summary: Complete response HT + RT vs RT: 26/57 (46%) vs 7/28 (25%). Relapses: 8/26 (31%) vs 2/7 (29%). Time to relapse: 1-15 months (median 4) vs 1 month					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Dunlop, 1986					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-2 Open label RCT N=116 lesions. 86 tumours considered evaluable for analysis. (9 evaluable receiving HT alone will be considered for safety only)	Patients with small superficial lesions of various histologies (adenocarcinoma of breast, lung and stomach; SCC of lung and head and neck; Kaposi's sarcoma and melanoma). Mostly breast adenocarcinoma.	Hyperthermia + radiotherapy Hyperthermia *Frequency:* Mostly microwave (frequency not specified). Also included US and RF. *Regimen:* Either 15-20 min or 4 hours post RT, usually twice-weekly (72 hr intervals) *Temperature measurement:* Yes. Aimed for 43°C for 60 min. Radiotherapy See Comparator	Radiotherapy alone Most tumours *Total dose:* 25-30 Gy *Fractions:* 10 fractions Melanoma only *Total dose:* 22.5 or 30 Gy *Fractions:* 7.5 Gy fractions one per week for 3 or 4 weeks	Tumour response: all clinical evidence of tumour had disappeared. Measured using plastic callipers. All measurements carried out by one investigator.	A. No. Patients with single lesions received HT + RT. If they had received prior RT then RT dose was reduced or were given HT alone. Patients with multiple lesions received both combined and RT only therapy. B. No but results assessed for 'useful heat sessions delivered and by different modes of treatment. C. Unclear. No loss to follow-up reported. D. Unclear. Subjective outcome and blinding of outcome assessment not reported.. Quality rating: Poor Note: Also included a HT alone arm which is not considered for efficacy (only safety)
Results summary: Complete response HT + RT vs RT: 27/45 (60%) vs 16/32 (50%). Of patients on HT + RT, 83-89% of patients receiving 2, 3 or 4 "useful" heat sessions had a complete response while only 30-38% of patients with 0 or 1 "useful" heat sessions.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Scott, 1984					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-2 Open label non-RCT N=31 patients with paired lesions	59 patients with superficial malignancies with at least 6 months follow-up. Of these 31 had paired lesions. Both lesions included in irradiated field but HT only applied to one. Included SCC, adenocarcinoma, melanoma.	Hyperthermia + radiotherapy Hyperthermia *Frequency:* 915 MHz *Regimen:* within 30 min of RT twice per week (most patients) or after all radiotherapy (5 patients) *Temperature measurement:* Yes. Aimed for 42-43°C for 45 mins or 43-44°C for 30 min Radiotherapy See Comparator	Radiotherapy alone Most tumours *Total dose:* 6000-6500 rads *Fractions:* 200 rads/day for 6-6.5 weeks 5 tumours *Total dose:* 4800-5000 rads *Fractions:* 400 rads/day 4 days/week	Tumour response	A. No. Lesions treated with hyperthermia had to be within 3 cm of skin surface so was usually a metastatic or recurrent lymph node while control was generally another lymph node or primary tumour. Therefore, significant potential for selection bias. B. No but a number of factors were considered and dismissed as potential prognostic factors including tumour size and tumour type. C. Unclear. No loss to follow-up reported. D. Unclear. Subjective outcome and blinding of outcome assessment not reported.. Quality rating: Poor
Results summary: Complete response HT + RT vs RT: End of treatment: 10/31 vs 3/31; 6 months: 27/31 vs 12/31; 12 months: 19/31 vs 10/31; 18 months: 8/31 vs 7/31; 24 months: 6/31 vs 5/31.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Breast cancer

Vernon, 1996; Sherar, 1997					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level II Open-label RCTs (actually combined analyses of five RCTs that had commenced but had poor recruitment) DHG trial MRC BrI trial MRC BrR trial ESHO trial PMH trial Netherlands, UK, Canada, Italy, Poland, Austria N=317 lesions (307 patients) but only 306 lesions in 306 patients included in analyses.	Patients with measurable breast cancer lesions where local therapy was indicated but surgery not feasible. After combination of the five trials, three groups of patients were present. Patients with: - untreated primary inoperable breast cancer - recurrent tumours in sites that had no previous irradiation - recurrences in previously irradiated areas. Refer to paper for more details of inclusion and exclusion criteria for each trial	Hyperthermia + radiotherapy (n=171) Hyperthermia *Frequency:* Predominantly 434 MHz, but some sites used 915 MHz or 2450 MHz *Machine:* Variable *Regimen:* Frequency of HT treatment was variable, and time from RT to HT varied from 30 mins to >90 mins, depending on trial. *Temperature measurement:* Yes. Aim was to maintain lowest tumour temperature of 43°C for 60 min in four trials or 42.5°C for30 min in the PMH trial. Radiotherapy see Comparator States "the doses administered were the same, regardless of the outcome of randomisation" however, the dose received by patients in the HT+RT and RT alone arms are not actually presented. *Mean dose*: not reported	Radiotherapy alone (n=135) Dose of radiotherapy in four of the trials depended upon whether radical or palliative treatment Effective radiation dose*: 40-69 Gy *Total dose:* 28-50 Gy *Fractions:* Variable depending on trial and whether radical or palliative *Mode:* Either high voltage photons or electrons through one or multiple ports. *Mean dose*: not reported *relative to 60 Gy given in 30 fractions in 6 weeks	Local response (at any time ie., not at a specific time after treatment, however complete response required confirmation 4 weeks later) Complete response: no evidence of tumour according to WHO criteria - patients who died before response could be assessed were deemed failures Median time to CR was the first date CR was observed. Time to local failure was time to local progression from date of randomisation - patients without a CR were assigned zero. Progressive disease: a >25% increase in tumour size Survival: Overall survival was calculated from date of randomisation to death, or was censored at the data last known to be alive.	A. Yes. Randomisation undertaken centrally in each trial. Some trials used stratification or uneven randomisation protocols. Refer to original papers. For the purpose of this paper, only one lesion per paper was reported, the first randomised. As expected, patient characteristics differed between the five trials however there were also differences between the RT and RT + HT arms. The RT + HT arm had a higher proportion of patients who had chemotherapy prior to randomisation (15% vs 7% in the RT arm), and also a greater median lesion size. B. Probably. Multiple logistic regression analyses stratified by trial and adjusted by baseline characteristics that were prognostic for complete response (maximum tumour diameter, area of lesions and presence of systemic disease) to give an adjusted odds ratio. The paper is contradictory with respect to whether or not previous chemotherapy was adjusted for or not (beginning p738 says adjustment made; but this variable not listed at end page 738) C. Yes. One patient excluded as inappropriately included. Only the first randomised lesion in each patient was included. Minimum follow-up of all patients was 5 months. Patients who died before response could be assessed were categorised as failures. D. Not clear. Paper states "majority of [lesion size] measurement were verified independently by personnel other then the clinical co-ordinators", but provides no further detail. Quality rating: Fair
Results summary: Following contains results as reported in the papers: Complete response rate HT + RT (101/171, 59%) vs RT (55/135, 41%), p<0.001 giving an ORstratified =2.3 (95%CI 1.4-3.8) NB. Magnitude of additive HT effect was greater in patients getting only palliative RT; Median time to CR was 81 days for RT + HT vs 101 days for RT; Local recurrence after CR was 31% for HT + RT and 16% for RT alone. However progression elsewhere and death were lower in the RT arm than the HT + RT arm, but overall survival at two years was not different. Two year actuarial survival was 36% for HT + RT vs 41% for RT alone (ns). Three year survival shows greater divergence (against RT vs HT), but no statistical comparison has been undertaken and this result is not reported or discussed elsewhere in the paper.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Rui-ying, 1990					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-2 Concurrent control group. N=40 patients, 64 lesions	Primary or recurrent breast carcinoma	HT + RT: n=42 lesions Hyperthermia *Frequency:* 915 MHz and 2450 MHz *Machine:* Not reported *Regimen:* 40 mins at 41–44°C, twice weekly, 15–30 mins after irradiation *Temperature measurement:* Yes, temperature measured in central part of tumour. Temperature results not reported in paper. Radiotherapy *Total dose:* 20–80 Gy (mean 48 Gy) *Fractions:* 2–2.5 Gy/day x 4–5/week Nature: Not reported	RT: n= 22 lesions Radiotherapy *Total dose:* 20–80 Gy (mean 47 Gy) *Fractions:* 2–2.5 Gy/day x 4–5/week Nature: Not reported	Complete response: defined as complete disappearance of tumour maintained for 2 months. Partial Response No response	A. Not randomised. Concurrent control used. Selection bias is inherent as all small tumours got RT alone and all large tumours got RT + HT B. No adjustments have been made for confounding. C. Not clear. Not reported how many patients were treated in total during this period. D. No. Not reported how tumour response was assessed, or if assessor was aware of treatment assignment. Quality rating: Poor, due to inherent selection bias and minimal reporting
Results summary: Results not extracted as incomparable lesions treated with RT + HT vs RT alone.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Perez, 1986					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-3 Presumably retrospective chart review (not stated). Historical control. N=164	Recurrence of breast carcinoma (95% chest wall) HT + RT group: Treated between March 1978 and December 1984. n=48 RT group: Treated between January 1964 and December 1984. n=116 For the RT group only, it is stated ' patients on whom complete excision of the recurrence was carried out were not included in the analysis. Not clear if this was also the case for the HT + RT arm.	HT + RT (n=48): Hyperthermia *Frequency:* 'majority' of patients got 915 MHz *Machine:* MCL 15222, Clini-Therm Mark IV. *Regimen:* 30–60 mins of heat beginning 15–30 min after radiation (every 72 hr) *Temperature measurement:* Yes, minimum of 2 temperature probes. 74% of small lesions reached prescribed temperature compared to 60% of larger lesions. Radiotherapy *Total dose:* 2000–4000 cGy *Fractions:* 400 cGy every 72 hr Nature: Delivered with electrons (9–16 MeV) and occasionally with cobalt-60. Wide local ports were used, with 2-3 cm margins. Chemotherapy 'Some patients received concomitant or sequential chemotherapy' (number and details not reported)	RT (n=116): *Total dose:* 2000–6000 cGy *Fractions:* usually in 200–300 cGy TD daily fractions Nature: 'Irradiation delivered with cobalt-60, 4 MeV photons or electrons (9–13 MeV), although occasionally patients were treated with superficial X-rays.'	Complete response within 3 month (no definition or information re. assessment of tumour response provided) Results were also assessed according to tumour volume and RT dose received.	A. Not randomised. Historical control used. Not reported if consecutive. Considerable overlap in time between two arms and not reported how patients were selected for each group during the overlapping period. Very likely to be selection bias. B. No adjustments have been made for confounding. And poor reporting of baseline difference between groups. Radiotherapy different in two arms and results likely to be biased against historical control due to technical improvements in radiotherapy since 1960s. Also, for the RT group only it is stated ' patients on whom complete excision of the recurrence was carried out were not included in the analysis. Not clear if this was also the case for the HT + RT arm. C. Not clear. Not reported how many patients were treated in total during this period. ie., were those with < 6 mth follow-up excluded? D. No. Not reported how tumour response was assessed, or if assessor was aware of treatment assignment. Quality rating: Poor, with misleading reporting.
Results summary: Results subject to considerable potential bias. Complete tumour response: Lesions 1–3 cm, 18/29 (62%) in RT + HT arm vs 48/73 (66%) in RT arm, ns; Lesions >3 cm, 13/20 (65%) in RT + HT arm vs 18/43 (42%) in RT arm, ns. Results reported in the abstract for tumours 1–3 cm are extremely misleading, as only those for the subgroup of patients getting 3001–4000 cGy.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Masunaga, 1990					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-3 Presumably retrospective chart review (not stated). Historical control. N=87 tumours Minimum follow-up 6 months	Locally advanced or recurrent breast carcinoma. All were invasive ductal cancers. HT + RT group: 11 locally advanced primary tumours, 6 locally recurrent tumours after surgery, 13 locally recurrent tumours after radiotherapy treated between August 1979 and April 1988. n=30 tumours RT group: 11 locally advanced primary tumours, 27 locally recurrent tumours after surgery, 19 locally recurrent tumours after radiotherapy treated between July 1962 and December 1979. n=57 tumours	HT + RT (n=30): Hyperthermia *Frequency:* 8, 13.56, 430 or 2450 MHz. Not reported how many patients got each - (although in a subgroup of 22 pts, 50% got either 430 or 2450 MHz.) *Machine:* Yamamoto; Tokyo Keiki; Minato Medical Science). *Regimen:* 30–60 mins of heat after radiation , 1–2 sessions/wk *Temperature measurement:* Yes, attempted to measure at deepest point of tumour. Radiotherapy *Total dose:* variable between 20–74 Gy *Fractions:* variable between 1.8–4 Gy, 2–5 days/wk Nature: Cobalt-60 gamma ray for primary and post-surgery recurrences, and high-energy electrons or soft x-ray for post-RT recurrent tumours. Chemotherapy Two primary tumours with distant metastases received concurrent chemotherapy	RT (n=57): Radiotherapy *Total dose:* variable between 30–81 Gy *Fractions:* 2–3 Gy, 5 days /wk *Nature:* Cobalt-60 gamma ray for primary tumours, and cobalt-60 gamma ray or high-energy electrons for recurrent tumours. NB. Time dose fractionation factor of post-RT recurrent tumours was significantly lower in the HT+RT group than the RT group (P<0.01)	Local response within two months, calculated as CR + PRa: PRa = 80–99% regression PRb = 50–79% regression NR = <50% regression Not reported whether independently assessed. Survival	A. Not randomised. Historical control used. Not reported if consecutive. Likely to be subject to selection bias. B. No adjustments have been made for confounding. Minimal reporting of baseline difference between groups. Radiotherapy different in two arms and results likely to be biased against historical control due to technical improvements in radiotherapy since 1960/70s. Two patients in HT+RT group got chemotherapy C. Not clear. Not reported how many patients were treated in total during this period. ie., were those with < 6 mth follow-up excluded? D. No. Not reported how tumour response was assessed, or if assessor was aware of treatment assignment. Quality rating: Poor.
Results summary: Results subject to considerable potential bias. Local response (CR + PRa): All tumours, 27/30 (90%) in RT + HT arm vs 46/57 (81%) in RT arm, ns (Fishers Exact performed by reviewer); No significant difference was present in any subtype of tumour (primary, post-surgery recurrence, post-RT recurrence), although in the primary tumours there was a trend toward a benefit for HT+RT. Survival results only reported for patients with primary tumours who did not have a salvage operation. NB. Results not reported separately for 430 and 2450 MHz frequencies.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Holt, 1982					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-3 Presumably retrospective chart review (not stated). Historical control (but selection method not reported). N=88 patients Minimum follow-up not reported	Minimal detail provided. HT + RT group: Stage 1 and 2 patients post mastectomy and axillary sampling or clearance between July 1974 and July 1979 (n=44) RT group: 'similar post-operative patients' (n=44) - no other detail reported	HT + RT (n=44): Hyperthermia *Frequency:* Assumed to be 434 MHz. *Machine:* Not reported for the breast cancer patients (possibly Tronado 434 MHz). *Regimen:* Not reported *Temperature measurement:* Not reported Radiotherapy *Total dose:* 3000 rads over 15 treatments to specific regions, interspersed with 6-9 treatments to whole area with 'combined' therapy to a total of 1200 rads Nature: X-ray	RT (n=44): Radiotherapy *Total dose:* 5000 rads over 25 treatments Nature: X-ray	Recurrence: No detail provided re. how and when measured. Not reported whether independently assessed. No detail provided re. when outcomes were measured etc. NB. Survival results presented in same paper do not appear to relate to this series of 44 patients, but no patients with widespread metastatic disease - for whom no treatment information is provided..	A. No. Not randomised. Historical control used. Not reported if consecutive. Likely to be subject to selection bias. B. No adjustments have been made for confounding. No reporting of baseline difference between groups. Radiotherapy different in two arms. C. No. Not reported when tumour response was assessed, or duration of follow-up, or what happened to patients lost to follow-up. D. Not reported how outcomes measured. Quality rating: Poor. Extremely poor reporting.
Results summary: States 3/44 of RT+HT vs 9/44 of RT group developed local recurrence (Fisher's Exact test undertaken by reviewer, ns) and 17/44 of RT+HT group vs 25/44 of RT group developed distant metastases (Chi-squared undertaken by reviewer, ns). however, methods and results extremely poorly reported. Unable to reliably interpret.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Gastric cancer

Shchepotin, 1994					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention Level II Single-centre open-label RCT N=293 subjects	Newly diagnosed, previously untreated gastric cancer Skin-tumour distance < 10 cm Excluded if they had metastatic disease, internal bleeding from tumour, significant anaemia or complete gastric obstruction with protein and electrolyte abnormalities Feb 84 – May 86 61% male Mean age 55 years	Hyperthermia + radiotherapy + surgery Hyperthermia *Frequency:* 460 MHz *Regimen:* Approximately 2 hours after each radiotherapy dose for 4 days *Temperature measurement:* Yes. Aimed for temp > 42°C however not achieved in most patients Radiotherapy + surgery See Comparator	Radiotherapy + surgery Radiotherapy *Total dose:* 20 Gy *Fractions:* 4 fractions 5 Gy over 4 days *Mode:* Not stated *Dose:* Not stated Surgery Could be exploration only, subtotal gastrectomy or total gastrectomy (similar between treatment groups) Note: surgery alone also examined although not included in this review	3- and 5-year survival	A. Probably. Randomised using random selection of sealed envelopes. No significant differences between treatment groups for prognostic or treatment characteristics B. No. However, results presented stratified by prognostic criteria. C. Unclear. It is not stated how many subjects were included in the analysis although it appears that patients who received < 4 treatments were excluded. Survival assessed at 3 and 5 years however how many people were lost-to-follow up is not stated. D. Unclear. Open-label treatment although objective outcome (survival) Quality rating: Poor Note: results reported as percentage surviving at each time point with variance estimate however unclear whether this is SE or SD
Results summary: 3-year survival (HT + RT + S vs RT + S): 57.6 ±6.3 vs 51.8 ± 6.8. 5-year survival: 51.4 ± 6.6 vs 44.7 ± 7.1. Some differences related to different prognostic factors.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Colorectal cancer

Trotter, 1996					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level II Open-label RCT Australia N=73 patients evaluable (75 randomised) NB. the HT+RT pts and RT pts were treated at different centres	Patients with locally recurrent or unresectable primary adenocarcinoma of the rectum. Groups relatively well matched for baseline characteristics except patients in the RT + HT group were older and had a slightly higher proportion with pelvic and distant disease.	HT + RT (n=36) Hyperthermia *Frequency:* 434 MHz *Machine:* Tronado *Regimen:* 2–3 times/day, at least 2 days/wk, within 20 mins of RT dose. *Temperature measurement:* No Radiotherapy *Total dose:* Intended maximum of 4000 cGy over 5–6 weeks *Fractions:* 160 *Mode:* External beam RT using four-field box technique, with some modification (see paper) NB. Actual RT dose exceeded protocol dose in 64% of pts Median dose: 4275 cGy Duration of RT: 48.5 days	RT alone (n=37) Radiotherapy *Total dose:* Intended maximum of 5000 cGy over 6 weeks *Fractions:* 180 cGy *Mode:* External beam RT using four-field box technique NB. Actual RT dose exceeded protocol dose in 24% of pts Median dose: 4500 cGy Duration of RT: 38 days	Local response by CT using UICC criteria - 'maximum' response, so assumed to be anytime during follow-up. Quality of life (Spitzer quality of life assessment). Possible range 5 (worst) to 15 (best). Overall survival NB. Paper states 'each patient was reviewed by an independent assessor' but does not state whether this relates to the physical examination only, or to CT tumour response. Furthermore it is not clear if this person was blind to treatment assignment.	A. Probably. Patients were randomised, but no details are provided. Small baseline differences were present between groups (ie., HT+RT gp were older 69 vs 60 yrs,;and higher proportion had primary disease, 17% vs 8%, relative to the RT gp. B. Probably. Results not adjusted per se, but separate analyses conducted in patients with and without metastases at baseline. However, differences in RT treatment between arms, and the fact the RT treatment for the two arms was conducted at separate centres remain a concern. C. Yes. Two patients excluded as ineligible. Minimum follow-up not reported. D. No. Elsewhere in the paper it is stated that patients were reviewed by an independent assessor, but not stated if this also applied to the CT assessment of tumour response and most importantly does not state if asessor was blind to treatment assignment. Study also likely to suffer from insufficient statistical power. Quality rating: Fair/Poor
Results summary: Following contains results as reported in the papers: Complete response rate: HT + RT (2/36, 5.5%) vs RT (2/37, 5.4%), ns. Estimated median survival: HT + RT = 8.5 months (95%CI 5.9-12.7) vs RT = 12.2 months (95%CI 9.5-17.4), ns. No difference in survival between treatments even after stratification by presence of metastases. Mean Spitzer Quality of Life score (average over time): HT + RT 11.5 vs 11.6, ns. There was a non-significant trend toward reduced pelvic pain in the HT + RT arm.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Holt, 1982; Holt, 1988					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Insufficient information to determine level of evidence Study design unknown N=48 patients Minimum follow-up not reported	Recurrent rectal cancer Treated 1975-1979 HT + RT group: Biopsy only, colostomy only and abdomino-perineal resection were 3, 2, and 19 pts respectively RT group: Biopsy only, colostomy only and abdomino-perineal resection were 1, 5, and 18 pts respectively	HT + RT (n=24): Hyperthermia *Frequency:* Assumed to be 434 MHz. *Machine:* Not reported for the breast cancer patients (possibly Tronado 434 MHz). *Regimen:* Not reported *Temperature measurement:* Not reported Radiotherapy No information provided	RT (n=24): Radiotherapy No information provided	Not reported what was measured in study, but crude survival and pain relief are reported. No detail re. when or how measurements were made, or by whom. No detail provided re statistical methods used to calculate and compare survival. Not stated whether 'crude survival' is mean, and no variance measured provided.	A. No. Study design not reported. B. No adjustments have been made for confounding. No reporting of baseline difference between groups. Details of radiotherapy not reported at all. C. No. Not reported when pain relief was assessed, or duration of follow-up for survival measures, or what happened to patients lost to follow-up. D. Not reported how outcomes measured, or is assessment was blind to treatment assignment Quality rating: Poor. Extremely poor reporting.
Results summary: Possibly subject to bias, but unable to determine as methodology not reported. Insufficient information to be able to interpret results. eg. Duration of follow-up, treatment of missing data, method of calculating crude survival (?mean) and median (?Kaplan Meier etc) not reported.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Mesothelioma

de Graaf-Strukowska, 1999					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-3 Retrospective chart review with selected 'matched' controls - not reported if from same period in time so assumed to be historical control. NB. Part of larger retrospective review of prognostic factors. N=42	Histological diagnosis of mesothelioma HT + RT group: 303 mesothelioma patients treated at this centre between 1979 and 1996, of whom 18 patients with chest wall recurrences got HT + RT (≥4 Gy fractions). RT group: The investigators then retrospectively 'matched' these with 24 patients with painful chest wall tumours, with a ECOG performance status = 2, and treated with a 4 Gy/fraction scheme. NB. However, p 513 implies that these 24 patients were approx. one third of all the patients meeting these criteria, and no details are presented with regard to their selection.	HT + RT (n=18): Hyperthermia *Frequency:* 'majority' of patients got 433 MHz *Machine:* Not reported. *Regimen:* 60 mins of heat beginning after radiation (median of 4 sessions) *Temperature measurement:* Yes. T90 (90% of all measurements) were above 39.8°C Radiotherapy Median dose: 42 Gy (range 24-44) *Fractions:* 4 Gy Nature: Not reported	RT (n=24): Radiotherapy Median dose: 40 Gy (range 20-40) *Fractions:* 4 Gy Nature: Not reported	Tumour response (time of assessment not reported - given retrospective review of case records, unlikely to be consistent). Authors state a lot of data was missing. CR = no tumour palpable PR = decrease of > 50% of original volume PD = progressive disease NB. Tumour responses were only determined when palpable chest wall lesions were present. Lesions were measured with calipers	A. Not randomised. Retrospective chart review. Not clear why patients were selected for HT + RT treatment within this centre. Historical 'matched' control used. But method of selecting patients out of all those meeting the criteria for matching is not reported - likely to introduce considerable selection bias. B. No adjustments have been made for confounding. Minimal reporting of baseline difference between groups. C. No. Not reported how many patients were treated in total during this period. Tumour response only assessed in some patients, with data missing in nearly 50% of the RT alone arm.. Timing of tumour response measurement not reported. D. No. Tumour response measurement not blinded and only assessed in some patients. Quality rating: Poor
Results summary: Results subject to considerable potential bias. Tumour response data not valid as data missing for 6% of the HT + RT arm and 46% of the RT arm.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Ovarian cancer

Hayashi, 1999					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level III-3 Historic control due to malfunction of hyperthermia equipment. Implies consecutive series. N=45	Stages Ic-IV superficial epithelial ovarian carcinoma. 45 patients treated since 1989, however 26 patients did not get HT due to equipment malfunction in 1993. Appear to have been more stage III-IV patients (n=18/26, 69%) in Surg + CT alone group than in Surg + CT + HT group (8/19, 42%) Duration of follow-up not reported	Surgery + CT + HT (n=26): Hyperthermia *Frequency:* alternate use of 434 MHz and BSD-1000 (freq not specified) *Machine:* TCA-434 and BSD-1000 *Regimen:* 60 mins of heat concurrently with chemotherapy *Temperature measurement:* Only core temp measured (rectal or vaginal temperature) Surgery + chemotherapy Bilateral salpingo-oophorectomy with total hysterectomy, omentectomy, intrapelvic and paraaortic lymphadenectomy and an appendectomy. CDDP + adriamycin + cyclophosphamide in 5-6 courses initially, then for maintenance at 6-8 week intervals for 11-12 courses	Surgery + CT (n=18): Surgery + chemotherapy Bilateral salpingo-oophorectomy with total hysterectomy, omentectomy, intrapelvic and paraaortic lymphadenectomy and an appendectomy. CDDP + adriamycin + cyclophosphamide in 5-6 courses initially, then for maintenance at 6-8 week intervals for 11-12 courses	Overall survival	A. Not randomised. Retrospective chart review. However appear to have been consecutive as treatment selection was enforced by equipment malfunction for a set period. B. No adjustments have been made for confounding. Minimal baseline characteristics reported. Appear to have been more stage III-IV patients (n=18/26, 69%) in Surg + CT alone group than in Surg + CT + HT group (8/19, 42%) - likely to have confounded the results C. Not clear. Duration of follow-up not reported. D. Yes, for survival outcome. However not clear if any patients we lost to follow-up. Quality rating: Poor, due to mismatching of patient groups
Results summary: Results likely to be confounded due to mismatching of patients with respect to staging. Overall survival different between groups: 5 year survival 68% for Surg + CT + HT vs 33% for Surg + CT alone, $p<0.05$, however heavily influenced by difference in the stage III-IV patients and the smaller number of these patients in the Surg + CT + HT arm.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Pancreatic cancer

