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.

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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