EXECUTIVE SUMMARY

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.