Yamada, 1992					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Non-randomised Historic control. Duration of follow-up not reported n=69	Pancreatic carcinoma treated at Tohoku University 1977-1987. IORT + HT: 21% stage I-II 79% stage III-IV IORT: 15% stage I-II 85% stage III-IV	Surg + IORT + CT + HT (n=14): Total RT: 25-30 Gy intraoperatively Non-operative RT (30-45 Gy) given in 12 pts 'Most' cases underwent chemotherapy RF capacitive heating device (freq not stated) Core temperature only measured	Surg + IORT + CT (n=55): Total RT: 25-30 Gy intraoperatively Non-operative RT (30-45 Gy) given in 5 pts 'Most' cases underwent chemotherapy	Pain relief Tumour response (only in some pts) Overall survival	A. Not randomised. Retrospective chart review with historic control. Not clear if consecutive B. No adjustments have been made for confounding. Minimal baseline characteristics reported. Appear to have been more stage III-IV patients (n=18/26, 69%) in Surg + CT alone group than in Surg + CT + HT group (8/19, 42%) - likely to have confounded the results C. Not clear. Duration of follow-up not reported. D. Yes, for survival outcome. However not clear if any patients we lost to follow-up. Quality rating: Poor Check all
Results summary: Results not extracted as frequency not specified					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Multiple cancer types

Gabriele et al, 1989					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level IV One arm from an open-label non-randomised controlled trial Italy N=66 lesions (50 patients) but only 26 lesions in an unknown number of patients included in relevant analyses.	Patients with recurrent or metastatic lesions of pre-treated malignant tumours., and whom further treatment with conventional therapies "wasn't possible". Total study population included 19 breast adenocarcinomas, 33 squamous cell carcinomas of the head and neck, 9 melanomas and 5 subcutaneous metastases of adenocarcinoma of the cevix, rectum and colon. However, the types of cancers included in the HT arm are not reported. All patients treated with HT alone had previously received high doses of radiation (>5000 cGy).	Hyperthermia alone (n=26 lesions) *Frequency:* 434 MHz or 915 MHz *Machine:* SAPIC SVO3, built by Aeritlaia, Turin *Regimen:* HT was 43 – 45 °C for 30 minutes of "effective heating", bi-weekly, for a total of 10 -12 heating sessions. *Temperature measurement:* Yes. Non-invasive heat mapping used for first 12 patients. Subsequent patients had ≥4 invasive intratumour thermometer probes inserted *Mean dose*: not reported	Hyperthermia + radiotherapy (n=37 lesions) Results not reported for this arm. See paper for further details of RT + HT regimen.	Local response (apparently at 6 months, but not stated explicitly) Complete response: evaluated by clinical and/or radiological examination Partial response: defined as >50% reduction in tumour mass No response:	A. No. Patients were not randomised to treatment but allocated according to cumulative dose of prior RT. Not stated if consecutive patients. B. No. No adjustments have been made for confounding C. Yes. Minimum follow-up of all patients was 6 months. It is not stated if any patients died before follow-up, and if so whether or not they were considered to be treatment failures. D. Not clear. No details are given regarding blinding of outcomes assessment. Quality rating: Poor
Results summary: The complete response rate for HT alone was 5/26 (19.2%). Results of other analyses (ie, maximum intratumour temperature, maximum diameter of lesion, tumour depth, and total dose of irradiation) are not reported, although the authors state there were no statistically significant differences for these outcomes. Analysis of all lesions in the study (regardless of treatment modality) showed there were no complete responses in lesions where the temperature did not exceed 41 °C. Thirteen patients in unspecified treatment arms experienced pain prior to treatment, and the authors report there was complete or partial pain relief immediately after the first or second heating session in ten patients.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

Gabriele et al 1990					
Study type Patient number	Patient group	Intervention	Comparator	Outcomes	Study quality
Intervention level IV Case-series, a subset of which may be reported as one arm from an open-label non-randomised controlled trial Italy N=60 lesions (57 patients)	Patients with recurrent cancer or metastases in which conventional therapies have failed. 59/60 sites had been irradiated, with or without surgery and/or chemotherapy. 43 cases had received total radiation doses >5000 cGy. The total study population included 35 lesions in the head and neck, 13 lesions in the chest wall, 10 lesions in the trunk and 2 lesions in the limbs. The histologic types consisted of 39 squamous cell carcinomas, 15 adenocarcinomas, 5 soft tissue sarcomas and one undifferentiated carcinoma. 56 lesions were superficial (ie, ≤5 cm in depth). Patients only included in the study if their life expectancy was ≥3 months	Hyperthermia alone (n=60 lesions) *Frequency:* 434 MHz or 915 MHz for superficial lesions. 27 MHz for 4 deep lesions. *Machine:* SAPIC SVO3, built by Aeritlaia, Turin *Regimen:* HT was ≥42 °C for 45 minutes, bi-weekly, for a total of 6 -10 heating sessions. *Temperature measurement:* Yes. Invasive intratumour thermometry was performed for all lesions, using ≥3 thermometer probes per tumour. The temperature at the master probe (typically the one in the deepest part of the tumour) was used to regulate delivery of HT. Treeatment time was measured from when the master probe first recorded 42 °C. *Mean dose*: 35/60 lesions achieved a temperature of ≥42 °C; average duration of heating approximately 31 minutes; with a mean of 7.5 HT sessions per lesion.	None	Local response determined by clinical examination and caliber measurements one to two months after therapy had ended. Ultrasound or CT scanning was used for "hard measuring or deeper lesions": Complete response: complete disappearance of tumour mass Partial response: defined as >50% reduction in tumour mass No response: ≤50% reduction in tumour mass Kaplan-Meier control curves Multivariate analysis to identify prognostic variables.	A. No. There are no statements regarding how patients were selected for study (eg, consecutive or not). B. No. No adjustments have been made for confounding C. Yes. Minimum follow-up of all patients appears to be 6 months. It is not stated if any patients died before follow-up, and if so whether or not they were considered to be treatment failures. D. No. No details are given regarding blinding of outcomes assessment. Outcomes assessment appears to have been conducted subjectively in the majority of cases. Quality rating: Poor
Results summary: The complete response rate observed in the study was 10/60 (16.6%), and the overall response rate (CR plus PR) was 24/60 (40%). Responses according to site were as follows: head and neck, 4/35 (11.4%); chest wall, 5/13 (38.5%); trunk, 1/10 (100%); and limbs, 0/2 (0%). The majority of complete and partial responses were obtained for smaller lesions with a higher number of heating sessions. The Kaplan-Meier analysis found that the probability of local control was approximately 15% eleven months after the end of therapy. The multivariate analysis found that the only variable correlated with response was a histologic type of adenocarcinoma.					

Study quality assessment questions (NHMRC, 1999):
(A) Has selection bias (including allocation bias) been minimised?;
(B) Have adequate adjustments been made for residual confounding?;
(C) Was follow-up for final outcomes adequate?;
(D) Has measurement or misclassification bias been minimised?

APPENDIX 10: ISSUES FOR DISCUSSION WITH DR HOLT (VISIT TO PERTH CLINIC, JANUARY 2005)

Inclusion/exclusion criteria

- Patient related – age; performance score
- Tumour related – tumour type; size/tumour burden; number of sites; clinical stage and disease progression (metastases, effusion)
- Previous treatments – eg. chemotherapy (all types or only some)

Current treatment – clinical aspects

- What is the current treatment regime – technique; dose; number of treatments; use of GBAs
- Treatment changes over time - when did Dr Holt start using this current treatment regime (his submission says 1991) – when did Tronado stop being used; since when has radiotherapy not been used (submission says 1991)
- Clarify that claim of effectiveness of microwave therapy is NOT due to hyperthermia
- Clarify claim of effectiveness of GBAs plus microwave being equivalent to x-ray therapy (as per letter 16 Dec)
- Has he sought to publish his outcomes of current treatment regime

Current treatment – technical aspects

- Equipment type – specifications (type, model, manufacturer (who, when, where)
- Are there any QA processes to ensure that the required dose is delivered accurately to the target site?
- What amount of energy is required – how is this measured
- What dose of radiation is delivered – superficial and deep
- Calibration of equipment
- Maintenance (who, regular preventive maintenance, how often)
- Safety protocols
- Do you have the services of a medical physicist who is an expert in the clinical use of 434MHz UHF
- Radiation safety procedures
- What amount of energy (mW/cm2) is required to be delivered to the target site per fraction and the what are the number of fractions used. Is this tumour dependent? How was this determined?
- How do you plan the treatment for superficial or deep tumours? Are there specific delivery procedures?
- Side effects (if any), are they dose dependent?

Treatment outcomes –evidence that treatment works

- How is tumour response measured –what objective criteria are used and recorded; at what time intervals
- How is palliation measured – how is this recorded ; at what time intervals
- What follow-up is recommended to patients; what does it entail; who does this; is this recorded routinely. How is follow-up managed with interstate patients
- Is there comprehensive routine data collection of his patient outcomes
- How are adverse outcomes measured; what objective criteria are used and recorded; at what time intervals
- Would he be willing to engage in a review of a consecutive sample of medical records as outlined in letters to Dr Holt Oct & Dec 2004

Patient issues

- How many new consultations per week, on average – how many of these would be suitable for treatment (treatment rate)
- How many patients receive treatment per week, on average.
- Do patients need to have a personal consultation in every case to assess eligibility
- What information do patients inquiring (by phone or letter)about your treatment receive
- What information do patients who are about to undergo treatment receive
- Is there a standard consent form prior to treatment
- Payment – cost to patient of each treatment – how is reimbursement gained

Gaps in research knowledge

- What are Dr Holt's views on this

APPENDIX 11: MINUTES OF VISIT TO PERTH CLINIC, JANUARY 2005

NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL REVIEW COMMITTEE ON MICROWAVE CANCER THERAPY

MEETING WITH DR HOLT

Saturday 8 January 2005

Issues for Discussion

1. Introduction
2. Inclusion/exclusion criteria
3. Current treatment – clinical aspects
4. Current treatment – technical aspects
5. Treatment outcomes –evidence that treatment works
6. Patient issues
7. Gaps in research knowledge

A delegation from the National Health and Medical Research Council's (NHMRC) Review Committee on Microwave Cancer Therapy meet with Dr Holt on Saturday 8 January 2005 at the Radiowave Therapy Centre, 2nd Floor, 31 Outram Street, West Perth, WA.

The purpose of the meeting was to discuss and clarify a number of issues arising from his submission to the NHMRC, and to provide an opportunity for Dr Holt to discuss the review process with the Review Committee. The meeting took place initially in his board room followed by a tour of the facility. Dr Holt and his team were very open about their treatment and the delegation was able to interview various team members informally and formally separately during the "walk around".

The process took 3½ hrs with an informal morning tea when each patient invited by Dr Holt was asked to speak to the committee about their own situation for 3-4 minutes. The patients attended from many different parts of Australia including NSW and QLD. Dr Holt was elderly but worked full time and was concerned that the potential use of UHF & radiotherapy may be lost as a potential curative treatment of cancer after he retires.

Present at the meeting were:

NHMRC Delegation

Dr Helen Zorbas	Chair – NHMRC Review Committee
A/Prof John Boyages	Member – NHMRC Review Committee
Dr Michael Jefford	Member – NHMRC Review Committee
Mr John Drew	Consulting Radiation Oncology Medical Physicist
Mr Phil Callan	Secretary – NHMRC Review Committee

Radiowave Therapy Centre

Dr John Holt	
Dr Michael Holt	
Mr Robert Fleay	Medical Physicist
Mr William Macham	Service Engineer
Ms Nikki Hillman	Office Manager & PA to Dr Holt
Ms Dawn Hillman	Practice Manager & Senior Nurse
Ms Jenny Pickworth	Legal representation – (identified herself as a member of Dr Holt's Family support)

The meeting also included 12 patients who presented personal accounts of their experience with Dr Holt. The names and treatment details of the patients have been recorded.

1. Introduction

At the commencement of the meeting, Dr Holt was advised that this review resulted from a request from the Minister for Health, The Hon. Tony Abbott MP to the NHMRC to review the therapeutic effectiveness and safety of microwave (UHF radiowave) cancer therapy. In response to the Ministerial request, the NHMRC established the Review Committee on Microwave Cancer Therapy.

Dr Holt was also provided with a copy of the following Terms of Reference for the Review Committee:

> The NHMRC has established the Review Committee on Microwave Cancer Therapy (UHF Radiowave in the range 300 MHz to 300 GHz) which will, having regard to the best available evidence and following consultation with relevant individuals and organisations:
>
> 1. Establish and describe the scientific basis of "microwave" (UHF Radiowave) therapy in the treatment of cancer; and
> 2. Assess the effectiveness and safety of "microwave" (UHF Radiowave) cancer treatments including the use of the Tronado machine; and
> 3. Identify gaps in research knowledge.
>
> The Review Committee will provide an evidence-based report and recommendations to Council by no later than 10 March 2005. Following the conclusion of the review, Council will provide its report to the Minister for Health by March 2005.

Dr Holt questioned the relevance of assessing the safety of UHF cancer therapy, as other cancer therapies are "incredibly unsafe" and a comparison between the UHF and conventional radiation therapy modalities would be more relevant. Dr Holt was advised that the assessment of other cancer treatments was outside the scope of the current review and that the Review Committee has been asked specifically to focus on microwave (UHF radiowave) cancer therapy.

Dr Holt was also advised that this meeting would be used to explore issues that have arisen as a result of the call for submissions undertaken by NHMRC in late 2004. At the conclusion of the consultation, 252 submissions had been received by NHMRC.

Following consideration of the submissions, including the submission from Dr Holt, the Review Committee prepared a list of discussion topics for this meeting. A list of the discussion topics is provided at **Appendix 10** above. The following represents the responses provided by Dr Holt and members of his support party during the meeting on 8 January 2005.

During the meeting, Dr Holt introduced the Review Committee to a number of long term surviving patients who had been treated with UHF therapy, in combination with either external-beam radiotherapy or with GBA. The technique of delivering UHF varied according to the time period of treatment. Patients had been treated for the following conditions.

- Acquired immunodeficiency Syndrome
- Non-Hodgkin's Lymphoma
- Invasive bladder carcinoma and multiple metastasis
- Malignant chordoma of the sacro-coccygeal area
- Mesothelioma
- Myxoid liposarcoma
- Primary oesteogenic carcoma with multiple lung secondaries
- Scleroderma
- Small cell carcinoma of the lung

The Review Committee was provided with a brief synopsis of the patient's condition, treatment and clinical outcome. The Review Committee welcomed the opportunity to discuss the treatment and outcomes with the patients, however, this report will not provide further consideration of these patients due to the lack of complete information. The Review Committee recognised that further examination of these cases might be a valuable part of this assessment and could be incorporated into the later, formal patient record assessment. The Review committee, however, acknowledges that most of these patients received UHF and conventional radiation therapy and attended Dr Holt with heavily pre-treated disease with medical assessments that "nothing further was possible" or that radical surgery was required such as removal of the bladder with associated ostomy bags or removal of a limb.

2. Inclusion/exclusion criteria

Patient related – age; performance status

Dr Holt advised that patients are not excluded due to age. This treatment is suitable for patients of any age, at any stage of disease.

Dr Holt stated that patients typically present with late/end stage cancer, seeking a miracle cure. This must be taken into consideration when comparing the results achieved through this treatment methodology compared with "conventional" therapies, where patients may present with earlier stage disease.

Tumour related – tumour type; size/tumour burden; number of sites; clinical stage and disease progression (metastases, effusion)

Patients are not excluded due to clinical stage or disease progression – Dr Holt believes that glucose blocking analogue (GBA) and Ultra High Frequency Radiowave (UHF) provides effective palliation in 100% of patients.

No disease site is excluded, however primary bowel cancers must be surgically removed prior to commencement of radiowave therapy, as the subsequent regression of the cancer may lead to perforation of the bowel with subsequent peritonitis.

Multiple metastases are not excluded.

Dr Holt advised that with GBA/UHF:

- All tumours <1 – 1.5 cm may result in complete remission
- Tumours <2 cm can be reduced in size with treatment
- Tumour >2 cm are difficult to treat. Dr Holt believes that this is due to a lack of blood flow to the centre of the tumour, and poor delivery of the GBA.
- With UHF and x-ray therapy (as opposed to GBA/UHF), tumours up to 25 cm can be treated (Patient example - Mr Claude Riordan)

Patients with PSA >1000 are excluded.

Previous treatments – eg. chemotherapy (all types or only some)

Previous chemotherapy is not necessarily a contra-indication, however there is a perception in some patients ("a philosophy") that previous adverse experience with chemotherapy may also be experienced with radiowave therapy. Dr Holt advised that this is not the case as the only adverse effect is a general warming. Patients are allowed treatment as outpatients.

Dr Holt advises in his pamphlet Information for you to use as a guide that if a patient has any of the following, that GBA + UHF treatment is unlikely to be of benefit;

- Any individual tumours larger than 2 cm in diameter;
- More than three cycles of chemotherapy;
- Previous cisplatin, oxaliplatin, or carboplatin chemotherapy;
- Patients with Thalassemia are excluded;
- Active disease; and
- Patients with any fluid build up in lungs or abdomen.

[Note: at the meeting on 8 January 2005, Dr Holt advised that pericardial, pleural or abdominal spaces must have fluid drained prior to UHF therapy as it tends to heat fluid which may lead to damage in the area. He also advised that UHF can be given to patients who received chemotherapy no earlier than 3 months before UHF.]

Prof Boyages, a radiation oncologist, confirmed with Dr Holt that UHF is a radiosensitiser and when combined with conventional radiation, doses need to be reduced from 200 cGy per day to 150 cGy and total doses reduced from around 5000-7000 cGy to 3000-3500 cGy. Dr Holt's detailed submission showed multiple cases of advanced tumours in the breast, bladder and limbs or trunk responding to normally low, usually ineffective doses of radiation.

3. Current treatment – clinical aspects

What is the current treatment regimen – technique; dose; number of treatments; use of GBAs

Clinical admission procedure:

- Referral from Doctor essential;
- Patient must provide histological proof of diagnosis;
- Patient records are maintained by the Clinic Staff, and stored on-site for 18 months; and
- Dr Holt is present for all procedures.

Current treatment regime:

- Venous injection of GBA (butterfly clip), on each day of treatment, (PICC line can be used in patients with poor veins).
- One of three GBA is administered,
  - cyclophosphamide (2.5 – 5 mg/day)
  - Cystine disulphide (1 g/day) (sourced from Japan)
  - Penicillamine disulphide (1 mg/day) (sourced from Germany)
- GBA is prepared in-house mixed in saline solution in 1L plastic bags, boiled for 30 minutes prior to local pharmacist loading syringes (e.g. 1 g cystine in a 30 mL syringe).
- Patient rests for 10-20 minutes prior to exposure to UHF to allow GBA to infuse tumour site.
- Patient lies on UHF machine and is passed through the antenna array to identify the point of highest reflectivity of UHF (the centre of the tumour) and is exposed to 20 minutes of 434 +1 mHz (this may be given in two or three sessions, currently patients receive two 10 minute sessions per day).
- Following treatment, patient rests in a recovery area to cool prior to discharge.
- Treatment is daily over 15 working days (three weeks).
- Patients are not referred to x-ray treatment following UHF as it is necessary to receive x-ray treatment 20 minutes post UHF (although Dr Holt mentioned that a second period of peak efficiency occurred 24 hours post UHF exposure).

Treatment changes over time - when did Dr Holt start using this current treatment regime (his submission says 1991) – when did Tronado stop being used; since when has radiotherapy not been used (submission says 1991)

Dr Holt "owned" both Tronado machines. One purchased in partnership with Dr Nelson and installed in private practice. The second funded by Premier Tonkin and allowed to be installed "wherever appropriate". It was decided to install in the Sir Charles Gardiner Hospital. The Tronado machine was last used in 1976.

Radiation therapy last used in 1989 when Dr Holt was excluded from access to X-ray equipment, since then the treatment has been exclusively a combination of GBA + UHF.

Dr Holt advised that:

- For small tumours (tumours<1.5cm diameter) GBA + UHF is effective
- For both small and larger tumours UHF + external beam radiotherapy is effective
- Tri-modality GBA/UHF + external beam radiotherapy is ineffective

There is no difference in treatment with respect to tumour size or location (for example, superficial versus deep tumours).

Clarify that claim of effectiveness of microwave therapy is NOT due to hyperthermia (as per letter of 16 Dec 2004)

Current treatment is not hyperthermia, although a heating effect is caused by the use of UHF.

Clarify claim of effectiveness of GBAs plus microwave being equivalent to x-ray therapy (as per letter 16 Dec)

Dr Holt claimed that GBA + X-ray is more effective than GBA + UHF, however due to his exclusion from X-ray equipment, he has had to refine his cancer treatment regimen to suit the availability of equipment.

Has he sought to publish his outcomes of current treatment regime

Dr Holt has not sought to publish data regarding the effectiveness of treatment utilising the GBA/UHF protocol. He advised that he submitted a paper describing the treatment of patients with bladder cancer treated with UHF in combination with external beam radiotherapy, however the paper was rejected, by a college journal with an accusation of lying.

4. Current treatment – technical aspects

Mr John Drew met with Mr. Robert Fleay, a retired medical physicist and Mr. Bill Machan, a service engineer in the medical imaging field and also an amateur radio enthusiast. Mr. Fleay provides informal advice to Dr. Holt but is not a paid consultant. Mr. Machan services the equipment as required.

Equipment type – specifications (type, model, manufacturer (who, when, where)

The original "Tronado" (12 x 200 kW generators) was bought during the seventies. It was replaced by a unit built by Huttinger (4 x 5 kW generators) probably in the early eighties and was taken out of service in 1989.

In 1989 Dr. Holt and Mr Machan built their own unit consisting of 4 generators of 1 kW power each which were sourced from the United States. The generators are actually run at 0.6kW power. This unit is still in operation. The unit started with the original antenna from the Tronado but has been replaced with a local design which reduced heating on the body surface.

Are there any QA processes to ensure that the required dose is delivered accurately to the target site?

There are no QA processes. This is in part probably due to the fact that the actual dose of UHF power required is not known. Experimentally, Dr. Holt has determined that he obtains the expected response with a standard treatment regimen. He is not aware of

the minimum dose (ie the dose which would not produce the desired response) or the maximum (which also may create saturation problems or unwanted side effects). He uses clinical indicators to guide him in his practice (insufficient response may mean the power is too low, too much patient heating may mean that the power is too high).

In this review it is impossible to determine whether the treatment is optimised. However, it is a good principle to know how much radiation is being delivered to each patient and not rely upon clinical indicators.

Recommendation:
A full QA process is established including regular frequency and power calibrations. This process and all the results must be fully documented.

What amount of energy is required – how is this measured

Dr. Holt delivers a standard treatment of 20 minutes (which may be broken into several periods with short gaps of a few minutes if the patient is feeling discomfort) of UHF power set at 2.4 kW (0.6 kW per generator). The power setting is measured by a Bird Watt Reflectometer which is built into each generator (see above recommendation).

What dose of radiation is delivered – superficial and deep

See above question for the first part of the question. It is claimed that the distribution of power through the irradiated volume is reasonably uniform and so there is no need to consider the location of the target.

Calibration of equipment

A Bird Watt Reflectometer (which measures power) is built into each generator. An independent unit is used as a check. A water calorimeter exists but it was unclear how often this was used.

A Tektronics Spectrum Analyser is used to check the frequency (434 MHz) of the system. An independent check is performed using some amateur radio equipment owned by Mr. Machan.

As 434 MHz is the same frequency used by a local taxi company, the "Post-Office" undertakes an annual check of the equipment.

Maintenance (who, regular preventive maintenance, how often)

Dr. Holt performs all the front line service (ie the immediate problem solving). When this does not fix the problem, Mr. Machan does the main maintenance. He is required, on average, every 4 to 6 months.

There is no routine preventative maintenance. There are no written protocols for service.

Recommendation:
A routine preventative maintenance program be put in place and written service protocols be developed.

Do you have the services of a medical physicist who is an expert in the clinical use of 434MHz UHF

Mr. Fleay is a consultant medical physicist. It is a procedure which appears to not require a lot of physics expertise.

Radiation safety procedures

The treatment room is contained within a Faraday cage (this prevents any leakage of UHF radiation outside the cage). It was checked with a sensitive UHF meter at the time and is checked annually by the telecommunications authority (the frequency used is apparently within the radio communications band width used by the local taxi cabs). Visual inspections of the door seals is carried out by Mr. Machan whenever he is doing service on the unit.

There is no door interlock into the treatment room.

Recommendation:
A door interlock be installed to provide a multi layer safety system.

In this case it is assumed that, while the UHF radiation is on the operator is always present to stop other persons from entering the treatment room and that the operator will never enter the treatment room. In principle this is probably always the case, but one layer of protection like this fails standard safety procedures and does not provide the necessary "defence in depth".

There are no written safety procedures.

Recommendation:
Written safety procedures be developed and always available. In particular, a copy must be located at the control desk.

There are no warning signs and no visible warning light when UHF radiation is on.

Recommendation:
UHF warning signs be placed near the unit and a visible warning light be installed near the door to the treatment room.

What amount of energy (mW/cm^2) is required to be delivered to the target site per fraction and what are the number of fractions used. Is this tumour dependent? How was this determined?

A claimed 0.6 kW is delivered per fraction for 15 fractions. It is not tumour dependent. The number of fractions was determined by observation of the tumour response. Dr Holt presented data on one patient where tumour growth is accelerated at higher frequencies.

How do you plan the treatment for superficial or deep tumours? Are there specific delivery procedures?

See earlier questions.

Side effects (if any), are they dose dependent?

This was covered in other sections.

5. Treatment outcomes –evidence that treatment works

How is tumour response measured –what objective criteria are used and recorded; at what time intervals

Due to the relatively short course of treatment, and that many of the patients travel from the Eastern States, Dr Holt dose not measure tumour response. This follow-up is managed by referring physicians, though Dr Holt often performs tumour marker assessments during / after treatment.

How is palliation measured – how is this recorded ; at what time intervals

Dr Holt advised that there are no records kept on palliation, however, referring physician are requested to undertake follow-up assessment of patients.

What follow-up is recommended to patients; what does it entail; who does this; is this recorded routinely. How is follow-up managed with interstate patients

Following treatment, the patients referring physicians are provided with a letter prepared by Dr Holt outlining the appropriate follow-up scans and specific cancer markers (tumour markers). Further follow-up is conducted by the referring physician.

Is there comprehensive routine data collection of his patient outcomes

In order for Dr Holt to accurately assess the patient on the day of consultation, the following information is required. This information is taken from the support group website and was verified by Dr Holt:

- A brief summary (not more than two pages) detailing diagnosis and staging (presence / site of secondary tumours), and listing all treatments undertaken, and including:
  - The dates of courses of chemotherapy undertaken including drugs given;
  - The dates of courses of radiotherapy given and to which areas of the body;
  - The names of surgical procedures that have been undertaken, and the date performed;
  - Any hormones taken including the daily dose;
  - Any antioxidants being taken;
  - If mistletoe extract or laetrile or similar substances are being taken;
  - Whether a smoker or not.
- A copy of the biopsy report from the original diagnosis.
- Copies of surgical reports.
- Copies of any recent blood tests (these test must be less than 4 weeks old).
- Copies of any recent cancer antigen blood tests (these tests must be less than 4 weeks old).
- X-rays, MRIs, CT scans, bone scans, PET scans or any other scans (including reports) less than four weeks old.
- Scans/x-rays immediately prior to latest scan for comparison purposes.
- Referral from GP.

Records were adequately bound and kept in a separate lockable office with all test results and correspondence stored in reverse chronological order.

How are adverse outcomes measured; what objective criteria are used and recorded; at what time intervals

Dr Holt advised that the only adverse outcome from GBA + UHF is a general warming as a result of exposure to UHF radiowaves. Patients are rested following treatment, and provided with electric fans to assist cooling, prior to being released for the day.

The only apparent absolute contraindication to therapy is thalassemia. One patient with thalassemia suffered severe haemolysis following treatment with UHF.

Would he be willing to engage in a review of a consecutive sample of medical records as outlined in letters to Dr Holt Oct & Dec 2004

Dr Holt agreed to the Review Committee's request to access the complete medical records for a consecutive series of 100 patients treated during 2001/02 provided:

- The review Committee provides the resources to access and examine those records and undertakes to maintain the contents of the records confidentially and only to report in connection with those records on a patient de-identifiable basis; and
- The Review Committee simultaneously accesses and examines the complete medical records for:
  - A consecutive series of 100 patients treated by Dr Holt at his former private practice using dual modalities of UHF and Radiation
  - Dr Holt's selection of his best clinical outcomes; and
  - A series of 39 bladder cancer patients referred to by Dr Holt during the meeting on 8 January 2005.

The Review Committee accepted Dr Holt's request to assess further study groups.

6. Patient issues

How many new consultations per week, on average – how many of these would be suitable for treatment (treatment rate)

On average, the clinic normally receives referrals for 6 or 7 new patients per week (approximately 300-350 new patients per year). Following recent media attention, this number has increased substantially and his waiting time for consultation is now 3-4 months.

Not all new patients are treated. It is estimated that approximately 50% fit the criteria outlined above, and are considered suitable for treatment.

How many patients receive treatment per week, on average.

Dr Holt advised that the absolute maximum capacity for the equipment is 15 patients per day (a typical treatment taking 30 minutes). Ideally, the daily capacity of the equipment would be limited to 10-12 patients.

Do patients need to have a personal consultation in every case to assess eligibility

Dr Holt advised that he required a personal consultation with every patient prior to acceptance for treatment. It is important to personally examine each patient and to assess/review medical records, including X-rays, in person.

What information do patients inquiring (by phone or letter) about your treatment receive

Patients receive the following two documents prepared by Dr Holt (see attachment 2):

- Radiowave therapy – A simple explanation: Treating Cancer by Ultra High Frequency Radiowaves;
- Checklist

These sheets provide the same information as that available on the patient support website (accessed January 2005).

What information do patients who are about to undergo treatment receive

In addition to the information provided above, Dr Holt advised that the treatment regimen is explained to each patient. Dr Holt indicated that he does not promise to cure patients.

Is there a standard consent form prior to treatment

Patients are not asked to sign consent forms. Dr Holt does not canvas patients. The patients come to his offices through their own volition, and consequently consent is implied.

Payment – cost to patient of each treatment – how is reimbursement gained

The three week course of treatment costs $6550, with a Medicare rebate (at 85% of the scheduled fee) or $2251.60 (as at 1 November 2004). The difference of $4289.40 must be paid during the first week of treatment.

Dr Holt and Ms Nikki Hillman advised that the Radiowave Therapy Centre uses the following MBS item numbers:

- 104
- 105
- 105-UF (This was approved by Medicare in 1976)
- 13915

7. Gaps in research knowledge

Dr Holt advised that he has done everything to prove this therapy works and that research for the last 40 years has been incorrectly targeted. The effectiveness and safety of conventional chemotherapy should be further researched.

Dr Holt advised that animal studies are not effective unless spontaneous tumours are studied. He argues that tumour cell lines are an inappropriate model. Similarly, in vitro investigations do not show a response.

Dr Michael Holt suggested that a prospective patient trial focussing on patients with advanced pancreatic cancer might be worth pursuing given the lack of effective therapies and the poor natural history of this disease. As well, a study of UHF, ideally in combination with radiotherapy, in patients with head and neck cancers, and as suggested in the 1970s, should be considered.

Some suggested research areas if it is felt that any further investigation is warranted. These topics were suggested by Mr. Fleay and Mr. Machan during discussions with Mr. Drew. Dr. Holt agreed with these suggestions during the final discussions:

- Investigate the significance of reflected power.
- Investigate the significance of the observed fluorescence (apparent in the presence of a tumour – can it be used as a marker?).
- The optimum frequency (not necessarily 434 MHz).
- The optimum power required (not necessarily 2.4 kW per fraction)
- The optimum number of fractions
- The distribution of power through a human body at different parts of the body

APPENDIX 12: DR HOLT'S RESPONSE TO DRAFT INTERIM REPORT

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4 March 2004

Dr Helen Zorbas
Chair
NHMRC Review Committee on Microwave Cancer Therapy,
MDP100
GPO Box 9848,
CANBERRA ACT 2600
Via Fax: 02 6289 9197

Dear Dr Zorbas

Draft Interim Report entitled "Review of Use of Microwave Therapy for the Treatment of Patients with Cancer, March 2005" ("Draft Report").

Thank-you for providing Dr Holt with a copy of the Draft Report.

Dr Holt has instructed me to respond to you on his behalf to request that the following matters be expressly dealt with in the final Interim Report and that various matters in the Draft Report be clarified or modified, as relevant.

1 General Comments

Before dealing with the detail it is appropriate to set out some general but very fundamental issues that Dr Holt has with the Draft Report and the Review Committee's interpretation of its Terms of Reference.

1.1 UHF and UHF/Radiotherapy –Terms of Reference.

(a) Given the fact;

- public money is being used by the NHMRC to prepare the Report;

- the NHMRC is aware Dr Holt is in his eightieth year and is to retire from practice in June this year in circumstances where no successor proposes to provide the current UHF treatment or the UHF/Radiotherapy treatment formerly provided by Dr Holt; and

- Dr Holt advises he is currently being forced to treat patients less than optimally by not providing them with UHF/Radiotherapy (because of lack of access to radiation equipment);

it was our clear understanding (as recorded in the taped record of interview with Dr Holt), that the focus of the Review Committee would be a pragmatic, sensible one, namely an examination of the benefits of UHF/Radiation as well as UHF as a single modality.

This understanding derived from discussions at the January meeting (refer to the typed record of the final 14 minutes of the record of interview with Dr Holt appended as Annexure A) and the agreement on the part of the Review Committee to examine the files of 100 patients treated with UHF as well as 100 patients treated with UHF/Radiotherapy.

(b) At page 81 of the Draft Report it states the Review Committee proposes to review, "a consecutive series of patients who have been treated with the current-available treatment regime of microwave therapy and "glucose blocking agents".

No mention is made of the counter-balancing review of 100 patients treated with UHF and Radiotherapy.

An accurate record of what was agreed is set out in my email of 11 January (copy attached as Annexure B));

(c) It is extraordinary, having regard to the matters outlined in (a) and (b), that the Review Committee has focused exclusively on the validity of the UHF modality currently applied by Dr Holt, as compared to the superior dual modality promoted by Dr Holt.

(d) The NHMRC's Terms of Reference do not restrict the NHMRC from examining the benefits of UHF/Radiotherapy.

(e) If it had been apparent (prior to provision of the Draft Report) that the Review Committee considered it was limited to strictly interpreting the Terms of Reference to,

"the (UHF) technology as it is currently administered in Australia",

a protest would have been lodged with the Minister and the NHMRC early in the process (just as a protest was lodged in connection with the incorrect reference to the Tronado machine and to "microwave therapy" as compared to "UHF").

(f) Dr Holt has been and is keen to remain co-operative with the Review Committee. He is anxious to ensure that valuable, effective treatment options are revived/retained in Australia and made available for the benefit of cancer patients after his retirement.

(g) Dr Holt agrees that further research in connection with UHF/Radiation and UHF treatment is desirable. Dr Holt has practised by himself for the last 14 years, endeavouring to meet an ever increasing demand. He has not had the time available to prove-up the treatments to the extent he would have given a lesser workload.

However Dr Holt is in no doubt, given his experience of treating some 35,000 cancer patients in WA since 1961 (in excess of 5000 with the dual modality (1973 to 1991) and 1500 with glucose blocking agents and UHF only (since 1991) that this latter modality is of significant curative or therapeutic benefit (at least equal to that of conventional treatments and without the adverse side-effects) to a large cohort of cancer sufferers.

(h) Put simply it is a waste of time and public money for the Review Committee to confine its brief to UHF only and to construe its Terms of Reference narrowly. Given the small window of opportunity (to June 2005 when Dr Holt retires) and the considerable cost of conducting the review it is plain, old fashioned common sense to review the two treatment regimes simultaneously.

1.2 The Science of Dr Holt's UHF Treatment Regime

(a) Dr Holt considers the Draft Report is inaccurate and misleading in its description of the science and mathematics of the UHF treatment he currently provides.

(b) It appears this inaccuracy largely derives from;

- lack of adequate distinction in the Draft Report between UHF and microwave ("Microwave" is the generic descriptor for 300 MHz to 3,000 GHz radiofrequency "UHF" is the descriptor given to the lowest band (300 MHz to 3 GHz) within the broad microwave range. Dr Holt applies 433-434 MHz (self-evidently within the lower range of the lowest UHF sub-band)); and

- a resultant mis-understanding that Dr Holt's treatment involves hyperthermia.

(c) At pages 14 and 15 of the Draft Report a scientific view is proffered to the extent that radiation induced hyperthermia preferentially damages cancerous cell's DNA. The Draft Report then states,

> "non-ionising electromagnetic waves (ie microwave therapy) do have the potential to heat human issue".

In the last paragraph on page 14 the Draft Report provides,

> "The overwhelming majority of microwave therapy researchers believe that any therapeutic effect of microwave therapy is related to heating of the tumour cell, either directly or indirectly"

Dr Holt maintains that this has never been proven. Heating is not the basis for the therapeutic effect of Dr Holt's treatment.

Dr Holt's treatment of UHF (433-434 MHz) comprising 20 minutes exposure at 2,400 watts, results in a minor, insignificant increase in body temperature (0.4 – 0.6 Degrees C). Hyperthermia involves increasing the body temperature up to the limit of human endurance (41.8 degrees C).

Additionally and significantly Dr Holt's treatment does not work by reference to its effect on DNA.

Rather the application of 433-434 MHz UHF results in an increase in the cancer cell growth rate (by a factor of up to 10 times the normal growth rate). This is attributable to the fact that cancer cells conduct electricity, so absorb energy at a greater rate than

healthy cells, in turn growing faster. This accelerated growth rate is then destroyed by preventing the cancer cell using glucose from the blood as its energy source or by treating with X ray therapy after UHF.

The non-thermal application of 433/434 MHz radiosensitises cancer by any factor from 100 to 10,000 times. (Dr Holt advises the cell kill without the application UHF of say 150-160 rads may be 1,000 cells, 20 minutes after UHF this dose will kill 100,000 to 10,000,000 cancer cells. This effect will occur with a cancer temperature elevation less than 0.5 degrees C).

Despite the fact that Dr Holt's treatment does not rely on heating cancer tumours, numerous references appear in the Draft Report hypothesising that it is not possible to determine whether the lack of "convincing and consistent evidence" is due to ..."a failure in the practice of microwave therapy due to inability to adequately heat the tumour".

1.3 Conflicts and Due Process

I refer you to my email of 11 January 2005 in which I sought advice that Dr Van Hazel (the WA member of the Review Committee, an oncologist and the principal of a competitor business (Perth Oncology) to Dr Holt's practice) had assured the Review Committee that he did not have a conflict in this matter.

I have never had a response to this issue.

I note with some alarm that Dr Van Hazel is recorded as having resigned from the Review Committee in January 2005 (refer Annexure 3). Could you please explain the basis for Dr Van Hazel's resignation.

Additionally, and with a greater degree of alarm, I note from Appendix 5 that the list of organisations and individuals invited by letter to make submissions to the Review Committee included Dr Van Hazel (of Perth Oncology) and Michael Jefford.

Did Dr Van Hazel and Mr Jefford make submissions to the Review Committee?

If so please provide a copy of the submissions as soon as possible (obviously prior to the provision of the Interim Report to the Minister).

It is essential that we have the opportunity to assess the input and influence of Dr Van Hazel (and potentially other members of the Review Committee) in this process so far.

2 Specific Issues

2.1 Availability of Dual Modalities – UHF and Radiation

(a) On numerous occasions the Draft Report makes mention of the fact that Dr Holt does not administer UHF in conjunction with Radiotherapy (see paragraph 2 page 7; paragraph 3, page 11; paragraph 1 page12; paragraph 1, page 16; paragraph 2, page 27 etc).

(b) What the Draft Report does not record is the fact that this is not through choice.

The failure of the Review Committee to recognise this fact is disappointing. The Review Committee (Assoc. Professor John Boyages) specifically undertook to ensure that the Draft Report would "acknowledge" ... that Dr Holt's current treatment "is an alternative method which I am using because I have been excluded from conventional. Therefore in my opinion if you want to do any research, you should not do it on glucose blocking agents" (refer 3rd last page of transcript appended as Annexure A).

(c) Ideally Dr Holt would apply the dual modalities to optimise treatment results for cancer patients. However this is not possible as it is not within Dr Holt's financial means to acquire the equipment necessary for radiotherapy treatment. Dr Holt has sought to work in tandem with local Radiotherapists but the Radiotherapists he has approached have not been amenable to the idea. (The UHF and Radiotherapy treatment requires Radiotherapy immediately following UHF treatment, necessitating co-operation of local radiolotherapists). The method can only be practiced by having adjoining UHF and x-ray therapy treatment rooms.

(d) Dr Holt has advised the NHMRC on a number of occasions that it is his view that the optimal treatment regime is the dual modalities (refer the taped record of interview with Dr Holt). Consistent with this, in my email of 11 January 2005, I recorded the fact that Dr Holt agreed to the Review Committee examining 100 consecutive patient files for the 2000-2001 year Provided they also examined,

> "a consecutive series of 100 patients treated by Dr Holt at his former practice using the dual modalities of UHF and Radiation".

2.2 Bias

The Draft Report demonstrates an unfair bias against Dr Holt.

To illustrate this bias;

- As mentioned in 2.1, no mention is made of the fact that Dr Holt does not use UHF in conjunction with Radiotherapy because Radiotherapy is not available to him. An impression is created that Dr Holt does not provide Radiation by choice.

- The very first paragraph of Chapter 1 recants the negative findings of the 1974 NHMRC review of Tronado treatment, without qualification. The prior review is unrelated to this review, is irrelevant and reference to it is unwarranted and highly prejudicial.

- On several occasions in the Draft Report (see pages 9 and 18) a statement is made to the effect;

  " In particular it was hoped that submissions and personal testimonies would be received from patients, their carers and medical practitioners, and that these would provide additional clinical efficacy and safety data for consideration by the Review Committee".

  The Draft Report suggests that such submissions were not received or, to the extent they were received, they were not supportive of Dr Holt's treatment.

No direct comment is made in the Draft Report as to whether the overwhelming tenor of patient, carer and medical practitioner submissions was positive or negative. At page 78 an oblique statement is made to the effect,

"Whilst difficult to interpret in isolation, and subject to all the caveats outlined above, such information (ie information provided by patient submissions) may suggest a treatment effect that then warrants further investigation using research methodology where biases are eliminated".

- At the top of page 12, when describing the administration of glucose blocking agents (GBA's) the Draft Report states,

"NB. Doses are not titrated to body weight".

The alarmist note in the Draft Report should either be deleted or qualified by reference to the fact that the cyclosphosphamide component of the GBA is approximately $1/10^{th}$ of "safe" levels used in other conventional therapies. Dr Holt advises he uses 2.5-5 mg as this dosage avoids epilation (hair loss).

The other components of GBA are benign because they are all present in living human bodies. (Dr Holt advises that cyclophosphamide is the only cytotoxic compound which inhibits anaerobic glycolysis (the energy source of cancer (glucose burnt without oxygen) – Reference K Wight, D Burk, M Woods, L Lane. National Cancer Institute Bethesda, MA, USA. "Inhibitory action of cyclophosphamide in vitro and in vivo on tumour respiration and glycolysis." Proceedings of the American Association Cancer Research 1960 (3) p162 et seq).

- In chapter 3 under the heading "Regulatory and Reimbursement Status in Australia" two statements are made relevant to TGA and HIC issues that are prejudicial.

Firstly the proposition is advanced that microwave equipment used in a therapeutic context is regulated as a medical device by the TGA under various Commonwealth legislation. The Draft Report notes Dr Holt has not notified the TGA of his UHF equipment or of any medical trials involving the device. The suggestion is that Dr Holt is operating unlawfully. Given the very low radiofrequency applied by Dr Holt he was unaware the UHF machine that he designed and built had to be registered with the TGA. He will rectify this immediately. Hopefully by the time the Draft Report is finalised this matter will be resolved.
It should be noted and recorded that Dr Holt's UHF machine is checked annually for radiowave compliance.

It should also be noted that Dr Holt is not conducting clinical trials using the UHF machine.

Secondly a statement is made that "the microwave procedure itself is currently not listed on the Commonwealth of Australia Medicare Benefits Schedule (MBS) for public re-imbursement".

To be accurate and informative the Draft Report should state that of the cost ($6,550.00);

- $2,251.60 is rebatable (for initial and repeat consultations and for cytotoxic chemotherapy); and

- of the balance $4,298.40 up to 80% may be rebated under the new "safety net" arrangements.

The HIC is well aware of Dr Holt's treatment and has paid rebates for it for many years.

- In Part 1 of Chapter 4 under the heading "Mortality" a reference is made to 5 deaths, 3 involving patients of Dr Holt's who had been receiving UHF/Radiotherapy.

These deaths are not put in a fair context, either in the context of the total number of patients treated by Dr Holt (11,500 or more) or the context of deaths occasioned by conventional cancer therapies. It is noted at page 62 of the Draft Report that "Mortality associated with microwave therapy should be considered in the context of the disease prognosis and the mortality associated with other treatment options", however no information is provided to inform the conclusion that mortality from UHF is insignificant when compared to conventional cancer therapies.

- Additionally, under the heading "Safety Summary" (Part 1 of Chapter 4, page 74) broad statements are made that largely relate to the application of microwave intended to induce hyperthermia, as distinct from UHF. No distinction is drawn between treatments involving hyperthermia and those that don't. Additionally and most relevantly no mention is made in the Draft Report about the safety warnings and disclosures provided to patients of Dr Holt. At page 75 the Draft Report states,

  "Safety concerns are not insignificant and should be clearly articulated to patients".

  Appendix 8 to the Draft Report sets out a copy of the information provided by Dr Holt to patients but oddly no mention is made of this fact in the body of the Draft Report.

- At pages 9 and 18 the Draft Report states the Review Committee had hoped to receive submissions from Patients that they were informed the safety issue. It is noted that the NHMRC Invitation to Make Submissions (refer Appendix 4 of the Draft Report) did not mention or require comment or input on this issue. Patients were simply unaware that the Review Committee required input on this topic.

2.3.1 Accuracy Issues re Description of UHF Treatment

In several sections in the Draft Report it states that there is a waiting time of 30 minutes after the administration of the GBA's to the provision of UHF. This is not correct. The optimal timing is an interval of between 10 – 20 minutes or shorter, when possible.

2.3.2 Patent/Confidentiality Issues

Dr Holt has patented the GBA/UHF treatment in Australia, England, New Zealand and Europe.

I attach a Schedule of Patent particulars as Annexure C.

As you will appreciate it is not appropriate for the Report to recite the name and amount of the GBA ingredients.

Please delete this part of the Draft Report.

Additionally could you please advise the names of the principals of Health Technology Analysts Pty Ltd and the names of the key researchers who carried out the literature search.

As you will appreciate, given the history of Dr Holt's relationship with the "traditional" oncology sector in Australia it is important that Dr Holt is satisfied he is being reviewed impartially.

2.4 The Non-Referral/Non-Disclosure Issue

In 2.4 I refer obliquely to the unhappy relationship between Dr Holt and the oncology community.

I note the Draft Report records 77 of 293 submissions were assessed to be irrelevant on the basis they either requested information concerning Dr Holt's treatment or his contact details.

This speaks loudly of the tacit collusion within traditional medical ranks to keep Dr Holt's treatment and successes under wraps. It is unfortunate that the Australian community has to rely on a current affairs program aired on television to learn about the UHF therapy provided by Dr Holt.

This makes it all the more critical that the final Report and Report are accurate, fair and comprehensive, addressing UHF and UHF/Radiotherapy.

3 Executive Summary

To ensure procedural fairness to Dr Holt could you please provide him with a copy of the executive summary a reasonable time prior to provision of the final form Interim Report to the Minister.

I assume the Draft Report has been provided minus a draft executive summary in order to enable the Review Committee to factor in Dr Holt's comments on the balance of the Draft Report.

4 Dr Holt's Preparedness to Assist /Co-operate with Clinical Trials

As mentioned at the outset Dr Holt will retire from practice in June this year.

He has instructed me to advise the Review Committee that he is prepared to make his UHF machine available for use in clinical trials if that is a Report Recommendation.

Alternatively he is happy to assist in locating and procuring a state of the art UHF machine for use in such trials.

5 Concluding Comments

I trust the Draft Report is revised to take account of the various matters raised in this letter.

I am providing a copy of this letter under cover of a short enclosure letter to the Honourable Tony Abbott, Minister for Health and Ageing. The intention is not to embarrass the NHMRC or the Review Committee, rather to alert the Minister to the fundamental, threshold issues outlined in 1 above that require Ministerial guidance prior to finalisation of the Interim Report.

On behalf of Dr Holt, thank-you for the opportunity to make a submission on the Draft Report.

Yours faithfully

J Pickworth

cc The Honourable Tony Abbott
Minister for Health and Ageing

Phil Callan
A/g Director
Health Advisory Section
NHMRC

Annexure A

TRANSCRIPT FROM NHMRC MEETING 8 JANUARY 2005

JENNY PICKWORTH
Helen can I suggest, given that timing is tight and resources, presumably, are fairly limited, having listened to all of this, it seems to me is it worthwhile spending finite resources examining 100 cases or files of John's using his limited treatment as distinct from prioritising the examination of the 100 cases that are kept at his old practise? It seems to me – you know – that should be the priority. Looking at the, quite frankly the treatment that John recommends but isn't able because of his circumstances, to provide.

HELEN ZORBAS
That causes me a little bit of anxiety actually because we've got to – you know, 300 patients a year coming here receiving a treatment...

JENNY PICKWORTH
Yep. Yes.

HELEN ZORBAS
....that I think we also need to investigate.

JENNY PICKWORTH
Ok

HELEN ZORBAS
I think that is most important and I have no problem with investigating the preferred treatment as well....

JENNY PICKWORTH
Alright. Yes.

HELEN ZORBAS
But I think we have a case where a certain number of people are coming here on the premise of the effectiveness and safety of the treatment and we need to investigate that.

JENNY PICKWORTH
Although I suppose where I'm coming from is ...look, quite frankly John might have 6 months of working life left. So my concern is, you know, the future viability and so where do we direct and prioritise our resources and I must admit I think we are looking at somebody else – a new John Holt – picking this up and running with it. And that's why I'm talking about prioritising what John himself recommends as the optimal treatment as distinct from perhaps spending a lot of time examining whether, you know, we should be endorsing John continually??? limited??

HELEN ZORBAS
I think there is a couple of questions there. We have to look at the past. We're committed to doing that.

JENNY PICKWORTH
But radiotherapy has moved on a hell of a long way since then as well. So I don't know that you could necessarily transpose those results to today.

HELEN ZORBAS
Ok.

JENNY PICKWORTH
So I think we'd have to be very careful about the interpretation of the findings and today this is what we've got to look at.

ASSOC. PROF JOHN BOYAGES
But I guess, you know, as a concurrent process – I'm just clearing it up in my head – it does worry me - you know I guess all of you are worried about how many years have we got left, you know. We've got all these years of research, you know, we haven't got protocols documented well. We haven't – you know, can you have a writing process that says in the ideal world this is how I would do it? You know, if I was to set up a department, lets say where I work at the North West of Sydney, how would you do it. How would you set it up? How much space do you need and where – you know, where does the room have to be situated, next to a bunker, close to a bunker? It doesn't look that complicated, a bed bay and a room but you know, how would we create that? If we gave you a million bucks to create another one, how would you do it?

BILL MACHAM
I've done some work on that.

ASSOC. PROF JOHN BOYAGES
Have you?

BILL MACHAM
Yes. You'd have 6 or ---MEV & LINACS In the back room, in the bunker and 2 UHF therapy rooms or more down below, or next to it, adjacent...

ASSOC. PROF JOHN BOYAGES
Allocated. Yep.

BILL MACHAM
...and it's a very simple thing.

ASSOC. PROF JOHN BOYAGES
Where would you get the equipment from?

BILL MACHAM
I've already researched this. There is an Italian manufacturer and some in Germany. There is digital technology upon us now, the equipment we have at the moment is valve final amplifiers and there are digital ones around and you can do meticulous control of the output of your transmitter. You can phase it,

HELEN ZORBAS
But I'm looking at recent cases too, that's the reason.

DR MICHAEL HOLT
Yeah I know, but what – as I say my submission was to try and just catch your interest to such that someone can research it and say there's got to be an explanation for this and that's what I think we really have to do.

HELEN ZORBAS
So what your saying is not a patient trial?

DR MICHAEL HOLT
Well no, a patient trial – a prospective patient trial now...

HELEN ZORBAS
Yes

DR MICHAEL HOLT
...and if a report comes out that's looking at 100 consecutive patients and they all die, and everyone says well this is bloody useless then I think we've done my father a great dis-service and that's my worry. Because that's how committees work.

HELEN ZORBAS
But with due respect, how would you establish the case for conducting a trial otherwise.

DR MICHAEL HOLT
Well as I say, take a tumour like the pancreas – it's universally fatal.

ASSOC. PROF JOHN BOYAGES
But I guess what we're thinking is okay, lets say we've got 200 cases – what I'm hearing is it will be - particularly the radiotherapy group – there will be, you know, some good responses there and I'm getting the sense that you are getting phone calls of benefit. If we do 100 consecutive cases and there is no response, I don't think you – do you doubt that there will be – I mean your gut feeling is that there would be some responses in 100 cases where they had ...

DR MICHAEL HOLT
Well there should be sure, but as I say, the difficulty is – I mean if you looked at 100 sequential cases of say, an oncologist, you might end up with 100 dreadful results and if you put the same – it gets back to what Jenny was asking earlier about the parameters – if you compared say, this to chemotherapy treatment, if you had 100 sequential chemotherapy patients you'll have some that died of cardiac failure, you'll have some that died of respiratory fibrosis, you'll have some that died of renal failure, you'll have some that have nerve palsys, you'll have open wounds with fungal infections that may kill them and I worry, as I say, that we end up with a report that killed

us 30 years ago. And I remember those times as a second year medical student when the scales opened my eyes and I realised that doctors weren't a band of brothers pushing together against this disease. When your father is accused of witchcraft on the telephone when you're trying to have your evening meal its hard and if that happens again then it's a tragedy.

HELEN ZORBAS
I want to, sort of, re-iterate that we are trying to find the most objective way of going forward that will meet the criticism perhaps that may be levelled at us in our work and you in your work. I mean, we need to find a way that is going to be mutually agreeable and that is transparent. I think that's most important.

JENNY PICKWORTH
Look, from what I am hearing – detecting there, will be appropriate balance – put 100 cases with the dual modality, 100 with the single modality, you examine the 39 – I can't remember what sort of cancers they were ....

DR MICHAEL HOLT
Bladder.

JENNY PICKWORTH
...bladder and you know you have the benefit of the 15 testimonials of those, quite frankly, spectacular results. You are seeing a balance. What I'm also hearing is that in real terms, you won't have time to have analysed and collated and concluded the clinical prior to the submission of your report.

HELEN ZORBAS
No. No way.

JENNY PICKWORTH
So I see that as a positive in that it is a staggered approach and I think that is extremely good. It means it will be slow and thorough and considered and I think if John is confident that that is going to be the approach – very much one of balance and thorough consideration, we're not going to see.....

HELEN ZORBAS
We have nothing to gain by not taking that approach.

DR MICHAEL HOLT
Thank you.

JENNY PICKWORTH
John?

DR JOHN HOLT
Fine.

JENNY PICKWORTH
So on that basis then John I think, is agreeable to the 100 and you're provided with the balance of the 39...

ASSOC. PROF JOHN BOYAGES
Just with Michael's point about the random – consecutive patients. Are you able to extract from your records of 100 bladder cases for example? Is that possible?

DR JOHN HOLT
No...

NIKKI HILLMAN
I doubt we'd have that many.

DR JOHN HOLT
...no I haven't got that many.

ASSOC. PROF JOHN BOYAGES
Right. I presumed because a lot of our cases are now bigger than the threshold.

DR JOHN HOLT
When I was using x-ray therapy in the Institute of Radiotherapy we did an awful lot.

ASSOC. PROF JOHN BOYAGES
You couldn't find 30 bladders here and 30 bladders there? No.

NIKKI HILLMAN
Maybe.

Lots of talking amongst each other. Voices overlapping – indiscernible.

DR JOHN HOLT
As I said to ... this is an alternative method which I am using because I have been excluded from conventional. Therefore in my opinion if you want to do any research, you should not do it on glucose blocking agents.

ASSOC. PROF JOHN BOYAGES
We'll acknowledge that in our report.

JENNY PICKWORTH ?
But you still acknowledge that it's effective.

DR JOHN HOLT
Well its effective when nothing else can be done in some cases. It's not universally effective, don't get me wrong. But when you're using x-ray therapy with the sensitisation beforehand, it can kill 10,000 more cancer cells for the same dose of x-rays. You've got a tool which is world-beating.

JENNY PICKWORTH
Could I also ask the Committee that perhaps they might consider it appropriate to make a comment on the state of the patient on presentation to John. In other words, I think that that could be quite a distinctive marker between the state of patient on presentation to traditional oncologist/ radiotherapist and perhaps that might be something appropriate for comment. In other words, these people are coming here at last dire stage.

HELEN ZORBAS
That would be part of the ....

MALE
That's fair ... I think – I hope that will provide Michael with some reassurance as well that 100 patients that have no other treatment approaches left, even if 5 per cent of them had improvement in their quality of life for 2 months, that's still a significant benefit. You know, when there's no other treatment options. We're not looking for 100 cures.

JENNY PICKWORTH
Because I think that is a very significant aspect of John's practice.

ASSOC. PROF JOHN BOYAGES
Its end of the line stuff.

MALE
And that will clearly come through from the audit of 100 patients.

DR JOHN HOLT
Fair enough.

JENNY PICKWORTH
All right?

DR JOHN HOLT
Yep, sure.

JENNY PICKWORTH
I hope you're satisfied.

HELEN ZORBAS
We really again want to say thank you for the opportunity of coming personally to meet with you and your team and to view your premises and appreciate you for making that offer.

DR JOHN HOLT
Thank you all for coming. I appreciate it.

MALE
Thank you.

you can measure many, many, many parameters instantaneously and log it. And we were talking about this fluorescence and the collected power from a tumour. You can instantaneously log – as you sweep over the patient, you can measure their reflective power as you go down the body and this is one of the techniques we discussed earlier. By minimising that reflective power when targeting the tumour, you can measure your results quantitatively.

ASSOC. PROF JOHN BOYAGES
My trouble....

BILL MACHAM
And its cheap. The UHF part of it is cheap. The LINAC may be not but the UHF part of it is.

ASSOC. PROF JOHN BOYAGES
Relatively cheap? What do you mean by cheap?

BILL MACHAM
Because they are TV transmitters and because they are everywhere – cheap.

ASSOC. PROF JOHN BOYAGES
But what do you mean by cheap? Just something in the air, what are we talking about? $20,000? $50,000? $100,000?

BILL MACHAM
Oh no, keep going.

ASSOC. PROF JOHN BOYAGES
$500,000?

BILL MACHAM
Oh yeah, between half a mil and a mil.

ASSOC. PROF JOHN BOYAGES
That's cheap?!

BILL MACHAM
I mean, oh yeah, we've put it in a room and we've put it together and etc.

HELEN ZORBAS
Sorry we've got planes to catch so we only have to wind up. Is there anything else anyone wanted to say?

DR MICHAEL HOLT
I would just like to re-iterate looking at 100 patients here and 100 patients there – I know what the problem is and I know that as you say we've all got cases where there has been ... and all the rest of it. My worry is that if we're looking at the past cases, we are looking at the past, then we are not going to progress this forward and I think what...

ASSOC. PROF JOHN BOYAGES
Thank you.

JENNY PICKWORTH
Helen, just in conclusion. Just to confirm if you would provide John with copies of the selection criteria for the documentation search and it would be very helpful I think, in terms of John's capacity to assist the draft report if, when that list was available – and assuming it is available prior to your draft report, that could be provided to John.

HELEN ZORBAS
The list, sorry?!

JENNY PICKWORTH
There was going to be a.....

MALE
Search Strategy

JENNY PICKWORTH
....search strategy.

HELEN ZORBAS
Oh the search strategy is known now. We've got that.

ASSOC. PROF JOHN BOYAGES
You mean the list of references and that.

JENNY PICKWORTH
The list of references, when that is compiled and available, if John could have that as well. Because presumably that would be appended to the draft report and I am just trying to make a point that staggered presentation to John in digestible chunks makes it easier.

ASSOC. PROF JOHN BOYAGES
What you're saying is that if he can, you know, read that bit....

JENNY PICKWORTH
Yep.

ASSOC. PROF JOHN BOYAGES
...when he is on holidays or wherever.

HELEN ZORBAS
I just have to be careful that we've completed that bit.

JENNY PICKWORTH
Yes.

HELEN ZORBAS
I could only pass that on once the Committee was satisfied that..

JENNY PICKWORTH
Yes. Okay.

HELEN ZORBAS
Again, thank you.

JENNY PICKWORTH.
Okay thanks very much.

Annexure B

From: "Jenny" <bowman@bigpond.net.au>
Subject: **Fw: Dr John Holt**
Date: 4 March 2005 1:26:01 PM
To: "Nikki Hillman" <nhillman@optusnet.com.au>
Reply-To: "Jenny" <bowman@bigpond.net.au>

----- Original Message -----
From: Jenny
To: philip.callan.@nhmrc.gov.au
Sent: Tuesday, January 11, 2005 3:33 PM
Subject: Dr John Holt

Dear Dr Zorbas,
(c/- Mr P Callan),

The purpose of this email is to record what was agreed at Saturday's meeting:

1. Your committee will provide Dr Holt with a copy of the criteria for the literature review and (as soon as it is complete) a copy of the results of that review;
2. Your committee will provide Dr Holt with a copy of its draft report to the NHMRC in late February (and will provide it to him by email if he is overseas at the time)and give Dr Holt one week (minimum) to make comment on the draft;
3. Dr Holt will allow your committee to access the complete medical records for a consecutive series of 100 patients treated during 2001/2002 **Provided;**

- your commitee provides the resources to access and examine those records and undertakes to maintain the contents of the records confidentially and only to report in connection with those records on a patient de-identifiable basis;
- your committee simultaneously accesses and examines the complete medical records for;

  a consecutive series of 100 patients treated by Dr Holt at his former private practice using the dual modalities of UHF and Radiation ;
  Dr Holt's selection of his best clinical outcomes;and
  the 39 bladder cancer patients referred to by Dr Holt at Saturday's meeting.

As discussed it is important for Dr Holt to see that the Committee is taking a careful, balanced approach to the assessment of his clinical outcomes over time .
It is acknowledged that the Committee has agreed to look for and note any factors of significance to clinical outcomes (eg a trend of patient referrals as a last resort ; palliation effects of UHF treatment etc).

Dr Van Hazel's inclusion on the Committee remains of some concern. There is some reason to believe that Dr Van Hazel has criticised Dr Holt's treatments and sought to persuade patients against seeking treatment from Dr Holt. It would be appreciated if you could seek an assurance from Dr Van Hazel that he has not acted in this way
I have checked with Dr Holt's office staff and they advise their records indicate Dr Van Hazel has never referred a patient to Dr Holt. I accept this, of itself, does not necessarily indicate a bias against Dr Holt.

On a personal note, thank you for your graciousness and professionalism on Saturday.Given the 1975 NHMRC report on Tronado Dr Holt was (understandably) very wary of the current enquiry and your committee. I think he was very comforted on Saturday to see that he is dealing with with open, fair minded, fellow professionals.

Kind Regards,
Jenny Pickworth.

Annexure C

SCHEDULE

Patent Applications

APPLICATION NUMBER	DATE FILED	SUBJECT MATTER
GB 0326870.3	18 November 2003	Therapeutic methods and compositions for use therein
GB 0407983.5	7 April 2004	Therapeutic methods and compositions for use therein
GB 0418363.8	16 August 2004	Therapeutic methods and compositions for use therein
AU 2004231179	17 November 2004	Therapeutic methods and compositions for use therein
EP 04257119.0	17 November 2004	Therapeutic methods and compositions for use therein
NZ 536659	18 November 2004	Therapeutic methods and compositions for use therein

SIGNED as a Deed by the said John Alfred Gorton Holt: John Alf. Holt

In the presence of: Nikki Hillman

Name: M Hillman

Address: 2/131 Edward Street
Osborne Park WA 6017
Australia

SIGNED as a Deed by the said Mark Rowan Gorton Holt:

In the presence of:

Name:

Address:

APPENDIX 13: REVIEW COMMITTEE RESPONSE TO DR HOLT'S RESPONSE TO DRAFT INTERIM REPORT

The Review Committee received the comments on the draft interim report from Ms Jenny Pickworth acting on behalf of Dr John Holt on Monday 7 March 2005. The Review Committee met by teleconference on Tuesday 8 March 2005 to consider the comments raised by Dr Holt (as presented by Ms Pickworth).

The following represents the Review Committee consideration and response to each of the issues raised by Ms Pickworth in her correspondence of 7 March 2005 (and included as Appendix 11 of this report).

1. GENERAL COMMENTS

1.1 UHF AND UHF/RADIOTHERAPY – TERMS OF REFERENCE

Item A

The Review Committee was aware that Dr Holt is in his eightieth year, and was informed during the meeting in Perth on 8 January that in all likelihood, Dr Holt would be retiring soon.

The Review Committee accepted that Dr Holt's preferred treatment modality was combination of UHF and radiotherapy, and that he was not providing this modality because of lack of access to radiation equipment. However, the Review Committee expressed concern that Dr Holt considered that he was "being forced to treat patients less than optimally by not providing them with UHF/radiotherapy". In addressing the issues in this matter, the Review Committee considered that it was beyond its remit to pass comment on the reasons surrounding Dr Holt's exclusion from traditional therapy.

Action
The Review Committee to include a statement in the draft interim report indicating that Dr Holt was not providing UHF in combination with radiotherapy because of lack of access to this equipment.

Item B

The Review Committee noted that the complete list of case-series identified for the patient audits as outlined on page 310 of the interim report had not been correctly transcribed to page 81 of the report.

Action
The Review Committee to realign details on the patient audit on page 81 with the correct list on page 310.

Item C

The Review Committee did not consider that it had focused exclusively on the validity of the UHF modality currently applied by Dr Holt. Rather, the Review Committee considered it was important, to preserve the integrity of this review, to assess the available literature as broadly as possible, as evidenced by the criteria of the literature review, including the dual modality of UHF and radiotherapy. It was considered that the assessment of dual modality is adequately addressed in the report.

Action
No change required to draft interim report.

Item D

Members agreed that the terms of reference of the Review Committee did not limit their ability to consider dual modality of UHF and radiotherapy and the review did consider all relevant evidence relating to dual modality.

Action
No change required to draft interim report.

Item E

The Review Committee considered its interpretation of its terms of reference did not restrict this review to the consideration of the treatment regimen currently offered by Dr Holt. The literature review clearly outlines the scientific literature that was considered, including an inclusion/exclusion criteria which outlines the selection process employed to identify the relevant literature used in this review. The Review Committee did not consider it has limited the scope of the terms of reference to the current regimen.

Action
No change required to draft interim report.

Item F

The Review Committee recognises and appreciates that Dr Holt, and indeed all the staff associated with Dr Holt's clinic, have been open and co-operative throughout this process. The Review Committee understands that Dr Holt is keen to have his previous modality (combined UHF/radiotherapy) revived. The Review Committee reiterated that it had taken into consideration all relevant evidence on a range of modalities not just the regimen currently offered by Dr Holt.

Action
No change required to draft interim report.

Item G

The Review Committee expressed concern that Dr Holt "has not had the time available to prove-up the treatments", however was "in no doubt, given his experience of treating some 35,000 cancer patients in WA since 1961 (in excess of 5000 with the dual modality (1973 to 1991) and 1500 with glucose blocking agents and UHF only (since 1991) that this latter modality is of significant curative or therapeutic benefit (at least equal to that of conventional treatments) and without the adverse side-effect".

The Review Committee did not consider that Dr Holt's opinion represents proof of efficacy and safety.

Action
No change required to draft interim report.

Item H

The Review Committee reiterated that it did not restrict the review to the current treatment regimen. The Review Committee was previously concerned about the distinct lack of information in relation to UHF and glucose blocking agents, and recognised that there was significantly more published literature on the dual modality of UHF and radiotherapy.

Action
No change required to draft interim report.

1.2 THE SCIENCE OF DR HOLT'S UHF TREATMENT REGIMEN

Item A

See item C below.

Action
As per item C below.

Item B

The Review Committee did not focus on 434 MHz, rather it considered a broader, more inclusive range through the entire microwave spectrum (300 MHz to 300 GHz – not 300 MHz to 3,000 GHz as suggested in Ms Pickworth's correspondence of 7 March). The frequency used by Dr Holt clearly lies within this bandwidth.

Action
No change required to draft interim report.

The Review Committee noted that Dr Holt does not consider application of UHF radiowaves in his treatment regimen produces a hyperthermic effect. The Review Committee had not been able to identify evidence that suggested that there was not a hyperthermic effect. Members recalled that following treatment, patients would spend time cooling down with cold packs or fans. The Review Committee questioned whether this heating could constitute hyperthermia, or was only localised heating. Due to the lack of clear evidence to support either likelihood, the Review Committee agreed not to amend the report.

Action
No change required to draft interim report.

Item C

The Review Committee confirmed the statement "non-ionising electromagnetic waves (i.e. microwave therapy) do have the potential to heat human tissue". The Review Committee also confirmed "the overwhelming majority of microwave therapy researchers believe that any therapeutic effect of microwave therapy is related to heating of the tumour cell, either directly or indirectly". It was noted that these effects were likely to be seen at temperatures higher than those achieved using Dr Holt's therapy.

Action
Amend sentence on page 14 to state therapeutic effect dependent on achieving increases in the temperature of the tumour, at higher levels than those achieved in WA. Sentence to be correctly referenced.

The Review Committee noted the explanation provided by Dr Holt on his treatment. While this hypothesis was not consistent with current knowledge of cell biology, and is not in line with current research findings, it was agreed to include the statement in the report to clarify Dr Holt's hypothesis.

Action
Include in Chapter 3:
"The application of 433-434 MHz UHF results in an increase in the cancer cell growth rate (by a factor of up to 10 times normal growth rate). This is attributable to the fact that cancer cells conduct electricity, so absorb energy at a greater rate than healthy cells, in turn growing faster. This accelerated growth rate is then destroyed by preventing the cancer cell using glucose from the blood at its energy source or by treating with X-ray therapy after UHF. (Ms Pickworth, pers comm)

1.3 CONFLICTS AND DUE PROCESS

Members noted the correspondence from Ms Pickworth on 11 January 2005 in which she wrote:

> *"Dr Van Hazel's inclusion on the Committee remains of some concern. There is some reason to believe that Dr Van Hazel has criticised Dr Holt's treatments and sought to persuade patients against seeking treatment from Dr Holt. It would be appreciated if you could seek an assurance from Dr Van Hazel that he has not acted in this way. I have checked with Dr Holt's office staff and they advise their records indicate Dr Van Hazel has never referred a patient to Dr Holt. I accept this, of itself, does not necessarily indicate a bias against Dr Holt."*

Following receipt of this e-mail, the Chair of the Review Committee discussed this issue with Dr van Hazel. On hearing these unsubstantiated concerns, Dr van Hazel assured the Chair that he had not acted in this way, however recognised that any perceptions of such a conflict could leave the Review Committee open to criticism. In recognition of this concern, Dr van Hazel immediately offered to resign from the Review Committee to ensure the integrity of the review. Dr van Hazel's resignation was reluctantly accepted by the Review Committee.

The Review Committee considered that this matter was an internal administrative matter, and did not consider that it had an obligation to advise Dr Holt's office of the outcome of this process.

Action
No change required to draft interim report.

The Review Committee noted the concerns raised in relation to the distribution of invitation letters to Dr van Hazel and Dr Jefford (members of the Review Committee) seeking their input into the call for submissions. The Review Committee recognised that the call for submissions conducted in October and November 2004 invited response from all oncologists in Australia. This process was managed by a mailing house on behalf of NHMRC, and letters were forward to the two members for quality assurance purposes. No member of the Review Committee made a submission to the consultation.

Action
No change required to draft interim report.

2. SPECIFIC ISSUES

2.1 AVAILABILITY OF DUAL MODALITIES – UHF AND RADIATION

The Review Committee acknowledges that Dr Holt no longer has access to radiotherapy equipment. The Review Committee had previously considered the implications of including a comment in the draft interim report noting that Dr Holt has been excluded from conventional therapies and felt that outlining the reasons for Dr Holt's exclusion from traditional therapies would be prejudicial. In addressing the issues in the response from Ms Pickworth, the Review Committee reaffirmed its previous position that it was beyond its remit to pass comment on the reasons surrounding Dr Holt's exclusion from traditional therapy.

However, the Review Committee previously agreed to include a sentence in the interim report noting that Dr Holt does not have access to traditional equipment.

Action
Previously addressed

The Review Committee noted that Dr Holt has sought access to traditional radiation therapy equipment, however it was either beyond his means, or he failed to gain agreement from local Radiotherapist for access to equipment.

Action
No change required to draft interim report.

The Review Committee reaffirmed the previous response to the inconsistency within the draft interim report in relation to the series of patients to be considered in the patient audit.

Action
Previously addressed

2.2 Bias

The Review Committee had previously agreed to include a statement that Dr Holt does not use UHF in conjunction with radiotherapy because this form of treatment is not available to him.

Action
Previously addressed

The Review Committee recognised that while the findings of the 1974 NHMRC report was considered useful background information, it could be considered prejudicial. The Review Committee agreed to remove reference to the 1974 NHMRC report.

Action
Remove reference to the 1974 NHMRC report from the draft interim report.

The Review Committee reaffirmed its position that it was difficult to interpret the information received through the call for public submissions. Overall, the tenet of the submissions was strongly in support of Dr Holt's treatment however the Review Committee recognised that this was a self-selected group, and as such represented a biased sample, and could not be considered as evidence of the efficacy of Dr Holt's treatment. The Review Committee agreed to include a statement within the report indicating the tenet of the submission, with a caveat that this does not constitute evidence.

Action
Include a statement in Chapter 4, part 2 outlining the tenet of the public submissions.

The Review Committee considered the administration of glucose blocking agents. Members agreed to remove "NB" from the statement "Doses are not titrated to body weight".

Action
Remove "NB" from the statement "Doses are not titrated to body weight".

The Review Committee expressed concern that Dr Holt was treating patients using a chemotherapy drug (cyclophosphamide) even though at homeopathic doses, and continues to claim against Medical Benefits Scheme for chemotherapy. The Review Committee expressed further concern that the other glucose blocking agents used by Dr Holt are "benign because they are present in living human bodies" however Dr Holt continues to claim against the Medical Benefits Scheme.

Action
No change required to draft interim report.

The Review Committee agreed that the statement relating to the lack of Therapeutic Goods Administration approval of the equipment used by Dr Holt is prejudicial, however the statement is accurate.

Action
No change required to draft interim report.

The Review Committee noted the concerns raised in regard to the reporting of deaths associated with the use of this treatment. As the report did not compare the mortality of this therapy against traditional cancer treatment, the Review Committee agreed to reduce the emphasis in the draft interim report.

Action
Chapter 4, Part 1 to be revised to reduce emphasis of the deaths associated with the use of this therapy.

In relation to comments on the "Safety Summary" and the issuing of warnings to patients, the Review Committee agreed that the warnings and disclosures provided to patients from Dr Holt should be included at page 75 of the report. It was noted that the brochures provided by Dr Holt to his patients was included in the draft interim report at Appendix 8.

Action
Include reference on page 75 to the brochures provided by Dr Holt to patients outlining safety concerns.

The Review Committee noted the statement that "the NHMRC Invitation to Make Submissions did not mention or require comment or input on [safety] issues". The Review Committee noted that the advertisement clearly stated the terms of reference, and included "safety" as an issue.

Action
No change required to draft interim report.

2.3.1 Accuracy Issues re Description of UHF Treatment

The Review Committee agreed that the waiting time between administration of GBA and radiowave therapy should be between 10-20 minutes.

Action
Amend draft interim report to reflect correct waiting time (10-20 minutes) between administration of GBA and radiowave therapy.

The Review Committee noted that Dr Holt had recently applied for six patents relating to his current treatment regimen, and the concerns raised regarding the inclusion of GBA ingredients and doses in the draft interim report. The Review Committee noted that Dr Holt had previously published information about the ingredients and the doses of the GBA in the open scientific literature, and as such it was appropriate to include the ingredients and doses in this report.

Action
No change required to draft interim report.

The Review Committee noted the request from Dr Holt to include the names of the principals of Health Technology Analysts in the report, and noted that the principals are already included on the verso page of the draft interim report. The principals from Health Technology Analysts are not oncology specialists, rather they are experts in undertaking literature reviews, assessing scientific evidence and preparation of reviews of evidence. The Review Committee recognised that it was important to maintain impartiality and that the review should be undertaken by experts outside the oncology field.

Action
No change required to draft interim report.

2.4 The Non-Referral/Non-disclosure Issues

The Review Committee noted the comments about the Australian public needing to rely on current affairs programs aired on television to learn about UHF therapy provided by Dr Holt. The Review Committee did not consider these comments relevant to this review.

Action
No change required to draft interim report.

3. EXECUTIVE SUMMARY

The Review Committee considered that it had been fair and open in providing Dr Holt an opportunity to comment on the draft report, and confirmed that the Executive Summary had not been included in the draft interim report provided to Dr Holt for comment to allow Dr Holt's comments on the draft interim report to be factored into the summary if necessary. The Review Committee considered the request to provide Dr Holt the opportunity to comment on the Executive Summary, but the Executive Summary simply provides an overview of the report already reported on by Dr Holt.

Action
No action required.

4. DR HOLT'S PREPAREDNESS TO ASSIST/CO-OPERATE WITH CLINICAL TRIALS

The Review Committee noted Dr Holt willingness to be involved in any future clinical trials.

Action
No change required to draft interim report.

APPENDIX 14: MINUTES OF VISIT TO PERTH (APRIL 2005)

NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL REVIEW COMMITTEE ON MICROWAVE CANCER THERAPY

MEETING WITH DR HOLT

Thursday 7 April 2005

A delegation from the National Health and Medical Research Council (NHMRC) Review Committee on Microwave Cancer Therapy met with Dr Holt on Thursday 7 April 2005 at the Radiowave Therapy Centre, 2nd Floor, 31 Outram Street, West Perth, WA.

The purpose of the meeting was to discuss and clarify the audit of medical records of patients treated by Dr Holt with his current and previous therapies, UHF radiowave combined with radiotherapy, and glucose blocking agents combined with UHF radiowaves respectively. The meeting also provided an opportunity for Dr Holt to raise issues in relation to the interim report.

Present at the meeting were:

NHMRC Delegation

Associate Professor John Boyages	Member NHMRC Review Committee
Mr Phil Callan	Secretary, NHMRC Review Committee

Radiowave Therapy Centre

Dr John Holt	
Dr Michael Holt	
Ms Jenny Pickworth	Legal representation

1. INTERIM REPORT AND EXECUTIVE SUMMARY

Ms Pickworth advised that there was some concern about the tenor of the draft interim report, particularly in relation to discussion on two cases in which male patient died during treatment. Dr Holt indicated that these patients were terminally ill. Prof Boyages indicated that he was also concerned about this section of the draft interim report during Review Committee discussions, and that the report had been redrafted following comments received from Dr Holt.

Dr Holt provided a photo of one of the two patients (entitled: *Whole Body Heating Rates under 12x200 watt moving fields).*

Ms Pickworth asked whether the report had been provided to the Minister for Health, and whether it was possible to obtain a copy of the Executive Summary. Mr Callan advised that the report had been forwarded to the Minister's office in early April 2005. Mr Callan made an undertaking to seek approval to provide a copy of the final Executive Summary to Dr Holt.

[Secretariat Note: A copy of the Final Executive Summary was provided to Dr Holt on Monday 11 April 2005.]

2. PATIENT AUDIT

Prof Boyages indicated that Review Committee's proposed project plan to undertake an audit of the medical records of patients treated by Dr Holt including assessment of

- 31 bladder cancer cases treated with UHF radiowave in combination with radiotherapy between 1973 and 1978;
- Approximately 50 bladder cancer patients treated with UHF radiowave in combination with radiotherapy fro the 1980s;
- Approximately 50 bladder cancer patients treated with UHF radiowave in combination with glucose blocking agents (GBA); and
- Approximately 50 bladder cancer patients treated with non-UHF therapies;

Prof Boyages indicated that the Review Committee was also committed to assessing the following groups:

- 100 consecutive cancer patients treated with UHF radiowaves in combination with radiotherapy;
- 100 consecutive cancer patients treated with UHF radiowaves in combination with GBA;
- The 10 best outcomes, any modality

Dr Holt advised that the patients treated with a combination of UHF with radiotherapy were treated by Drs Holt, Nelson and Leckie at the Perth Radiation Oncology Centre, or at the Sir Charles Gairdner Hospital. The medical records are stored at those locations.

Prof Boyages noted that following discussions with Dr Chris Harper, Managing Partner of the Perth Radiation Oncology Centre, medical records are routinely destroyed 10 year after death, consequently some records will no longer be available.

Ms Pickworth undertook to contact Mr Neil Fong, Western Australian Health Department to gain quick access to all medical records.

Dr Holt agreed with the identified series however considered that there was little value in assessing records of bladder cancers from the current practice due to the potentially low number of patients treated and that assessment of the treatment of head and neck cancers should be considered by the Review Committee.

Prof Boyages indicated that the Review Committee was committed to assessing the bladder cancers and that an assessment should be made of as many bladder cancer patients as possible treated with UHF in combination with GBA. Consideration of further patient series, including the head and neck series, would need to be made following completion of these initial series.

Ms Pickworth questioned why the Review Committee were interested in assessing patients treated with UHF and GBA when Dr Holt continues to advise that UHF in combination with radiotherapy is the preferred modality. Prof Boyages advised that the Minister had requested the NHMRC to assess microwave "UHF radiowave" therapies and that this included the treatment currently offered by Dr Holt. Prof Boyages indicated that the Review Committee would be negligent if it were to exclude the UHF/GBA modality from the patient audit.

HISTORY

Dr Holt provided the following brief chronology of his practice:

1961	Private practice opened by Drs Holt and Leckie
1973	Tronado equipment purchased (1 installed at Sir Charles Gairdner Hospital, 1 installed in private practice)
1978	Denied accessed to public institution
1978-1991	continued to practice at private practice
1991	Left practice

CLOSE OF MEETING

At the close of the meeting, Dr Holt provided copies of the following papers for the consideration by the Review Committee:

- Correspondence from Robert Stanford associates (dated 31 May 1975) 434MHz EMR power absorption in breast cancer and normal breast tissue. Comparison between each breast at corresponding sites.
- Correspondence from Robert Stanford associates (dated 8 June 1979) – A comparative study of the Tronado equipment in use at the private practice of Drs J.A.G. Holt and A.J. Nelson and that owned by Sir Charles Gairdner Hospital
- The UHF X-radiation target
- Hornback NB, Shupe R, Shidnia H, Joe BT, Sayoc E, George R, Marshall C (1979) Radiation and microwave therapy in the treatment of advanced cancer, Radiology,130:459-464
- Dr Holt showed Professor Boyages and Mr Callan his slide collection

APPENDIX 15: MICROWAVE AUDIT FORM

Microwave Audit Form

Data manager _____

Patient factors

1. Case Number _____ 2. Unit MRN _____ 3.Initials _____

4. Date of birth ___/__/___ 5. Gender ☐ Male ☐ Female 6.State of Residence _____

Referral

7. Source of referral ☐ specialist ☐ GP ☐ self ☐ not known

Name and contact details of surgeon	Name and contact details of GP

8. Patient status prior to commencing study treatment;

☐ new patient (no prior treatment)
☐ new post chemo
☐ metastatic
☐ new post-op (surgery before referral)
☐ recurrent (ie loco-regional)
☐ other (specify)

_____

Tumour factors

9. Date of initial cancer diagnosis ___/__/___

10. Is a pathology report showing cancer in the record? ☐ initial ☐ subsequent ☐ both ☐ none

11. Primary site of cancer (ICD-10 code) _____

12. Histology

☐ non malignant
☐ carcinoma
☐ sarcoma
☐ melanoma
☐ seminoma
☐ non-seminoma
☐ small cell carcinoma
☐ NHL
☐ Hodgkin's
☐ myeloma
☐ leukaemia
☐ not known

13. Histological grade ☐ low grade (1) ☐ moderate grade (2) ☐ high grade (3)
☐ not known/indicated

14. Bladders only ☐ T1 ☐ T2 ☐ T3 ☐ T4 ☐ n/a ☐ n/k

15. Degree of spread [stage] at beginning of study treatment ☐ localised to the tissue of origin

☐ invasion of adjacent tissue or organs
☐ regional lymph nodes
☐ distant metastases
☐ not applicable
☐ not known

16. Tumour status prior to commencing study therapy ☐ none or microscopic ☐ macroscopic
☐ not known

17. Please indicate method of determining tumour status. Enter assessment date and where possible tumour size (mm) below.

	SITE	Clinical	Cystoscopy/ Endoscopy	Imaging	Pathology	Other
Lesion 1						
Lesion 2						
Lesion 3						

Treatment factors

18. Treatment intent (re study therapy) ☐ curative ☐ non-curative ☐ prophylactic

Surgery

19. Prior surgery to index site ☐ no surgery
☐ resection – no evidence of macroscopic residual disease
☐ resection – evidence of residual macroscopic disease

20. Date of surgery ___/___/___

Radiotherapy

21. Did the patient receive treatment with radiotherapy? ☐ yes ☐ no

	Radiotherapy Type	Site	UHF y/n	Start date	Stop date	Gy	No of fractions	No. Fields (spec)
1	Study Therapy							
2	Prior to study therapy – Course 1							
3	Prior to study therapy – Course 2							
4	Prior to study therapy – Course 3							
5	Post study therapy – Course 1							
6	Post study therapy – Course 2							
7	Post study therapy – Course 3							

Comments

Chemotherapy

22. Did the patient receive chemotherapy for index lesion or metastatic disease? ☐ yes ☐ no
If 'yes √ timing of chemotherapy';

Chemotherapy	Yes	No	No of Regimens
chemotherapy prior to study treatment			
chemotherapy concurrent with study treatment			
chemotherapy post study treatment			

UHF factors

23. Did the patient receive treatment with UHF? ☐ yes ☐ no

24. Date first treatment ___/___/___ Date last treatment ___/___/___

25. Total number of kW _____ 26. Total number of minutes _____

27. No of treatment days _____ 28. Total no of fractions _____

29. Anaerobic glycolytic blocking before UHF ☐ yes, (specify) _____ ☐ no ☐ not known

Outcome – Tumour Response

30. Was tumour response assessed post-treatment? ☐ yes ☐ no ☐ not known

31. If 'yes', please indicate method of evaluation by entering assessment date and where possible tumour size (mm) in the boxes below .

	SITE	Clinical	Cystoscopy/ Endoscopy	Imaging	Pathology	Other
Lesion 1						
Lesion 2						
Lesion 3						

32. Tumour response post-treatment ☐ CR ☐ PR ☐ SD ☐ PD ☐ n/k

Recurrence

33. If patient CR, PR or SD did they subsequently experience a recurrence? ☐ yes ☐ no ☐ n/a ☐ n/k

34. If 'yes', date of recurrence __/__/__

35. Method of assessment ☐ clinical ☐ cytology ☐ pathology ☐ imaging
☐ cystoscopy/endoscopy ☐ n/a ☐ other (specify) _____

Treatment Post Study Therapy

36. Did the patient receive further treatment post study therapy? ☐ yes ☐ no ☐ n/k

If 'yes' please √ which of the following apply;

No of courses	UHF+RT (no of courses)	UHF+ GBA (no of courses)	RT alone (no of courses)	Chemotherapy (number of regimens)	Surgery (number of surgeries)	Other
1						
2-3						
≥4						

37. Best response to total subsequent treatments ☐ CR ☐ PR ☐ SD ☐ PD
☐ n/a ☐ n/k

Outcome Toxicity

38. Was the patient assessed for toxicity during and/or up to 6 weeks post-treatment?
☐ yes, date __/__/__ ☐ no
☐ not known

39. Were there any toxicities during treatment? ☐ yes ☐ no
If 'yes' specify;

	Toxicity	Mild	Moderate	Severe	Life Threatening	Requiring hospital	Requiring termination Rx early
1							
2							
3							
4							
5							
6							

Outcome Symptoms

40. ECOG status; Pre-treatment (circle) 0 1 2 3 4 n/k date __/__/__
Post-treatment 0 1 2 3 4 n/k date __/__/__

41. Were there any documented symptoms pre-treatment? ☐ no ☐ yes (specify)

42. Was there a resolution or relief of symptoms at 3 months post-study therapy? ☐ yes ☐ no ☐ n/a ☐ n/k
If yes, specify

	Symptom	Date of amelioration/resolution
1		
2		
3		
4		
5		

Comments

Outcome Status

43. Patient status ☐ alive ☐ dead – cancer related ☐ dead – not cancer related ☐ not known

44. Disease status at last follow-up, notification or death ☐ CR ☐ PR ☐ SD ☐ PD ☐ n/k

45. Disease status based on ☐ clinical ☐ cytology ☐ pathology ☐ imaging
☐ cystoscopy/endoscopy ☐ n/a ☐ other (specify)_____

46. Date of last follow-up or death __/__/__

Comments

_____

_____

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		Study group			Comments	
Group (circle)	Year	Group		Date	Comment	Initials
A	70-91	Bladder RT only				
B+D	70-91	Bladder RT+UHF				
C	'90's	Bladder UHF+GBA				
E	'90's	Any invasive cancer				
F	70-91	Any invasive cancer				
G	Any	10 best Cases				

Verification Documents (indicate if source document verification performed by auditor)

Copy of Pathology Report	Y N	Copy of referral letter	Y N
Evidence of response (eg scan report)	Y N	Evidence of progression	Y N
Evidence of tumour measurements	Y N	Radiotherapy and or UHF report	Y N

Date Entered ___/___/___ Date Entry Checked ___/___/___ Auditor (circle) JB MJ Other (spec)____

APPENDIX 16: PATIENT AUDIT FORM COMPLETION GUIDELINES

Patient Factors

1) Case number

Study number assigned to each patient. Study numbers will be assigned by the data manager completing the case forms. Data managers will also complete a patient log which will link patient number with their name for the follow-up process. Access to this log will only be afforded to the sub-group of the study team responsible for documenting patient follow-up status. The list will be stored under secure conditions.

The study numbers will be derived from the study cohort (A, B, C, D, E, F or G) followed by a sequential number starting from 1. One data manger will assign odd numbers and the other even numbers to ensure no duplication of study numbers.

2) Unit MRN

Medical record number. In some cases more than one record number may exist for a patient (eg, a medical record number plus a radiotherapy file number, etc). In such situations multiple record numbers should be documented with an annotation.

3) Initials

Christian name, middle name, surname with a "-" if there is no middle name.

4) Date-of-birth

5) Gender

6) State of Residence

NSW, WA, Vic etc for follow-up purposes. If international specify OS.

Referral

7) Source of referral

Document the source of referral, that is the person who made the referral for study therapy. Details of the referring physician, (if applicable) and primary care physician should be provided for follow-up purposes (if necessary).

It is necessary for Medicare purposes to obtain a GP referral and so in some cases of self-referral a GP letter will also be found. However, if a patient has clearly instigated the consultation themselves document this as a self-referral.

8) Patient status prior to commencing study treatment

a. New patient = newly diagnosed patient, no prior treatment for index lesion; this includes patients with any stage of disease who have had no treatment.

NOTE a newly diagnosed patient presenting with metastatic disease (Stage IV at first diagnosis) would be classified as 'new' not 'metastatic' as they have had no pre-treatment.

b. *New post-op:* = presenting for the first time for study treatment but has received prior surgery for index lesion

c. *New post-chemo:* = presenting for the first time for study treatment but has received prior chemotherapy for index lesion (e.g neo-adjuvant chemo)

d. *Recurrent – loco-regional* = patient with recurrent disease locoregionally (invasion into local tissue or regional lymph nodes) after a previous treatment

e. *Metastatic* = patient who has been previously treated and presents with metastatic disease, such as a bone or lung secondary

f. Other- e.g second opinion

Tumour factors

9) Date of Diagnosis

The date of first histo-pathological diagnosis of disease. This does not necessarily correspond with the date of first symptoms. It is the date of the first diagnosis of cancer. For new patients this is usually in the same year as their primary treatment; for other patients it is in the months (or years) before treatment.

If no pathology has been performed, and if applicable, date of diagnosis may be determined by the date of first imaging. In the absence of imaging, pathology, or any other objective date of diagnosis, then the first clinic date can be used with an appropriate comment.

10) Is the Pathology Report present?

Where possible the primary pathology report which confirms the patient's initial diagnosis should be attached, de-identified as a source document. In some situations the only pathology available will be from a secondary cancer. Please attach this with an explanatory note in these situations.

11)Primary Site of Cancer

See Attachment 1 (of these guidelines) for ICD-10 Codes.

In cases where a patient has two primaries it may be necessary to complete two data forms and attach together, (eg bilateral breast cancer).

12) Histology

As defined by the pathology report.

13) Histological Grade

Low grade ('well differentiated')	= Grade 1,
Moderate grade ('intermediate')	= Grade 2
High grade (or 'poorly differentiated' or 'anaplastic')	= Grade 3

14) T stage

For bladders only please supply the T stage at the time of treatment (See Attachment 2 of these guidelines)

15) Degree of Spread at Beginning of Study Treatment

Refers to spread of the disease prior to starting UHF or RT in the case of the bladder cohort RT alone arm. Only one category should be ticked.

Note, a tumour may be described in the pathology as 'highly invasive' but in fact is still localised. Invasion of varying degree into bladder wall is still classified as localised disease. It is only when the tumour extends into the tissue surrounding the bladder or into other organs that it enters the "invasion of adjacent tissue or organs" category.

16) Tumour status

'None' or 'microscopic' if full surgical excision has been performed, or complete remission achieved from radiotherapy or chemotherapy. 'Macroscopic' if disease is detectable on imaging, physical examination or operative report.

17) Tumour Size Prior to Commencing Study Treatment

Where possible an indication of the size of the tumour pre-study therapy should be provided.

Tumour Measurement

- Tumour measurements should be given in mm's (single longest diameter) will be utilised.
- Enter measurement into the box which relates to the mode of measurement
- Some patients have more than one lesion that can be measured. Cite up to three lesions which can be measured (e.g breast, axillary node, SCF node)

Treatment factors

17) Treatment Intent

Intention of treatment with study therapy. In the case of radiotherapy, it is classified as 'curative' if it is instituted in cases where treatment intention is cure. This includes adjuvant radiotherapy or definitive high dose radiotherapy without prior surgery.

'Non-curative' means palliative treatment instituted where there is no reasonable hope of cure. In the case of radiotherapy this usually this involves lower doses of radiation (30gy in 10 fractions; or 20Gy in 5 fractions etc) although sometimes high doses may still be given to patients with "palliative" intent.

'Prophylactic' treatment will only apply very rarely and includes such treatment as prophylactic cranial irradiation for patients with certain leukaemias.

Each of the below categories, (surgery, RT, chemotherapy) refers to treatment to the index site prior to commencing study therapy. For the most part study therapy will be UHF, but for the radiotherapy alone arm of the bladder cancer patients (A) it will be radiotherapy.

Surgery

19) Prior surgery to index site

Some patients may have undergone local excision followed by more complete resection. In this case more than one box will be checked. The date, however, should be for the definitive surgery, (ie the complete resection).

i) No surgery

This includes diagnostic or incisional biopsy.

ii) Resection – no evidence of macroscopic residual disease

This includes excisional biopsy and any excision made with attempt at assessing/ achieving clear surgical margins. In the case of bladder cancer it would also include cystoscopically-guided removal of deposits on the bladder wall, (unless it was specified in the urologist's report that residual tumour remained).

iii) Resection – evidence of macroscopic residual disease

Where the surgical intent has been resection of as much disease as possible but for technical reasons, (eg very advanced disease) this has been impossible and the surgery has only removed as much diseased tissue as possible. Includes gross macroscopic disease left behind, "cut-through" of tumour.

20) Date of Surgery

Where there have been multiple surgeries to the index site the date of the definitive surgery should be provided, (ie, the primary attempt at complete surgical resection).

Radiotherapy

21) Radiotherapy administration

Please enter the start and stop dates of radiotherapy administered pre, post and concurrent with study therapy.

Dose should be provided in cGy as per Radiotherapy Treatment Summary.
Note 50Gy = 5000 rads = 5000cGy.

Number of fractions are also given on Radiotherapy Treatment Summary. This is the number of actual treatment attendances. Occasionally patients may have two fractions a day (hyperfractionation) or two or three fractions per week (hypofractionation)

The number of fields is detailed on Radiotherapy Treatment Summary. Arc treatment counts as one field.

Chemotherapy

22) Chemotherapy administration

Chemotherapy may have been administered either to treat the index lesion or metastatic disease from it. If chemotherapy was given please indicate whether it was prior to, concurrent with or post study treatment. Please also indicate the number of different regimens (note, not different cycles).

It may be that multiple chemotherapy regimens have been given at different stages in treatment in which case more than one box would be checked.

Hormonal and immunological therapies are not to be entered in this section including intra-vesical BCG.

UHF Factors

23) Did the patient receive treatment with UHF?

24) UHF Factors

Date of First Treatment, (ie date of commencing therapy – not first consultation date). The patient may have received multiple cycles of UHF. Details of only the first course should be entered here. Subsequent courses are accounted for in Q36.

25) Total Number of Kilowatts

Total number of kilowatts. Generally four generators are used per dose, A, B, C, and D. Each delivers a wattage which is usually (but not always) the same, therefore this must be multiplied by four to obtain watts per dose. (If fewer generators are used then just add up the total dose).

The total kilowatts for the whole treatment schedule should be entered here.

26) Total number of Minutes

The number of minutes for each treatment sometimes varies a little and so a total time for the whole course in minutes should be entered.

27) Number of Treatment Days

Number of days of treatment. Will not include weekends, but only the actual days treatment was administered.

28) Number of Fractions

This is the number of treatments. It is generally the same as total number of treatment days but not always.

29) Anaerobic Glycolytic Blocking Agent (GBA)

Some patients received intra-venous medication of a GBA pre-treatment to potentiate the effect of the therapy. Please specify the drug(s) given if possible.

Outcome Tumour Response

30) Was Tumour Response Assessed Post Treatment?

This necessitates imaging or some mode of assessment within a reasonable temporal period post the end of treatment, (eg in the case of ca bladder the post treatment cystoscopy is generally performed 3 months after treatment).

31) Tumour measurements

Please enter the post treatment tumour measurements into the relevant boxes as in Q17.

32) Tumour Response Post Treatment

CR = complete response

PR = partial response

SD = stable disease

PD = progressive disease

Where possible these response criteria should comply with RECIST definitions (Attachment 3 of these guidelines). In the case of bladder carcinoma, bladder-specific criteria are applied (Attachment 4 of these guidelines).

Where it is impossible to comply strictly with these criteria because of lack of information, a determination of response should be made on the best available evidence and an annotation added.

Recurrence

33) Recurrence

For patients who achieved any response – even stable disease – details of date of recurrence should be entered where possible in order to be able to determine disease-free survival.

34) Date of Recurrence

Please enter the recurrence date. Where possible this date should coincide with the clinical investigation at which recurrence is diagnosed, event though the symptoms of recurrence may pre-date this. Sometimes a pathological diagnosis is not achieved in which case a clinical diagnosis of recurrence is acceptable.

35) Method of assessment

Indicate the imaging or tumour evaluation modality utilized.

36) Further Treatment

The patient may have received multiple treatment modalities for recurrent disease. In the table below please enter all the treatments the patient received between recurrence and last follow-up/death.

Subsequent treatments may be to the index site or to sites of metastatic disease;

1) UHF + RT
   The number of courses should be entered. A patient may receive multiple courses of UHF/RT treatment separated by weeks, months or years.
2) UHF + GBA
   Please enter the number of courses.
3) RT
   Similarly the number of courses of radiotherapy should be entered. Sometimes this will simply be an isolated, palliative fraction, on other occasions it will be a whole course. In both instances, a 'course' or 'single fraction' counts as a separate episode.
4) Chemotherapy
   Enter the number of different regimes (not different cycles) employed. Immunotherapy and hormonal therapy should also be entered here.
5) Surgery
   Enter the total number of subsequent surgeries for primary and metastatic disease. These may be major such as a salvage total cystectomy, or minor such as palliative excision of a troublesome metastatic lesion. Each episode counts as a separate event.

37) Best Response

This applies to the sum of the treatments administered for metastatic disease. The best status the patient reached post recurrence should be entered into this field; complete response, partial response, stable disease, progressive disease, or unknown.

Outcome -Toxicity

38-39) Was the patient assessed for Toxicity?

Please document any treatment-related toxicities, ie signs and symptoms occurring during study treatment or during the 6 weeks subsequent to study treatment. Indicate whether these symptoms were mild, moderate or severe. Pre-existing symptoms should not be included unless they have significantly worsened during study treatment.

The grading of 'mild', 'moderate' and 'severe' is based on the Common Terminology Criteria (http://ctep.cancer.gov/forms/CTCAEv3.pdf) and correspond with grades 1, 2, 3 and 4 on this scale.

Please also indicate whether the toxicities necessitated hospitalisation or early termination of study treatment.

Outcome - Symptoms

40) ECOG status

Please enter the ECOG status of the patient pre-treatment (see Attachment 5 of these guidelines). If not provided in the notes an evaluation of status can sometimes be made from the clinical information provided. However, in some cases this will not be adequate to make an accurate judgement in which case the response should be 'unknown'.

41) Were there any Symptoms present pre-treatment?

42) Was there any improvement in Symptoms?

Please document whether any symptoms pre-dating study therapy were documented as resolving post study therapy. Post-treatment symptom response should allow for treatment-related toxicity and therefore the post-treatment determination of symptom response should be made greater than 6 weeks post therapy.

Retrospective assessment of symptom response is difficult. Please enter any comments that may be necessary to clarify symptom response to treatment.

Outcome - Status

43-46) Date of and Patient status at last follow-up

Patient status should correspond with the last documented entry in the patient record. If the patient was alive at this time, (even if it is likely that their status has now changed) they should be entered as alive pending more accurate data from the Cancer Registry.

44) Disease status

The best assessment possible should be made from the patient record of disease status at time of follow-up or death. Sometimes the information for this is limited and if necessary a comment should be made in cases where there is lack of clarity.

Office Use Only

Comments Box

Here the data manager can assign the patient to the relevant study cohort and enter any comments pertinent to any section of the form.

Verification Documents

The data entry person should indicate whether the records were available in the patient record.

1) Copy of the original referral letter
2) Evidence of response refers to objective evidence of response such as a scan report or cystoscopy report.
3) 'Evidence of tumour measurements' should only be checked if there are good, objective measurements provided pre- and post treatment.
4) Copy of the referral letter
5) Copy of any documentation of disease progression once again refers to objective evidence of progression or a clear entry in the medical record of clinical evidence of progression.
6) Please indicate if the radiotherapy treatment summary and UHF report is available in the record.

Data of data entry is completed by the data manager and the date of data checking by the auditor who also identifies themselves at the bottom of the form.

Glossary of Terms

Bladder symptoms
Bladder-related symptoms occurring after six weeks post completion of therapy.

Bladder toxicities
Bladder-related symptoms occurring during or within 6 weeks of treatment that were not present prior to treatment

Index Site or lesion
'Index site' refers to the principle treatment site, i.e. the site causing the symptoms and the site having the study treatment.

Study Treatment
'Study treatment' refers to the investigational treatment, ie UHF+/- GBA+/-RT. In one cohort of bladder cancer patients (the RT alone cohort), the RT is the study treatment. If the patient has had surgery this is the post-operative tumour status.

Attachment 1 to Appendix 16

ICD Codes	Sites	ICD Codes	Sites
	Unknown	C01	Base of tongue
C80	Malignant neoplasm without specification of site	C10.0	Valleculae
	1. Skin	C10.9	Oropharynx, unspecified
C43	Malignant melanoma of the skin	C11	Nasopharynx
C44	Other malignant neoplasms of the skin	C12	Piriform sinus
	2. Lymphoreticular System	C13.0	Post Cricoid
C85.9	Non Hodgkins lymphoma	C13.2	Subglottis
	Unspecified type	C32.1	Supraglottis
C81	Hodgkins disease	C32	Glottis
C90	Multiple myeloma	C32.9	Larynx, unspecified
C95.90	Leukaemia unspecified without mention of remission	C31	Accessory sinuses
C90.2	Plasmacytoma, extramedullary	C30	Nasal cavity and middle ear
C47.0	Histiocytic and mast cell tumours of uncertain and unknown behaviour	C08.9	Major salivary gland, unspecified
	3. CNS	C77.0	Secondary neoplasm of lymph nodes of head, face and neck
C69	Eye and adnexae	C76.0	Head, face and neck
C70	Meninges		**5. Breast**
C71.0	Cerebrum	C50	Breast
C71.5	Ventricles nos		**6. Lung/Thorax**
C71.7	Brain stem	C34	Bronchus and lung
C71.6	Cerebellum	C39	Other respiratory and intrathoracic sites
C72.4	Nerve, acoustic	C38.4	Pleura
C75.1	Pituitary		**7. Alimentary Tract**
C72.0	Spinal cord	C15	Oesophagus
C72.1	Cauda equina	C16	Stomach
C72.9	CNS unspecified	C18	Colon
	4. Head and Neck	C20	Rectum
C00	Lip	C21	Anus and anal canal
C02	Tongue other than base	C24.9	Biliart tract nos
C04	Floor of the mouth	C25	Pancreas
C06.2	Retromolar trigone	C22	Liver and intrahepatic bile ducts
C06.0	Cheek mucosa	C26	Other digestive organs
C03	Upper and lower gum		**8. Urinary Tract**
C05.0	Hard palate	C64	Kidney
C06.9	Mouth unspecified	C65	Renal pelvis
C09	Tonsil	C66	Ureter
C05.1	Soft palate	C67	Bladder
C10.2	Oropharynx, lateral wall	C68	Other urinary organs
C10.3	Oropharynx, posterior wall		

Continued over page ➤

ICD Codes	Sites	ICD Codes	Sites
	9. Female Genital		**12. Musculo-skeletal**
C53	Cervix uteri	C40	Bone and articular cartilage of the limbs
C54	Corpus uteri	C41	Bone and articular cartilage of other (non limb) sites
C52	Vagina	C49	Other connective and soft tissues
C56	Ovary	C46	Karposis sarcoma
C51	Vulva	C47	Peripheral and autonomic nerves
C57	Other female genital organs		**13. Endocrine**
	10. Testis	C73	Thyroid
C62	Testis	C74	Adrenal gland
	11. Male Genital	C75	Other endocrine glands
C61	Prostate		
C60	Penis		
C63	Other male genital organs		

Attachment 2 to Appendix 16

T staging for bladder cancer

Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall or abdominal wall
T4a	Tumour invades prostate, uterus, vagina
T4b	Tumour invades pelvic wall, abdominal wall

American Joint Committee on Cancer (2002). Urinary bladder. In *AJCC Cancer Staging Manual*, 6th ed., pp. 335–340. New York: Springer-Verlag.

Attachment 3 to Appendix 16

RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)

Quick Reference: http://imaging.cancer.gov/clinicaltrials/imaging/

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

  Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

  Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

  Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.
- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* *Complete Response (CR):*	Disappearance of all target lesions
* *Partial Response (PR):*	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* *Progressive Disease (PD):*	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* *Stable Disease (SD):*	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* *Complete Response (CR):*	Disappearance of all non-target lesions and normalization of tumor marker level
* *Incomplete Response/ Stable Disease (SD):*	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* *Progressive Disease (PD):*	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/ biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

Attachment 4 to Appendix 16

Bladder Specific Response Criteria (per TROG 02.03)

Complete Response (CR)

Requires, at three or more month post randomisation, the absence of any invasive tumour in the tumour-site biopsy specimen or elsewhere and a bimanual exam that does not indicate the presence of a tumour mass. For a primary tumour response following treatment, a urine cytology specimen that is not positive is also required (in the absence of CIS/dysplasia elsewhere in the bladder urethelium).

Partial Response (PR)

Requires all the response criteria of a CR except that the urine cytology remains positive (in the absence of CIS/dysplasia elsewhere in the bladder urithelium).

No response/ Stable Disease (SD)

Requires continued presence of tumour in the tumour-site biopsy specimen, or elsewhere.

Progressive Disease (PD)

Requires an increase of 50% or more in the largest diameter of the endoscopically appreciable tumour and the continued presence of tumour in the tumour-site biopsy specimen.

Attachment 5 to Appendix 16

ECOG status

Grade	ECOG
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg light office work, house work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed of chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.
5	Dead.

APPENDIX 17: SITE OF PRIMARY CANCER

Site	Tumour site					
	Bladder			Any invasive		Any – 10 best
	RT alone (A)	RT + UHF (B)	UHF + GBA (C)	UHF + RT (D)	GBA + UHF (E)	UHF + GBA ± RT (F)
	N=34	N=11	N=18	N=56	N=49	N=10
C00 lip				1		
C02 tongue					1	
C08 salivary glands				1	1	
C11 nasopharynx				1		
C15 oesophagus					1	
C16 stomach				1	1	
C18 colon					5	
C20 rectum/anus				2	1	
C32 larynx				5		
C34 trachea, bronchus, lung				6	6	1
C38 pleura					4	2
C40-C41 bone/articilar cartilage					1	1
C43 melanoma				1	4	
C44 skin cancer				2	3	
C49 connective/soft tissue				2		1
C50 breast				21	6	1
C53 cervix					2	
C61 prostate				6	2	
C64 kidney				2	2	
C67 bladder	34	12	18			2
C70, C72 other & unspecified nervous system					2	1
C71 brain				1	3	
C73 thyroid gland					2	
C39, C77, C80 unknown primary site				2	1	
C85 non-Hodgkin's lymphoma				2	1	1

APPENDIX 18: BRIEF SYNOPSES OF PUBLICATIONS BY DR JOHN HOLT

Yoffey JM, Ancill RJ, Holt JAG, Owen-Smith B, Herdan G (1954) The Effect of Compounds E,F, and A on the Bone Marrow of Normal Guinea Pigs. *J Anat* 88 (2): 115–132

Relevance to current review: Not relevant, no patients treated with microwave therapy.

This paper reports the result of daily intraperitoneal injections of various steroid hormone (5 mg of cortisone, hydrocortisone or compound A) in guinea pigs. Specifically, the paper reports the impact of the interventions upon the bone marrow.

Hadfield GJ, Holt J (1956) The Physiological Castration Syndrome in Breast Cancer. *BMJ* 27: 972–973

Relevance to current review: Not relevant, no patients treated with microwave therapy.

This short paper reports clinical observations for a case series of patients with metastatic breast cancer with a view to providing information on factors affecting the course of the disease.

Methods

The paper states that all patients in the case series were diagnosed before the menopause and all had progressed to metastatic disease. The patients received various treatments, but the paper focuses on the patients' responses to natural menopause, oophorectomy (referred to as castration = removal of the ovaries) and adrenalectomy.

The paper reports three series of patients: a) those with oestrogen-dependent tumours (n=19); b) those with oestrogen-independent tumours (n=11); and a small group treated with stilboestrol[a] (n=7).

No information is provided regarding the diagnosis of hormone-dependent cancer or how tumour regression was measured.

Results

The paper reports that women with hormone-dependent tumours experienced temporary regression of their metastases after oophorectomy, ranging in duration from 2 months to 4 years. Similarly, after subsequent adrenalectomy these patients' metastases regressed for between 2 and 22 months. In contrast, patients with tumours that were not hormone-dependent had no regression. The authors state that stilboestrol administration generally aggravated metastatic growth (data and number of patients not reported), although they list seven patients who experienced some regression on stilboestrol (but appropriate denominator not reported).

The authors conclude that the behaviour of metastatic breast cancer during natural or artificial menopause indicates the probability of hormone-dependence.

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[a] Di-ethyl-stiloestrol (DES) is a synthetic form of the female hormone oestrogen, prescribed to women from 1938 until the early 1970's mainly during pregnancy. In 1971, a link between the use of DES and a rare form of cancer found in the daughters of women who had taken the drug was discovered. Consequently, the FDA banned the use of DES during pregnancy. DES has since been linked to a number of health problems in women who were given the drug during pregnancy and children born to women who took DES during their pregnancy.

O'Donnell JM, Bremner J, Joyce PR, Holt JAG (1964) From ?Epidermal Naevus to Mycosis Fungoides to Sarcoma. *Med J Aust* 1:642-646

Relevance to current review: Not relevant, patient not treated with microwave therapy.

This case study reports a patient with a skin lesion of the thigh with the clinical appearance of naevus verrucosus. The condition was subsequently diagnosed as mycosis fungoides. The patient ultimately developed large masses in the inguinal region and their histopathology was indistinguishable from reticulum-cell sarcoma. The patient received surgical and radiation therapy, and responded well.

Holt JAG (1964) The Acute Radiation Pneumonitis Syndrome. *J Coll Radiol Aust* 8:40-47

Relevance to current review: Not relevant, patient not treated with microwave therapy.

This paper reports a retrospective case series of all patients who had received radiotherapy of the thorax at the authors institution in the previous five years (n=102). The paper describes an acute condition caused by radiation therapy that the author labels 'acute radiation pneumonitis'. The author makes a case that this is distinct from late radiation-induced fibrosis of the lung.

Methods

This paper reports the findings of a retrospective review of 102 lung cancer patients treated with radiotherapy at the Institute of Radiotherapy in Western Australia.

Results

Fifteen of the 102 patients had radiographic evidence of lung reactions that occurred within 12 weeks of radiotherapy. Seven cases appeared within five weeks of therapy and all died of pneumonitis.

The author discusses the lack of physical signs of acute radiation pneumonitis syndrome and the radiographic distinction from fibrosis. The author proposes that the reaction is an acute necrotizing desquamative lesion of the lung that is equivalent to an acute moist skin lesion.

The author states that the development of acute radiation pneumonitis syndrome is related to dose rate rather than total dose. It is fairly common at more than 1,000 rads TD of 4 MeV X-rays per week. It is stated that patient with Hodgkin's disease are particularly susceptible.

The author concludes that acute radiation pneumonitis syndrome is responsible for considerable morbidity and mortality amongst patients undergoing radiotherapy of the lungs.

Vaughan BF, Holt J (1964) Lymphography. *J Coll Radiol Aust* 8:59-77

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This paper describes the visualisation of the lymphatic vessels and glands of the limbs, pelvis and abdomen using an intra-lymphatic injection of iodised oil. The technique had been adopted by the Royal Perth Hospital and the paper describes 10 illustrative cases.

Holt J (1964) The Management of Patients suffering from Bronchial Carcinoma. *J Coll Radiol Aust* 8 (3):237-242.

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This symposium review discusses the management of bronchial cancer. The author states that there is acrimony between the surgical and radiation teams that causes confusions, however makes the argument that a standard approach can be formulated for these patients.

The author discussed the value of post-operative X-ray therapy, stating that its value increases the smaller amount of tumour that remains after surgery. However, this logical assumption is incorrectly evidenced by retrospective survival data from four cohorts of patients who had had varying levels of surgical intervention - with no regard to the fact that the disease status (including likelihood of metastatic disease) would clearly have been different between these cohorts. The author then goes on to contradict the previous statements arguing for uniformity of approach depending on the size of the post-surgical remnant, to state that even cancers of the same size, situation and shape would all respond differently to exactly the same X-ray treatment.

In the group of patients with 'incurable' lung cancer, the author argues that 'words are more valuable and more valued than actions and visits and discussions are more important than treatments'. He states that the clinicians treatment plan for these patients is further complicated as 'family personalities, preconceived ideas learnt from the Press, previous doctors, relatives with the disease, and so on, make for a multitude of possibilities to which only experience will give any help in the management'.

The author believes that chemotherapy should be limited to patients who cannot have X-ray therapy and who have superior vena caval obstruction; patients with multiple skin secondaries too extensive for X-ray therapy; patents with severe osteoarthropathy not relieved by X-ray; and patients with effusions.

The paper concludes by discussing the promise of hyperbaric treatment of cancer, stating that "the evidence at present is that under full oxygen saturation almost 100% of cancer cells are destroyed by present accepted maximum safe dose levels" (of X-ray). To conclude, the author speculates that the results of clinical trials of hyperbaric treatment in lung cancer "might be startling and send all radiotherapy departments into a fever of development".

Holt JAG (1965), The place of radiotherapy in the management of laryngeal cancer. *The Nisbet Symposium* pp. 199-203.

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This symposium review is similar to the previous publication in that it discusses the relative merits of surgery and radiotherapy, however in this case relating to laryngeal cancer.

Holt J (1965) A Trial of Thiethylperazine ("Torecan") in Patients Suffering from Radiation Sickness. *Med J Aust* 9(3): 199-203

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This report describes the incidence and severity of radiation sickness symptoms in patients, and compares two difference radiation sickness treatments.

Methods

The publication reports data from two retrospective cohorts of patients; approximately half of the patients treated between May 1961 to May 1962 and approximately half of the patients treated between May 1962 and Sept 1963. Differences in the X-ray treatment regimens between the two groups are not reported.

Patients in the early cohort (Group 1) had radiation sickness treated with dimenhydrinate 100 mg three time daily (with or without intramuscular pyridoxine), whilst those in the latter cohort (Group 2) received thiethylperazine (variable dose ranging from 6.5 mg tablet 1–5 five times daily).

Results

The rates of nausea and vomiting were similar in the two groups. Thiethylperazine provided nausea relief to 78% of affected patients, compared to 47% amongst the dimenhydrinate-treated patients. Vomiting was relieved in 76% and 54%, respectively. Some side effects were present with thiethylperazine.

The thiethylperazine-treated patients were then analysed according to the radiation dose they received (low, medium, high). The following results were obtained:

	Lose dose radiation (n=37)	Mid dose radiation (n=34)	High dose radiation (n=20)
Complete relief	65%	50%	35%
Fair relief	22%	18%	50%
Poor relief	13%	32%	15%

The author's interpretation of these data are that they "confirm the impression that the severity and difficulty in relieving radiation symptoms are proportional to the daily integral dose of radiation used". The author selectively refers only to the complete relief data, as this is not the picture if one considers complete + fair relief together. These data do not support such a statement.

Holt J (1965) The Biological Effects of Ionizing Radiations at very low dose rates. *Aust Dent J* 10(1): 38-40

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This publication is the transcript of a conference paper describing known or possible biological effects of low dose ionising radiation to a dental conference.

Holt J, Woodlife HJ, Davis RE, Neal JR (1967) Radiation and Marrow Infusion in Leukaemia. A patient with CGL Treated with Whole Body Irradiation and Infusion of Isogenic Marrow. *Aust Radiol* 11:63-66

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This publication reports a case study of a patient with chronic granulocytic leukaemia who was treated with radiation and an infusion of isogenic marrow from his monozygotic twin. The patient developed pneumonitis and died two months later. The value of marrow infusion, the radiation dosimetry and the problem of radiation pneumonitis are discussed.

Holt JAG (1971) The Value of Chemotherapy in Ovarian Cancer. *Aust Radiol* 15(2):160-163

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This publication reports a retrospective review of patient records of the radiotherapy departments and public hospitals of Western Australia, for 1955–1965 (although patients treated outside this time period are also discussed).

A total of 162 primary ovarian malignancies with appropriate histology were discovered in these hospitals during these years. The author states that these patients fall into two categories. Category 1 originally had suspected ovarian malignancy, followed by laparotomy and removal of all or most of the primary disease was possible. These patients had no ascites or evidence of spread beyond the pelvis. Category 2 have their diagnosis made by the presence of ascites together with evidence of malignancy in and outside of the pelvis. In the series under consideration, the author states that 53 patients would fall into category 1, whilst the remaining 109 patients would fall into category 2. The paper reports the treatment and five year survival of these two groups of patients.

Category 1:

The first group were predominantly treated with surgery (hysterectomy and bilateral salpingo-oophorectomy) with post-operative radiotherapy.

After 5 years, 30/53 (57%) were still alive, although seven had had a recurrence retreated within this time.

Category 2:

It is difficult to determine the treatment of the second group as this is poorly reported. To add to the confusion, the paper suddenly refers to an additional 39 patients' records retrieved from pre-1955, then sub-divides the patients into pre-1961 and post-1961.

With respect to the pre-1961 group, the paper states the "survival of the majority of these patients... was approximately 10 weeks". The author states there was no evidence at all that large-field X-ray therapy had appreciably altered the average survival, although their survival was longer (~14 weeks), they were more likely to have had a better prognosis when the decision was made to treat with X-ray therapy (ie., selection bias).

In the post-1961 group, various chemotherapy regimens replaced radiotherapy in this group. Patients were often treated with sequential trials of cyclophosphamide, chlorambucil and thio-tepa (dose regimen information is poorly reported, if at all). These drugs were used in that order, but starting with a different drug for each patient as they turned up in sequence. The length of time in remission on the drug on which they started was noted. This was then repeated for the next two drugs. The author states that "it is my opinion cyclophosphamide is the best of these three drugs". The paper states that 41 of 53 patients "have a clinical remission of their disease with reduction their ascitic fluid, and in the case of 28... the abdomen has apparently returned completely to normal". The average time to recurrence was 9 months, and the average survival for the entire group was 27 months.

No data is tabulated in this publication, and it is difficult to determine imbalance between the subgroups of patients who received each chemotherapy treatment first line, without the impact of cross-over treatments.

Toward the end of the paper, the author makes reference to an additional five patients with late ovarian cancer, massive ascites and secondary deposits throughout the abdominal cavity, who were treated with chemotherapy. The author states the response of these patients to cyclophosphamide was dramatic, "and within a few weeks the patients were apparently back to normal health". However on closer examination, all had residual abdominal tumours, which were then surgically removed, with or without post-surgical radiotherapy. "These patients remain alive four, three, two and one year after their second laparotomy or the radiotherapy following it."

In summary, the author concludes ovarian cancer is one cancer "for which chemotherapy has, in my opinion, offered an extremely effective method of palliation".

Holt JAG (1971) The Results of Treatment of Carcinoma of the Cervix in WA. *Aust Radiol* 15(2): 164-176.

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This publication is similar to the preceding report, although it refers to cervical cancer. The paper is a retrospective review of the treatments of cervical cancer in Western Australia between 1953 and 1965, although the report also includes a selection of patients treated between 1965 and 1968.

The authors presents the patients in groups, by disease stage and treatment received.

Results for patients treated Jan 1953–Feb 1962

Stage, number of pts	Treatment	Outcome
T1, n=32	Radiation alone	75% 5 yr disease-free survival
T1, n=28	Radiation then surgery	50% 5 yr disease-free survival
T2, n=46	Radiation alone	27% 5 yr disease-free survival
T2, n=32	Radiation then surgery	22% 5 yr disease-free survival
T3, n=22	Radiation + "occasionally surgery"	27% 5 yr disease-free survival
T4, n=15	No treatment information provided	13% 5 yr disease-free survival

Results for patients treated Feb 1962–June 1965

Stage, number of pts	Treatment	Outcome
T1, n=39	Radiation alone	69% 5 yr disease-free survival
T1, n=8	Radiation then surgery	38% 5 yr disease-free survival
T2, n=58	Radiation alone	59% 5 yr disease-free survival
T2, n=9	Radiation then surgery	44% 5 yr disease-free survival
T3, n=22	Radiation +/- surgery	23% 5 yr disease-free survival
T4, n=23	No treatment information provided	13% 5 yr disease-free survival

Results are also presented for a highly selected sub-set of surgically-treated patients who were later referred to RT departments. This takes no account of the outcome of patients who received surgical treatment alone.

Once again the investigator makes no allowance for the fact that patients with different prognoses may have been candidates for different treatments (ie., selection bias) which is likely to have had considerable impact. For example, patients who received treatment with both radiation and surgery may have had more extensive disease.

The investigator concludes that the results "lead me to the conclusion that in Western Australia the natural history of carcinoma of the cervix is such that primary surgery should not be performed for a T1(in situ), T1 and T2 carcinoma". Such a conclusion is certainly not supported by a retrospective review such as this, that is likely to suffer from inherent selection bias.

Herrmann RP, Dougan L, Holt JAG, Jackson JM, Matthews MLV, Nelson AJM, Stenhouse NS, Woodlife HJ (1972) Chronic Granulocytic Leukaemia - Comparison of Uracil Mustard and Busulphan. *Med J Aust* 1:789-791

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This publication reports 22 patients with chronic granulocytic leukaemia, who received alternating courses of intermittent busulphan and uracil mustard therapy. Remission criteria were i) total white cell count falling to 20,000/µl or less; ii) splenic size reduced by 50%. It is not clear whether either or both of the criteria had to be met.

Patients received sequential alternate courses of the two drugs, and all courses were included in the analyses - ie., irrespective of whether an initial and subsequent course.

Time to induction of remission and duration of remission were the same with the two treatments, as were side effects.

Holt JAG (1973) The detection of breast abnormalities by thermography. *Australasian Radiology* 17: 453-463.

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This publication describes two years of use of the AGA Thermovision Unit in Western Australia for the thermographic examination of female breasts. A total of 1,512 women were screened with 1,025 read as 'normal' and 487 'abnormal'. None of the former group were found to have breast carcinoma, although the follow-up period was too short to confirm this. Only 35 of the 487 patients with abnormal actually had carcinoma. In summary, thermography in isolation has poor sensitivity with an unacceptably high false positive rate.

Holt JG (1974) The Cure of Cancer. A Preliminary Hypothesis. *Aust Radiol* 18: 15-17.

Relevance to current review: Not a clinical study, opinion piece.

The author presents a list of opinions relating to various treatments for cancer (eg. surgery, x-ray radiation therapy, cytotoxic chemicals and microwave radiation therapy).

This publication postulates that: "Cancer can be cured when the method of treatment specifically kills cancer cells only without damage to the normal. Microwave radiation therapy complies with both criteria and can thus cure cancer."

The author presents a list of factors that, in his opinion, will stop patients being cured from cancer by microwave radiation therapy. The author states:

"Therefore one cannot cure patients:

a) who cannot stand erect for a few minutes

b) whose cardiac physiology is insufficient to tolerate moderate stress

c) in whom uptake of microwave energy does not occur. To date all patients have shown uptake and include carcinomata of tongue, pharynx, larynx, oesophagus, skin, stomach, pancreas, colon, rectum, cervix, ovary, vagina, lung and sarcomata such as chondrosarcoma, rhabdomyosarcoma, fibrosarcoma, reticulum cell sarcoma, lymphosarcoma and all the lymphoma tried. The glioma also takes up energy and appears curable. Metastases are equally sensitive.

d) in whom the necrosis of their cancer will cause major calamity…."

The author presents a list broad ranging and largely unsubstantiated implications that in his opinion will occur due to the introduction of microwave radiation therapy. The author states:

"The implications of this discovery are tremendous.

1) **No patient will ever become a chronic cancer nursing problem again if treated correctly with microwave radiation**.

2) Inpatient accommodation for microwave radiation patients will be much less than required for all other types of therapy.

3) **Cytotoxic therapy is "dead" in its present form**. Perhaps it may occasionally survive in association with other methods for some rare cancers.

4) X-ray therapy is of value for pituitary adenomata, artificial menopause, intracranial arterio-venous malformations, syringo-myelia, rheumatic diseases, pterygia and warts, etc.

5) **Cancer surgery will be revolutionised.** It will be needed to make diagnosis and perform such operations as are essential to prevent complications which will arise from tumour necrosis. **Radical cancer surgery is therefore unnecessary. Surgery need only remove the primary and microwave therapy will be able to kill the metastases**."

The author concludes that: "**All current cancer research in the world becomes pointless, except that relating to experiments relating to human cancer and microwave therapy.**"

The author states: "**There is therefore no need to wait five or ten years to predict that this type of microwave radiation therapy can cure cancer.The author can predict without fear or favour that this will be found to be correct in due course.**"

Holt JAG (1975) The Principles of Hyperbaric and Anoxic Radiotherapy. *Brit J Radiol* 48: 819-826.

Relevance to the current review: Excluded, not a microwave therapy study.

Describes a number of factors that the author believes require exact control if hyperbaric therapy is to be used to full advantage. These factors are as follows:

1) Rate of pressurisation of the chamber
2) Soaking time
3) Decompression rate
4) Gas temperature
5) Humidity
6) Type of anaesthesia
7) Treatment planning and patient set up
8) Optimum dose
9) Contradictions for treatment

The author discusses anoxic therapy and where he believes the therapy can only be rationally used, the essential features of the treatment and the essential steps, which he believes, must be taken after the tourniquet is put in place.

The author presents a number of case studies of patients treated with x-ray therapy and anoxia. The author also presents a case series of patients treated with hyperbaric therapy.

The author concludes on the basis of these uncontrolled case studies that: "These two methods [anoxia and hyperbaric radiotherapy] have produced such excellent clinical responses that those malignancies which experience has taught can be best treated must indeed be so managed if the patient is to be given the best chance of cure or palliation. No other ethic or moral decision is possible."

Holt JAG (1975) The Use of V.H.F Radiowaves in Cancer Therapy. *Aust Radiol* 19(3): 223-241.

Relevance to the current review: Portions of this publication were included in the safety section of the systematic review.

Initially the publication describes the equipment used to generate V.H.F. radiation for cancer therapy. The author describes the apparent effect of V.H.F. radiation in a series of case reports. These case reports include patients with: astrocytoma; carcinoma of the breast with multiple metastases; primary pancreatic carcinoma; squamous carcinoma of the neck. The publication then details the death of one child treated with V.H.F. for a glioma in the left posterior parietal region.

The author states: "It is our opinion, however, that the best results come from using V.H.F. synchronously with x-ray therapy. Under such circumstances it is our experience that V.H.F. is a radio-sensitiser without equal."

The author describes, in brief, the first 363 patients treated in the first 9 months of the microwave facilities operation. The publication then presents 13 separate case reports of patients with a variety of cancers treated with V.H.F. (eg. Squamous cell carcinoma of the pyriform fossa, papillary adenocarcinoma of the thyroid, carcinoma of the descending colon, etc).

Holt JAG, Nelson A. (1976) Four Years of Microwaves in Cancer Therapy. *J Belge Radiol* – Belgisch Tijdschr Radiol 62: 467-476.

Relevance to the current review: Included in the safety portion of the systematic review. The relevant patient data has been extracted from the publication and is presented in the systematic review. Excluded from systematic review of efficacy as wrong study design to address research question (or duplicate data).

The publication presents a collection of previously reported case series of patients treated with combinations of VHF, radiotherapy and cytotoxic compounds. The case series include patients with: 1) head and neck cancer; 2) breast and axilla cancer; 3) bone metastases; 4) liver metastases; 5) primary or metastatic brain cancer lesions; 6) lung cancer; 7) abdomen cancer; 8) rectal cancer; 9) bladder and prostate cancer; 10) sarcomata; and 11) lymphoma.

The authors conclude that: "**VHF constitutes a non-toxic form of therapy applicable to all cancers, in all stages and all sites, even after conventional methods have failed.** It has proven to bet the best radio-sensitiser so far."

Holt JG. (1977) Increase in X-ray Sensitivity of Cancer After Exposure to 434 MHz Electromagnetic Radiation. *Journal of Bioengineering*. 1: 479-485.

Relevance to the current review: Included, contains duplicate patient data. Relevant patient information has been extracted from the publication and is presented in the accompanying systematic review.

The publication presents a series of 52 patients with head and neck cancer treated with 434MHz electromagnetic radiation and x-radiation. This group of patients was

compared with two selected historical control groups, one treated with x-irradiation alone, and the other treated with x-irradiation under 3 atmospheres hyperbaric oxygen at 37 degrees Celsius. It should be noted that these types of comparisons are prone to high levels of bias. Despite this, the authors conclude that: "The use of 434 MHz H-wave electromagnetic waves has been shown to be an 'exquisite radiosensitiser' in our preliminary clinical experiences. This appears to be partly non-thermal."

Nelson AM, Holt JG (1977) The problem of clinical hyperthermia. *Aust Radiol* 21: 21-30.

Relevance to the current review: Included, the relevant patient data has been extracted from the publication and is presented in the accompanying systematic review.

The authors discuss the historical origins of hyperthermia usage. The researchers then discuss in vitro and animal model cancer cell responses to radiation and heat. The publication presents different methods of heating tumours (eg. whole body heating and VHF) and the variation of response different tissues have to VHF radiation. The authors then detail the results of a number of whole body hyperthermia experiments conducted in Perth and why the researchers decided to use VHF to induce hyperthermia instead. The next section of the publication describes the Tronado equipment used to generate the VHF for cancer treatment. The researchers also discuss the putative benefits of heat on cytotoxic drug action.

The authors present a case series of 27 patients with secondary cancer in the bone treated with a combination of VHF (via the Tronado machine) and various combinations of 'cytotoxic drugs' and radiotherapy. The authors state that all patients were relieved of pain after the first course; nineteen patients lived 11-26 months; seven died after 7-20 months.

The publication presents a case series of 12 cancer patients with a large painful liver (in 10 patients a liver scan showed large deposits) that were treated with radiotherapy and VHF and injections of cyclophosphamide. The author states that all patients had complete and fairly rapid pain relief; five deaths occurred at 2-13 months; seven other cases survived 3-18 months; and one other patient died in the subsequent five months.

A previously reported case series of 52 patients with ENT cancers treated with 434MHz electromagnetic radiation and x-radiation are presented. This group of patients was compared with two selected historical control groups, one treated with x-irradiation alone, and the other treated with x-irradiation under 3 atmospheres hyperbaric oxygen at 37 degrees Celsius. It should be noted that these types of comparisons are prone to high levels of bias. Despite this, the authors state that: " … in all respects the hyperthermia combination is almost twice as effective as hyperbaric therapy, or three to four times as effective as conventional therapy."

The authors state: "**It was clear to us that except in a few rare cases, the microwave form of hyperthermia used alone would not provide a cure for cancer.**"

The researchers conclude that: "… hyperthermia is to be considered as a powerful adjuvant to conventional cancer treatment methods. **It would be unethical to conduct a controlled trial to test hyperthermia alone against other modalities, as it is clear that used alone it is unlikely to cure or do more than temporary objective palliation.**"

Nelson AM, Holt JAG. (1978) Combined Microwave Therapy. *Med J Aust.* 2: 88-90.

Relevance to current review: Included, patients with head and neck cancer.

The publication describes 52 cases of advanced head and neck cancer treated with 434MHz radiowave hyperthermia combined with cobalt radiotherapy and/or gold grain implant. The authors compare these results with the results of: 1) 52 patients treated with radiotherapy and hyperbaric oxygen over two years, and; 2) 52 patients treated with super-voltage therapy alone, before 1970.

The authors state: "**No local cures could be obtained by this microwave hyperthermia alone, but where radiation was added, a marked sensitivity was seen**, …"

It should be noted that these types of comparisons are prone to high levels of bias. Despite this, the authors state that: "**According to every parameter, the combined microwave treatment was two or three times better than conventional treatment**…"**And**, "**microwave hyperthermia appears to be a superior and effective adjuvant to treatment with ionising radiation for advanced cancer of the ear, nose and throat group**."

Holt JG. (1979) The Cause of Cancer: Biochemical Defects in the Cancer Cell Demonstrated by the Effects of Electromagnetic Radiation, Glucose and Oxygen. *Medical Hypotheses*. 5: 109-143.

Relevance to the current review: Included in the safety portion of the systematic review.

Note about this journal: Medical Hypotheses is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. **Medical Hypotheses takes a deliberately different approach to peer review**. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. **Medical Hypotheses will publish radical ideas**, so long as they are coherent and clearly expressed. In Medical Hypotheses, the authors' responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a "chooser", and not a "changer".

The publication lists various theories regarding VHF, glucose metabolism and carcinogenesis.

The author discusses 380 patients with a wide variety of primary cancers (eg. lung, breast, prostate etc) treated with VHF alone ("after they had been unsuccessfully treated by all other appropriate conventional methods"). The researcher also discusses 322 seemingly unrelated patients with vertebral collapse due to metastatic cancer that were treated with x-ray therapy and/or cytotoxics. The author makes the following statement based on his comparison: "In contrast, [to the group treated x-ray therapy and/or cytotoxics] VHF can not only palliate the disease by killing cancer cells but in addition influences the normal tissue to regenerate in their former shape and appearance." The researcher presents various histological photographs and radiographs of case studies to attempt to support these hypotheses.

In Appendix A the author presents the methodology used for temperature measurements in 41 of the 380 patients treated. Photographs of a patient with malignant Schwannoma treated with x-ray and VHF are also presented.

In Appendix B the author postulates that VHF has non-thermal effects on cancer. Previously reported data on patients with head and neck cancer and patients treated by whole body heating are presented to attempt to support this hypothesis. The author concludes: "VHF has non specific thermal and specific thermal effects on cancer."

In Appendix C the author argues that VHF at 434MHz is cancericidal. The author attempts to support this hypothesis by presenting three patient case studies.

Appendix D discusses a number of hypothesised effects of low intensity 434MHz radiation on cancer.

Appendix E discusses temperature increases and power consumed by the VHF apparatus when it was used in: 50 patients with widespread cancer, 22 volunteers with no cancer and saline phantoms. The deaths of two patients during VHF therapy are also discussed.

In Appendix F the researcher postulates that 434 MHz VHF therapy at an intensity of 11 m w/sq cm increases cancer-doubling time unless patients are anoxic and hypoglycaemic, in which case the 'stimulant effect' of VHF on cancer colonies is prevented. The researcher attempts to support this theory by comparing a small series of patients that received VHF to various parts of the body to another group of patients that had cancer metastases to their forearms. The patients in the latter group had a tourniquet applied to their forearms and were instructed to gently exercise their forearm prior to VHF therapy to induce anoxia or were treated with systemic insulin to induce severe hypoglycaemia.

The author states that: "**Most patients expressed their interest [in the study] and said that they were prepared to undergo any simple experimentation to try and find the cause of cancer.**"

In Appendix G the author presents a crude study to support the hypothesis that the application of VHF appears to accelerate normal skin healing processes and improve the cosmetic appearance of biopsy scars.

Appendix H presents additional patient data on the 380 patients discussed in the body of the publication.

Holt JG. (1980). Alternative therapy for recurrent Hodgkin's disease. Radiotherapy combined with hyperthermia by electromagnetic radiation to create complete remission in 11 patients without morbidity. *Brit J Radiology* 53: 1061-1067.

Relevance to current review: Excluded from systematic review as wrong study design to address research question.

This publication describes the methods used and the results obtained when 11 patients with recurrent Hodgkin's disease were treated with various doses of combined radiotherapy and hyperthermia.

The author also describes two separate pieces of equipment used to deliver hyperthermia treatment (ie. 12 dipole x 200W device and a 4 dipole x 0.1 – 2 kW device). Additionally, the publication briefly describes temperature measurement studies

using these hyperthermia devices on a phantom of agar jelly. These studies showed significant rises at axial points in the phantom up to 20 cm outside the radiation space. They also indicated the existence of hotspots in cross-sections of the phantom.

The author also discusses the use of streptokinase therapy in conjunction with hyperthermic therapy.

Nelson AM and Holt JG. (1980) Microwave Adjuvant to Radiotherapy and Chemotherapy for Advanced Lymphoma. *Med J. Aust.* 1: 311-313

Relevance to the current review: Excluded from systematic review as wrong study design to address research question.

This publication describes the treatment of 40 patients with recurrent Stage IV lymphoma. The patients received a combination of a wide variety of cytotoxic drugs, radiotherapy and 434MHz microwave therapy. The author states: "A complete remission, represented by total disappearance of masses, a good health, and a normality of blood count, occurred in 34 (85%) of patients after the first definitive treatment. Twelve of these developed some evidence of disease after six or more months, and received appropriate treatment with further remission. "

The author provides theories regarding the thermal and non-thermal effects of VHF. The author also discusses theories regarding glucose metabolism and cancer treatment.

The author concludes that: "…VHF microwave hyperthermia therapy is a powerful synergist to conventional agents with a considerable potential for treatment of advanced and recurrent malignant tumours."

Holt JAG (1980) The Extra Nuclear Control of Mitosis and Cell Function. A Theory of Cellular Organisation. *Medical Hypotheses*. 6: 145-192.

Relevance to the current review: Excluded from the systematic review, wrong outcomes reported.

Note about this journal: Medical Hypotheses is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. **Medical Hypotheses takes a deliberately different approach to peer review**. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. **Medical Hypotheses will publish radical ideas**, so long as they are coherent and clearly expressed. In Medical Hypotheses, the authors' responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a "chooser", and not a "changer".

The author postulates many theories regarding mitosis, cell division, glucose metabolism, cell growth, and VHF, etc.

The author describes around 700 cancer patients who were treated with VHF alone or in combination with x-ray therapy and/or cytotoxics. The author describes the two forms of equipment used to generate VHF. The author presents measures of 'reflected power' in 7 selected patients.

The researcher discusses clinical observations (primarily 'reflected power measurements') of patients treated with VHF and various other agents. These other agents included: 1) Ethanol; 2) D-fructose; 3) L-glucose ; 4) 'Glucose analogues'; 5) D- and L-mannose;

6) D- and L-Fucose; 7) Azaserine and DON; 8) Insulin; 9) Biguanides/Sulphonyl Ureas; 10) Streptokinase; and 11) Steroids. From these observations the author draws conclusions about glucose metabolism in cancer and normal cells.

The author states: "patients with advanced widespread cancer treated whilst they were clinically inebriated achieved long term remission of their cancer …" The author then presents a list of theories to explain his observation.

The author expounds a theory that the cell has a CEO (Chief Executive Officer) and this 'CEO' "has an existence as the entity which controls every cell's destiny." The researcher explains that this 'CEO' "Interprets the nuclear blueprint and builds the adult cell and whole body to its genetic information." The author believes that the 'CEO' resides in the ENCC (extra nuclear cell constituents) and has "two 'foremen' which whilst interconnected probably supervise the two distinct areas of (a) maintenance of normal, cellular perfection and (b) supervision of function of the cell."

The publication presents theories on the following topics: 1) VHF induced resonance in compounds in cancer cells; 2) the interaction between VHF and cytotoxic compounds; 3) the metabolic requirements of cancer cells; 4) mechanism of spontaneous remission in cancer; 5) oxygen's effect in radiotherapy; 6) insulin tolerance of patients with cancer; and 7) cytotoxic chemicals.

The author states: "**The place of conventional cytotoxics is thus seen (with very few exceptions) to be as agents for euthanasia rather than for therapy.**"

Holt J (1982) 434MHz as an Adjuvant in Cancer Therapy: A Survey of Results Obtained and the Biochemical Knowledge Derived from the Use of this Therapy. *Progress in Radio-Oncology II*. 425-433.

Relevance to the current review: Portions of this publication were included in the systematic review.

The publication describes the two pieces of equipment used by the researchers to generate VHF for cancer treatment.

The authors present a collection of case series some of which have been reported previously. The relevant patient data has been extracted from the publication and is presented in the accompanying systematic review. In summary, the patients in these case series were treated with various combinations of VHF, radiotherapy, 'glucose analogues', hypoglycaemia and streptokinase. The case series include patients with: 1) Hodgkin's disease; 2) Non-Hodgkin's lymphoma; 3) rectal cancer; 4) breast cancer; 5) head and neck cancer; 6) bladder cancer; 7) prostate cancer; 8) primary brain cancer; and, 9) other cancers.

The publication revisits a hypothesis reported in Holt (1979) where the researcher states that 434 MHz VHF therapy at an intensity of 11 m w/sq cm increases cancer-doubling time unless patients are anoxic and hypoglycaemic, in which case the researcher believes the 'stimulant effect' of VHF on cancer colonies is prevented. The researcher attempts to support this theory by comparing a small series of patients that received VHF to various parts of the body to another group of patients that had cancer metastases to their forearms. The patients in the latter group had a tourniquet applied to their forearms and were instructed to gently exercise their forearm prior to VHF therapy to induce anoxia or were treated with systemic insulin to induce severe hypoglycaemia.

The researcher concludes that: "**Under VHF stimulation cancer cells loose all their characters of differentiation and function, i.e. they become 'primitive', yet without the potential of embryo cells to form more adult structures**."

The author also presents various theories on glucose metabolism and carcinogenesis.

Holt JG. (1983) Cancer, a Disease of Defective Glucose Metabolism. The Energy for Mitosis Appears to Come From a Glutathione Mediated Glycolysis. *Medical Hypotheses*. 10: 133-150.

Relevance to the current review: Excluded, not peer-reviewed, not a clinical study, opinion piece.

Note about this journal: Medical Hypotheses is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. **Medical Hypotheses takes a deliberately different approach to peer review**. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. **Medical Hypotheses will publish radical ideas**, so long as they are coherent and clearly expressed. In Medical Hypotheses, the authors' responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a "chooser", and not a "changer".

The author postulates various theories regarding the interplay between glucose metabolism, cell cycling, carcinogenesis, mitosis, glutathione and VHF radiation.

The author also presents theories regarding the radiosensitising effects of VHF on cancer.

Holt JG. and Nelson AM (1985) Squamous-cell carcinoma treatment. *Med J Aust*. 142: 79-80.

Relevance to the current review: Excluded not a peer reviewed clinical study, letter to the editor.

This letter to the editor requests more information regarding a publication on the response to combination cytotoxic treatment of squamous cell carcinoma conducted by Woods *et al.* (1984).

The author states: "However, our own work suggests that a microwave adjuvant with radiotherapy results in a striking clearance of these advanced tumours, and with a lower than usual radiation dose."

Holt JG. and Nelson AM (1985) Combined Microwave Therapy. *Med J Aust*. 142: 707-708

Relevance to current review: Non peer-reviewed letter presenting previously described patient data.

The publication presents the crude 3 and 5-year survival rates of a series of ENT patients treated with microwave therapy and/or conventional therapy.

The authors discuss other centres that have been involved in similar research. They believe that 16 major US oncology centres are using apparatus similar in concept to the Tronado machine. The authors also discuss a Japanese company that has developed an 8MHz hyperthermia device, which is to be used as an adjuvant to radiotherapy or chemotherapy.

The authors conclude that it is time to conduct some "serious randomised controlled trials". The researchers believe that in their experience adjuvant 434MHz hyperthermia is more effective than other wavelengths or whole-body hyperthermia.

Holt JG and Stanford RW (1986) The synergism between hyperthermia and ionising radiation. *The British Journal of Radiology*. 59: 795-796.

Relevance to current review: Excluded, previously reported patient data.

The author discusses the use of Electromagnetic non-ionising radiation (EMR) in combination with x-ray therapy. The author postulates that EMR induced hyperthermia has the potential to "shield" normal tissue while maintaining its increased cell kill ratio per x-ray dose applied. The author also believes that there is no categorical evidence, which indicates X-irradiation sequelae are deleteriously enhanced by the use of EMR.

The publication presents previously published crude survival data for three series of patients treated for head and neck cancer (Nelson and Holt, 1978). The first group was treated with EMR and ionising radiation, the second was treated with ionising radiation and hyperbaric oxygen and the third was treated with ionising radiation alone.

The author also presents previously reported crude survival rates for two later series of patients treated with combination therapy or conventional therapy (Holt and Nelson, 1985).

The author compares these case series of patients treated with combination therapy (ie. EMR and ionising radiation) and those treated with ionising radiation alone. It should be noted that these types of comparisons are prone to high levels of bias. Despite this, the author concludes that the most beneficial treatment regimen "has to be" some combination of EMR and ionising radiation.

Holt JG, (1986) The Fundamental Chemistry of Life. *Medical Hypotheses*. 12: 359-367.

Relevance to current review: Excluded, not a clinical study, opinion piece.

Note about this journal: Medical Hypotheses is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. Medical Hypotheses takes a deliberately different approach to peer review. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. Medical Hypotheses will publish radical ideas, so long as they are coherent and clearly expressed. In Medical Hypotheses, the authors' responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a "chooser", and not a "changer".

This publication presents a list of hypotheses regarding life's creation and evolution. In addition the publication presents theories on: control of exponential growth, carcinogenesis, the Pasteur effect etc.

The author advocates the now discredited evolutionary mechanism, Lamarckism. The publication states: "In theory, Lamarckism would appear to be the only effective possible method of preserving survival in any species …"

Lamarckism argues that traits that are acquired (or diminished) during the lifetime of an individual organism can be passed on to the offspring (for example: a blacksmith, through his work, strengthens the muscles in his arms. Lamarckism theorises that this blacksmith's sons will have similar muscular development when they mature).

Holt JG (1986) Clinically derived dose-effect relationship for hyperthermia given in combination with low-dose radiotherapy. *The British Journal of Radiology*. 60: 100-101.

Relevance to the current review: Excluded, not a clinical study, letter.

The author notes that they (Holt and Nelson) have treated in excess of 6000 patients with combined therapy using non-EMR heating or EMR as an ionising radiation adjuvant. The researchers note that they measured the temperature "in most of the first 1000 or so patients" treated. The authors have "abandoned routine temperature measurements in 1977 and now solely use the regime [regimen] of 434MHz EMR delivered before 150-180cGy (rads) X-ray therapy on two or three occasions per week."

The author states: "Irradiation at 434 MHz quickly followed by X-ray therapy produces responses so different from any other regimen as to suggest a non-thermal mechanism." The author supports this statement by referring to a low level of evidence, poor quality 'historically controlled' trial of patients with head and neck cancer. These types of comparisons are prone to high levels of bias. Regardless of this fact, the author states: "If 434MHz (frequently inducing a low temperature rise, often well below 41.8 degrees C) plus x-ray therapy produces a survival three times as good as that from x-rays alone or from an identical (or larger) dose of X-ray therapy proceeded or succeeded by simple hyperthermia to 41.8 degrees C, then only a non-thermal EMR induced sensitisation could account for the difference."

Holt JG and Nelson JM (1988) Synchronous Radiation and Chemotherapy. *Med J Aust*. 148:370

Relevance to the current review: Excluded not a clinical study, letter

This letter contains a response to a review of synchronous radiation and chemotherapy for locally advanced cancer by Dr Denham of Newcastle Mater Misericordiae Hospital. Dr Denham concludes that most results are not decisively better than are those of the existing treatments and he urges further large-scale trials. Dr Holt and Dr Nelson disagree.

A previously reported case series of 52 patients with otolaryngological cancers treated with 434MHz electromagnetic radiation and x-radiation is presented. This group of patients was compared with a historical control group. It should be noted that these

types of comparisons are prone to high levels of bias. Despite this, the authors conclude that: "The three-year apparent cure rate [of those patients treated with 434MHz] was three times that of historical control subjects."

Dr Denham replies by stating: "The letter by Dr Holt and Nelson contains a mixture of facts, supposition and innuendo which potentially is confusing to the reader and has little to do with the substance of my review article."

Holt JG. (1988) Microwaves Are Not Hyperthermia. *The Radiographer*. 35 (4): 151-161

Relevance to current review: Included in the review. Some patient data reported previously.

This publication postulates that microwaves at 433-434MHz radio-sensitises cancer without having to induce hyperthermia. This hypothesis is largely based on the author's assertion that cancer 'fluoresces' when treated with microwaves at 434MHz. The author also presents a previously reported historically controlled series of 52 patients with head and neck cancer treated with 434MHz electromagnetic radiation to 'prove' that 434MHz "must have specific non-thermal effect on cancer." It should be noted that these types of comparisons are prone to high levels of bias and the benefits the author has perceived to be due to 434 MHz may be due to the inherent bias present in these types of studies. However, even if this were considered adequate evidence of clinical effect, this would in no way provide evidence to support the author's putative mechanism of action.

The author describes the equipment originally used to deliver microwave therapy (Tronado machine, 12 x Erbe UHF 200 W generators) and a redesigned version of the equipment (4 x 1-2kW generators).

The publication presents various groups of cancer patients treated with microwave therapy. These groups include patients with: 1) head and neck cancer; 2) oesophageal cancer; 3) gastrointestinal cancer; 4) rectal cancer; 5) bladder cancer; 6) hodgkin's disease; 7) lymphoma and non-hodgkins lymphoma; 8) other cancers; and 9) skin cancer.

The author concludes that: "In the author's opinion UHF is the greatest advance in cancer therapy since the discovery of radioactivity by Madame Curie."

Holt JAG (1991). Untitled letter to the editor, *The Journal of Microwave Power and Electromagnetic Energy* 2(3): 126-127.

Relevance to current review: Excluded from systematic review as non-peer reviewed letter only. Refers to his hypotheses of non-thermal effects of microwaves. A peer-review of the letter was sought by the journal's editor-in-chief.

This letter to the editor is a response to an Editorial that discussed the question of whether or not there are any athermal effects of microwave on food spoilage organisms. The response by Dr Holt is accompanied by a reply by Dr John Osepchuk (requested by the Editor), which is also referred to here.

Dr Holt commences the letter by referring to two of his publications relating to the non-thermal effects of 434 MHz radiation on cancer (Holt 1986 - actually Holt and Stanford; Holt, 1988). The hypotheses put forward in these publications are largely based on 1)

the author's assertion that cancer 'fluoresces' when treated with microwaves at 434MHz, and; 2) that the results of a previously reported **historically controlled** series of 52 patients with head and neck cancer treated with 434MHz electromagnetic radiation were so impressive that they 'prove' that 434MHz "must have specific non-thermal effect on cancer." It should be noted that these types of comparisons are prone to high levels of bias and the benefits the author has perceived to be due to 434 MHz may be due to the inherent bias present in these types of studies. (Even if this were considered adequate evidence of clinical effect, this would in no way provide evidence to support the author's putative mechanism of action.) Despite this, the author believes that the radiosensitivity of cancer cells can be two or more decades higher following exposure to this type of radiation than it is after heating the cancer to the maximum tolerable body temperature (41˚C). He states that "the non-thermal effect on cancer is not present at any of the other frequencies that I have tested and has resulted in my abandoning these frequencies for practical clinical purposes".

Dr John Osepchuk of the Raytheon Research Division in USA responds by pointing out that the diathermy exposure at 434 Mz reported in Holt & Stanford 1986 can be characterised as 8 times the whole body limit of 0.4 watts/kg specified by ANSI C95.1-1982 standard. The exposures used in Holt 1988 were up to 80 times the C95 limit - and therefore if there is any athermal effect it is unlikely to be of relevance to lower exposure limits.

Dr Osepchuk states that "whether or not there is an athermal effect in Dr Holts work is debatable". He states that the simple comparison of the UHF effect with that obtained when a similar temperature is created by non-electromagnetic waves (eg. hot bath) ignores a) differences in temperature-time history and b) differences in heating and distributions throughout the tissue volumes. He states that Dr Holt's claims that athermal effects are site-specific, frequency-specific and that one can not expect to discover any non-thermal effect in a target which displays uniform absorption are "**sweeping generalities not likely to be endorsed by many at either end of the spectrum of believers to skeptics**".

Dr Osepchuk also points out that there is no evidence of measurements to support Dr Holt's claim of a 'fluorescence' that is peculiar to his irradiation with the Tronado machine.

Holt JAG (1993). The glutathione cycle is the creative reaction of life and cancer. Cancer causes oncogenes and not vice versa. *Medical Hypotheses* 40(5): 262-266.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

Note about this journal: Medical Hypotheses is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. **Medical Hypotheses takes a deliberately different approach to peer review**. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. **Medical Hypotheses will publish radical ideas**, so long as they are coherent and clearly expressed. In Medical Hypotheses, the authors' responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a "chooser", and not a "changer".

This paper contains a diverse range of ideas, that have not been subject to peer-review. The deviate quite considerably from accepted medical knowledge and from accepted understanding of biology. The paper makes several extreme and selective leaps of logic between varies hypotheses, without evidence.

The following points are made by the author:

- The glutathione cycle (oxidation and reduction) is the creative reaction of life and cancer.
- 434 MHz microwave radiation (and 434 MHz alone) stimulates cancer growth rate by forcing this cycle into activity
- Cancer causes oncogenes and not vice versa
- Genetic material will only reproduce if placed within an immortal cell in which all controls of the glutathione system have been lost, as in a cancer cell.
- All life forms die if any or all of their chemical reactions are reversed.
- Comparative photograph of a biopsy pre- and immediately post UHF treatment is presented. On the basis of one pathologist's review of these pre- and immediately post-UHF biopsies, "UHF had altered the microscopic appearance so grossly that one cancer had changed into a different one". NB. This patient was treated with 20 mW/cm2 - approximately 20 times the ANSI C95.1 1999 maximum permissible exposure limits.
- The authors argues that the increase in the mortality rate for chronic myeloid leukaemia in the late 1960s was due to the advent of television ("3 high powered TV transmitter, radiating 90% of the population"). He does not presented mortality from any other cancers for the same time period. He cites this as evidence supporting "the hypothesis that cancer can be influenced by factors which do not influence genetically controlled situation".
- Brief clinical details of 11 highly selected patients in listed in an Appendix. Most of these patients have been presented elsewhere in Dr Holts clinical papers.

Holt JAG (1995) Some characteristics of the glutathione cycle revealed by ionising and non-ionising electromagnetic radiation. *Medical Hypotheses* 45(4) 345-368.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

Note about this journal: Medical Hypotheses is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. M**edical Hypotheses takes a deliberately different approach to peer review**. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. **Medical Hypotheses will publish radical ideas**, so long as they are coherent and clearly expressed. In Medical Hypotheses, the authors' responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a "chooser", and not a "changer".

This publications expands upon the glutathione cycle hypotheses presented in the Medical Hypotheses publication above (Holt, 1993).

In addition the author states:

- The glutathione reaction produces the energy for mitosis and is kept in controlled inactivity until needed to maintain perfection of form and function by energising mitosis.
- UHF changes the glutathione reaction from inactive to active and in doing so causes resonance and/or fluorescence of the glutathione cycle.
- The glutathione reaction is intelligent compared with non-exponential reactions but cannot be the basis of intellectual brain functions which must be based on non-exponential chemical processes.
- One's brain mutates to increase its learning (referred to by the author as chemical evolution). The author provides a discussion about the increases in intelligence within an individual and also the inheritance of intelligence.
- Evolution therefore cannot be by chance and the Darwinian theories must be incorrect. Adaptation to environment as it is exemplified by the automatic combination of the glutathione cycle and Pasteur reaction controlling it indicate that evolution is automatic and of Lamarckian form.
- The author introduces the concept of electrical evolution (the glutathione cycle) and states this is the "direct cause of the evolution of the species".
- It is proposed that Alzheimer's disease is due to an excessive chemical reaction leading to the overgrowth of neuronal proteins, thus producing the classic 'tangles' of neural tissue.
- Simple heating (ie., achieved by means other than UHF) doubles the radiosensitivity of cancer, but UHF may increase it by up to 20 times.

The author commences the Discussion with the statement "Cancer does not have the characteristics of an inherited disease and cannot be recognised as can all genetically-controlled life eg. elephants, tigers etc". The publication concludes with the statement "Life is an atheistic phenomenon of the electrochemical reactions of glutathione".

Holt J (1996) Cancer therapy by immobilizing mitotic energy sources. *Journal of Orthomolecular Medicine* 11(2): 100-111.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

Note about this journal: This is the quarterly journal of the Orthomolecular Society. Orthomolecular medicine is a branch of complementary medicine that describes the practice of preventing and treating disease by providing the body with optimal amounts of substances which are natural to the body. In the orthomolecular view, the provision of vitamins, amino acids, trace elements or fatty acids in amounts sufficient to correct biochemical abnormalities will be therapeutic in preventing or treating diseases such as atherosclerosis, cancer, schizophrenia or depression.

This is a further publication referring to the importance of the glutathione reaction in the creation of life, cancer and the treatment of cancer.

The Methods section of the paper lists treatment information for seven patients treated seven different ways, but makes no reference to histopathological investigation or cell culture procedures. However, then the Discussion section proceeds to discuss the rate of cell kill that appears to be purely theoretical speculation. This is misleading for the reader as it implies that cellular measurements were actually made.

Holt, J. (1997) A theoretical biochemical basis of cancer: confirmation by electromagnetic radiation. *Journal of Orthomolecular Medicine* 12(3): 149-163.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

Note about this journal: This is the quarterly journal of the Orthomolecular Society. Orthomolecular medicine is a branch of complementary medicine that describes the practice of preventing and treating disease by providing the body with optimal amounts of substances which are natural to the body. In the orthomolecular view, the provision of vitamins, amino acids, trace elements or fatty acids in amounts sufficient to correct biochemical abnormalities will be therapeutic in preventing or treating diseases such as atherosclerosis, cancer, schizophrenia or depression.

This paper is a purely theoretical paper that expands upon the previous hypotheses the Dr Holt has presented. The author presents a system "to explain the non-chaotic basis of all life in contrast to the chaotic basis of everything inanimate in the universe". The author states:

- that he has the ability to cure HIV infections through application of these principles
- that radiowave pollution is the most likely cause of the demise of certain types of animal life and the reduction of sperm counts in humans
- that schizophrenia can be successfully treated with vitamin B3
- that "in a survey of 50,000 patients with cancer treated in Western Australia over a 40 year period the radiotherapists have only treated one patient who was diagnosed with schizophrenia. This is the basis of teaching the students that to avoid cancer one should become a schizophrenic".

Holt J & Nelson A (1997). Letter responding to "Adjuvant VHF therapy in locally recurrent and primary unresectable rectal cancer (Trotter *et al*, 1996)". *Aust Radiol* 41(3): 317-318.

Relevance to current review: Excluded non-peer reviewed letter. A reply letter from Dr Trotter appeared in the same edition, and is also referred to here.

This is a letter to the editor in response to the Trotter *et al* 1996 paper in the same journal. Drs Holt and Nelson contend that the Trotter rectal cancer study should not have been published without the "correct historical perspective" - meaning that the authors should have referred in more detail to the poorly controlled head and neck cohorts from the 1970s.

They also state that the rectal cancer study (which Dr Holt was actually involved in as a principal investigator) was agreed to under duress as rectal cancer was not their cancer of choice for the trial. They state this is "why we have refrained from having one or both of our names on the paper".

In his reply, Dr Trotter points out that Dr Holt was involved on the management committee of the rectal cancer trial and that indeed it was he who recommended the doses of VHF therapy and radiation for the combined treatment arm. He clarifies that Dr Holt endorsed the choice of rectal cancer, and that Dr Holt had at the time drawn attention to a survival advantage observed in rectal cancer in a retrospective comparison of radiotherapy vs VHF plus radiotherapy that had been undertaken in Perth (Cassidy, 1990) - indeed similar in design to much-reported head and neck series.

The fact that the early rectal cancer observations were not able to be replicated in a randomised controlled trial reiterates the need for caution to be exercised when assessing studies with consideration selection, intervention and measurement bias.

Holt JAG (2001). The metabolism of sulphur in relation to the biochemistry of cystine and cysteine: Its fundamental importance in biology. A cyclic interchange between their mono- and di-sulphides is the unique reaction creating life and intelligence. *Medical Hypotheses* 56 (5): 658-676.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

Note about this journal: Medical Hypotheses is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. **Medical Hypotheses takes a deliberately different approach to peer review**. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. **Medical Hypotheses will publish radical ideas**, so long as they are coherent and clearly expressed. In Medical Hypotheses, the authors' responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a "chooser", and not a "changer".

The author presents various theories about the creation of life and intelligence. The author again advocates the now discredited Lamarckian evolutionary mechanism. The author states: "**Evolution is therefore 'pushed' by an intelligent ER_{ex} [a theorised 'exponential reaction that creates life from non-life'] and must be of Lamarckian form.**"

And,

"**Physical evolution is thus pushed by ER_{ex} and is Lamarckian and automatic. Any block to the evolutionary progress will be overcome and chance Darwinian response can play little or no part in such a system.**"

And,

The author discusses, "**Life in another solar system.**" He states:" **'Starlings' would automatically evolve to survive on star world like all life on earth and would certainly be totally different in physical form but have identical ability to adapt to star world environment. Evolution there would also be Lamarckian.**"

Lamarckism argues that traits that are acquired (or diminished) during the lifetime of an individual organism can be passed on to the offspring (for example: a giraffe, by continuing to stretch his neck will pass down to its offspring an increased stretching ability and the long neck that goes with it).

The author postulates that three unique characteristics create life. "These are: exponential growth proportional to time; the irreversibility of this exponential growth; and the transference of these two features to create generations of life from non-life." The author states that cancers obey all these three criteria of life. The author also states cancer can only arise from stem cells.

The author reiterates various theories about glutathione, glucose metabolism and the Pasteur reaction.

The author believes that heat treatment (hyperthermia) does not generate a clinical response in any patient except relief from bone pain. The author believes 434MHz selectively kills cancer cells, the author states: "… this selective lethality to cancer cells is unique to 434MHz radiation amongst every other cancer therapy." The author postulates that cancer uniquely 'resonates' and 'fluoresces' when subjected to 434MHz radiation. The author also reiterates his theory that 434MHz has a non-thermal radiosensitising effect on cancer. The author believes that "ERex [a theorised 'exponential reaction that creates life from non-life'] must be the only primary target of ionising radiation." The author concludes: "… 434MHz before X-ray therapy converts disaster to triumph!"

The author discusses the use of hyperbaric oxygen and anoxic radiotherapy for cancer treatment.

The author believes that every: multiple sclerosis, scleroderma, herpes zoster, hepatitis, amyotrophic lateral sclerosis, ankylosing spondylitis, and systemic lupus erythematosus patient has benefited and most have had their disease eliminated by treatment with 434MHz therapy.

The author also believes 434MHz can cure Alzheimer's disease.

The author states that 434MHz can unequivocally cure AIDS. The author states: "A patient with seroconversion in 1988 progressed to AIDS in 1992 and had four courses of therapy over the next three years … He appears unequivocally cured of his infection."

The author also believes it is possible that Creutzfeld-Jakob disease (a Prion disease) should be eminently treatable by 434MHz.

The author presents a number of theories on crocodile populations and the war's effect on population growth and compares these to the biology of cancer.

The author presents theories on virology, neurones and cancer.

The author postulates theories on overcrowding, starvation, 'the creed of greed', consciousness, and the suppression of consciousness.

Holt J (2003) Ultra high frequency radiowave cancer therapy. *Reviews in Clinical Oncology*. 1 (2): 16-17.

Relevance to current review: Excluded non-peer reviewed letter.

The author states: "In 1973 I discovered that Ultra High Frequency Radiowaves (UHF) would increase the radiosensitivity of otherwise unresponsive cancers by any factor up to 10,000 times the cancer cell kill, when used before a dose of radiotherapy compared with the effect of a similar or greater dose used in isolation."

The author presents the results of a 'phase I trial' of patients with mesothelioma (see table below).

Group		Site	Treatment	No patients	Survival (weeks)	
					Average	Maximum
1	A	Lung	Cytotoxics before UHF	27	12	20
	B	Lung	UHF before Cytotoxics	16	7	13
2	A	Lung	X-ray therapy before UHF	28	43	57
	B	Lung	UHF before X-ray therapy	24	87	2 at 260+
3	A	Abdomen	X-ray therapy before UHF	7	12	23
	B	Abdomen	UHF before X-ray therapy	7	34	65

It is very important to note that no details regarding the staging of these patients' disease were presented in this letter and no description of how the patients were assigned to treatment groups were shown. Therefore, it is unclear if 'UHF before X-ray therapy' had any beneficial treatment effect in these patients or if the apparent difference in average survival was simply due to biased patient allocation or the patient populations simply being different at baseline.

The author states: "**In 1986 the radiotherapy was abandoned in favour of anaerobic 'glycolytic blocking agents' (oxidised glutathione, cystine – disulphide form and other disulphide amino acids) before UHF therapy.**"

The author presents information about 14 mesothelioma patients treated with UHF and 'glycolytic blocking agents.' The author lists a series of Australian patent numbers that cover this therapy and states: "Anyone interested in this method can apply to me for a franchise on the method …"

Holt J (2004). The unique exponential growth of life is powered by anaerobic glycolysis. *J Molecular Liquids* 114: 193-206.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

The author postulates various theories regarding:

- Ionising radiation, normothermic, normobaric therapy
- Non-electrical hyperthermia
- Anoxic, normothermic, normobaric and radiation therapy
- 'Synergism between 434MHz UHF and X-rays'
- 'Anaerobic glycolytic blocking before UHF'
- The importance of the glutathione reaction in the creation of life, cancer and the treatment of cancer.
- Pasteur's reaction
- 'Exponential growth of life and cancer'
- Putative 'athermal effects of non-ionising radiation / 434MHz UHF'
- Neurones, glial cells and cancer
- Nanobug life 'peppered' throughout the universe

The author believes that: "**The epidemics of influenzas appear to be directly correlated with the amount of radiowave pollution in the atmosphere.The influenza virus will not only be electrically conductive and stimulated by radiowave pollution but will have a decreased mutation time such that a lethal new disease can be created readily at any time. The first epidemic of influenza occurred when Faraday was commencing his experiments on electromagnetic induction.**" The author continues by stating: "**It is tempting to suggest that the enormous radiowave pollution generated by massive naval and military installations was responsible for the 1918 epidemic of influenza.**"

The author also states: "**In NSW where chronic lymphatic leukaemia figures were analysed, there is an increased incidence of this disease proportional to the radiowave pollution levels associated with TV transmitters …**" The author concludes that: "**… radiowave pollution will increase the rate of growth of both chronic myeloid leukaemia and chronic lymphatic leukaemia but that it is also a causative agent in chronic lymphatic leukaemia.**"

The author concludes: "ionising radiation is the only biological killer of cancer available in the universe."

Holt J A G (2004), The energy system creating life and cancer from inanimate compounds. *Journal of Orthomolecular Medicine*. 19 (3): 141-161.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

Note about this journal: This is the quarterly journal of the Orthomolecular Society. Orthomolecular medicine is a branch of complementary medicine that describes the practice of preventing and treating disease by providing the body with optimal amounts of substances which are natural to the body. In the orthomolecular view, the provision of vitamins, amino acids, trace elements or fatty acids in amounts sufficient to correct biochemical abnormalities will be therapeutic in preventing or treating diseases such as atherosclerosis, cancer, schizophrenia or depression.

The author postulates various theories regarding:

- Glutathione and glycolysis
- Cancer and neurones
- Cancer 'resonating' and 'fluorescing' when subjected to 434MHz radiation
- Pasteur's reaction
- Non-thermal effects of 434MHz
- Out of body experiences
- Out of life experiences
- Anoxic therapy versus UHF therapy

The author advocates the now discredited Lamarckian evolutionary mechanism and rejects Darwinian evolution. The author states: "**Evolution is pushed by ER_{ex} [a theorised 'exponential reaction that creates life from non-life'] and must be of Lamarckian form, rather than according to Darwin's chance theory.**"

Lamarckism argues that traits that are acquired (or diminished) during the lifetime of an individual organism can be passed on to the offspring (for example: a giraffe, by continuing to stretch his neck will pass down to its offspring an increased stretching ability and the long neck that goes with it).

APPENDIX 19: SYNOPSES OF RECENT *IN VITRO* PUBLICATIONS BY UNSW RESEARCH GROUP

Harvey C, French PW (1999) Effects on protein kinase C and gene expression in a human mast cell line, HMC-1, following microwave exposure, *Cell Biology International*. 25(11): 739-748

This publication describes an *in vitro* study investigating the effect of microwave exposure (864.3 MHz) on the human mast cell line (HMC-1). The cells were treated with three 20 minute exposures each day for a seven day period. Another group of cells were treated in an identical fashion without the application of microwave to act as a control group. The researchers did not actively control the temperature of the cell cultures but temperature measurements of the cell cultures were made.

The temperature was different in the electromagnetic radiation exposed culture and the unexposed cell cultures however this difference did not reach statistical significance (control: 25.8°C; exposed group: 26.5°C).

The researchers found no significant morphological differences between the control (unexposed) and the exposed cells at any time point in the exposure period. The authors note that there was only a small number of cells available for morphological assessment.

The researchers note that in four experiments there was "a consistent trend" for an increase in the amount of immunoreactive protein kinase C in the membrane fraction of the exposed cells and a concomitant decrease in the cytosolic fraction. However, the researchers do not provide details of the number of experiments where no difference between the exposed cells and the control group occurred.

In two experiments changes in expression between the exposed and control HMC-1 cells were seen in only three genes out of a total of 588 genes screened (0.5%). The researcher notes that this indicates that such exposure does not have a broad effect on gene expression and indeed the effects on specific genes are moderate rather than substantial. Again, the researchers do not provide details of the number of experiments in which no difference between the exposed cells and the control group was found.

The researcher note that there was some variability between the experiments. **Some genes were altered in one experiment but not the other, and some genes were altered in different directions between experiments. The authors note that this may have been due to differences in cell passage number, stage of the cell cycle, or physical variations within the exposure chamber.**

The researchers state: "This indicates that for this exposure set up, the effect of athermal exposure is quite small." Despite the discussion of an 'athermal effect' the authors discuss the possibility that localised 'hot spots' within the culture vessel may have given rise to the modest effects observed.

French PW, Penny R, McKenzie DR (2000) Mobile phones, heat shock and cancer. *Differentiation*. 67:93-97

This publication presents the **hypothesis** that mobile phone radiation is not physiologically inert and primarily acts to induce the heat shock response in the brain tissue of phone users.

The authors discuss the role of heat shock proteins in cancer.

The authors then postulate that if chronic RF exposure induces the heat shock response, which leads in turn to increased cancer proneness, this could explain the significant increase in lymphoma seen in transgenic mice exposed to 900 MHz at low SARs (specific absorption rates).

The authors present the theory that non-thermal RF radiation may induce heat shock response in cellular targets. They discuss, in brief, some experimental results obtained in a study of C. Elegans (a nematode model) that showed a significant difference in the expression of heat shock proteins between control and RF exposed nematodes. The researchers state: "Our own recent work has indicated that Hsps [heat shock proteins] are induced by chronic non-thermal exposure of rat mast cells to pulsed RF radiation", however, this data is not shown.

The researchers also discuss a report in which RF microwave radiation at much larger SARs failed to induce the heat shock response in HeLa (a breast cancer cell line) cells and CHO (Chinese Hampster Ovary) cells.

French PW, Donellan M, McKenzie DR (1997) Electromagnetic radiation at 835MHz changes the morphology and inhibits proliferation of a human astrocytoma cell line. *Biochemistry and Bioenegetics*. 43:13-18

This publication describes an *in vitro* study of astrocytoma cell line that was exposed to electromagnetic radiation at 835 MHz at a power density of either 40 $mWcm^{-2}$ or 8.1 $mWcm^{-2}$ for 20 minutes, 3 times a day for 7 days. A control group of cells were handled in an identical fashion except that they were not exposed to electromagnetic radiation. The researchers did not actively control the temperature of the cell cultures but the temperature of the cell culture medium was measured at the conclusion of exposure with a thermocouple temperature probe. The exposed and unexposed cells were then subjected to a proliferation assay (^{3}H-thymidine uptake) and confocal scanning laser microscopy.

In both electromagnetic radiation exposed cultures the temperature was higher than recorded in the unexposed cell cultures (control: 26.2 ± 0.6°C; low power group: 27.0 ± 0.9°C; high power group: 34.0 ± 0.1°C).

There was no difference in the rate of proliferation between the exposed cells and the cells treated with 40 $mWcm^{-2}$. The proliferation rate of the cells treated with 8.1 $mWcm^{-2}$ was significantly different from both the control cells ($p = 0.019$) and the cells irradiated at 40 $mWcm^{-2}$ ($p = 0.018$) using the students t-test.

After 7 days the cells exposed at 8.1 $mWcm^{-2}$ showed a marked alteration in cell shape. The cells normal spherical morphology had disappeared, and instead the cells had adopted a flattened, spread shape. At the same time, the cells lost the actin-containing cell surface projections observed in the control cells. Similar results were seen for

the 40mWcm-2 exposure, the difference being that the flattened cells exhibited actin aggregates (blebs) localised at specific sites on the cell membrane.

The authors postulate that the changes in morphology of the cell lines detected in cells exposed to microwave energy at 40 mWcm-2 were presumably due to thermal effects of the microwave irradiation on either the culture medium or the cells. The authors state: "At lower power, no significant heating is detectable, and the actin blebs are not present." The authors discuss the hypothesis that the reduction in the proliferation of the astrocytoma cell line treated at 8.11 mWcm-2 was due to an effect on the mitogen-activated protein kinase (MAPK) cascade.

The authors do not discuss the possibility that localised 'hot spots' within the culture vessel may have given rise to the effects observed. This possibility is raised in a subsequent paper published by in Harvey and French in 1999.

The authors acknowledge the contribution of Dr J.A.G Holt of the Microwave Therapy Centre, Perth, Western Australia, who initiated the project, provided funding, most of the consumables, the exposure tank and associated materials.

Laurence JA, French PW, Lindner RA, Mckenzie PW (2000) Biological effects of electromagnetic fields – mechanisms for the effects of pulsed microwave radiation on protein conformation. *J Theor Biol*. 206: 291-298.

This publication presents a **theoretical model** in which pulsed microwave radiation causes a triggering of the heat shock or stress response by altering the conformation of proteins through transient **heating** of the protein and its close environment.

The researchers hypothesise that:

"At low power levels, a partial unfolding of specific target protein(s) occurs, which will be insufficient to induce the stress response, but sufficient to alter protein function. A biological effect (eg. on cell proliferation) will be observed."

"At higher power levels a more unfolded (molten globule) conformation is induced. The stress response will be activated, protecting the protein, and preventing an observable biological effect."

"At very high power levels, protein aggregation and precipitation occurs, and despite the activation of the entire stress response, a catastrophic biological effect (eg. cell death) will be observed."

Donnellan M, McKenzie DR, French PW (1997) Effects of exposure to electromagnetic radiation at 835MHz on growth, morphology and secretory characteristics of a mast cell analogue, RBL-2H3. *Cell Biology International*. 21(7): 427-439.

This publication describes an in vitro study of a mast-cell line, that was exposed to electromagnetic radiation at 835 MHz for 20 minutes, 3 times a day for 7 days at a power density of 8.1 mW/cm2. A control group of cells were handled in an identical fashion except that they were not exposed to electromagnetic radiation. . The researchers did not actively control the temperature of the cell cultures but temperature measurements of the cell cultures were made. The exposed and unexposed cells were then subjected to a proliferation assay (3H-thymidine uptake) and an assay of B-hexosaminidase (a marker for granule secretion). Immunofluorescence and confocal microscopy were used to determine the effect of 835 MHz exposure on F-actin distribution and cell morphology.

The exposed cell cultures were found to be on average 0.8± 0.4°C greater in temperature than the unexposed cultures.

For the first five days of exposure the rate of 3H-thymidine uptake was similar. After the first five days the rate of 3H-thymidine uptake in the control cells declined due to the cells reaching confluence. This decline was not seen in the exposed cells.

After seven days of exposure the appearance of actin-containing cell surface ruffles which were not detected in the control cells appeared.

When the researchers averaged data from three separate experiments they detected a difference in B-hexosaminidase secretion from stimulated cells that had been exposed to electromagnetic radiation for greater than 4 days compared with the un-irradiated cells.

The authors hypothesise that the effects of exposure to an electromagnetic field at 835 MHz may be mediated via a signal transduction pathway.

The authors conclude: “Which, if any, of the above mechanisms are operating to produce the effects reported above of electromagnetic field-associated cellular changes requires further detailed study.”

The authors acknowledge the contribution of Dr J.A.G Holt of the Microwave Therapy Centre, Perth, Western Australia, who initiated the project, provided funding, most of the consumables, the exposure tank and associated materials.