

APPENDIX 13: REVIEW COMMITTEE RESPONSE TO DR HOLT'S RESPONSE TO DRAFT INTERIM REPORT

The Review Committee received the comments on the draft interim report from Ms Jenny Pickworth acting on behalf of Dr John Holt on Monday 7 March 2005. The Review Committee met by teleconference on Tuesday 8 March 2005 to consider the comments raised by Dr Holt (as presented by Ms Pickworth).

The following represents the Review Committee consideration and response to each of the issues raised by Ms Pickworth in her correspondence of 7 March 2005 (and included as Appendix 11 of this report).

I. GENERAL COMMENTS

I.1 UHF AND UHF/RADIOTHERAPY – TERMS OF REFERENCE

Item A

The Review Committee was aware that Dr Holt is in his eightieth year, and was informed during the meeting in Perth on 8 January that in all likelihood, Dr Holt would be retiring soon.

The Review Committee accepted that Dr Holt's preferred treatment modality was combination of UHF and radiotherapy, and that he was not providing this modality because of lack of access to radiation equipment. However, the Review Committee expressed concern that Dr Holt considered that he was "being forced to treat patients less than optimally by not providing them with UHF/radiotherapy". In addressing the issues in this matter, the Review Committee considered that it was beyond its remit to pass comment on the reasons surrounding Dr Holt's exclusion from traditional therapy.

Action

The Review Committee to include a statement in the draft interim report indicating that Dr Holt was not providing UHF in combination with radiotherapy because of lack of access to this equipment.

Item B

The Review Committee noted that the complete list of case-series identified for the patient audits as outlined on page 310 of the interim report had not been correctly transcribed to page 81 of the report.

Action

The Review Committee to realign details on the patient audit on page 81 with the correct list on page 310.

Item C

The Review Committee did not consider that it had focused exclusively on the validity of the UHF modality currently applied by Dr Holt. Rather, the Review Committee considered it was important, to preserve the integrity of this review, to assess the available literature as broadly as possible, as evidenced by the criteria of the literature review, including the dual modality of UHF and radiotherapy. It was considered that the assessment of dual modality is adequately addressed in the report.

Action

No change required to draft interim report.

Item D

Members agreed that the terms of reference of the Review Committee did not limit their ability to consider dual modality of UHF and radiotherapy and the review did consider all relevant evidence relating to dual modality.

Action

No change required to draft interim report.

Item E

The Review Committee considered its interpretation of its terms of reference did not restrict this review to the consideration of the treatment regimen currently offered by Dr Holt. The literature review clearly outlines the scientific literature that was considered, including an inclusion/exclusion criteria which outlines the selection process employed to identify the relevant literature used in this review. The Review Committee did not consider it has limited the scope of the terms of reference to the current regimen.

Action

No change required to draft interim report.

Item F

The Review Committee recognises and appreciates that Dr Holt, and indeed all the staff associated with Dr Holt's clinic, have been open and co-operative throughout this process. The Review Committee understands that Dr Holt is keen to have his previous modality (combined UHF/radiotherapy) revived. The Review Committee reiterated that it had taken into consideration all relevant evidence on a range of modalities not just the regimen currently offered by Dr Holt.

Action

No change required to draft interim report.

Item G

The Review Committee expressed concern that Dr Holt “has not had the time available to prove-up the treatments”, however was “in no doubt, given his experience of treating some 35,000 cancer patients in WA since 1961 (in excess of 5000 with the dual modality (1973 to 1991) and 1500 with glucose blocking agents and UHF only (since 1991) that this latter modality is of significant curative or therapeutic benefit (at least equal to that of conventional treatments) and without the adverse side-effect”.

The Review Committee did not consider that Dr Holt's opinion represents proof of efficacy and safety.

Action

No change required to draft interim report.

Item H

The Review Committee reiterated that it did not restrict the review to the current treatment regimen. The Review Committee was previously concerned about the distinct lack of information in relation to UHF and glucose blocking agents, and recognised that there was significantly more published literature on the dual modality of UHF and radiotherapy.

Action

No change required to draft interim report.

1.2 THE SCIENCE OF DR HOLT'S UHF TREATMENT REGIMEN

Item A

See item C below.

Action

As per item C below.

Item B

The Review Committee did not focus on 434 MHz, rather it considered a broader, more inclusive range through the entire microwave spectrum (300 MHz to 300 GHz – not 300 MHz to 3,000 GHz as suggested in Ms Pickworth's correspondence of 7 March). The frequency used by Dr Holt clearly lies within this bandwidth.

Action

No change required to draft interim report.

The Review Committee noted that Dr Holt does not consider application of UHF radiowaves in his treatment regimen produces a hyperthermic effect. The Review Committee had not been able to identify evidence that suggested that there was not a hyperthermic effect. Members recalled that following treatment, patients would spend time cooling down with cold packs or fans. The Review Committee questioned whether this heating could constitute hyperthermia, or was only localised heating. Due to the lack of clear evidence to support either likelihood, the Review Committee agreed not to amend the report.

Action

No change required to draft interim report.

Item C

The Review Committee confirmed the statement “non-ionising electromagnetic waves (i.e. microwave therapy) do have the potential to heat human tissue”. The Review Committee also confirmed “the overwhelming majority of microwave therapy researchers believe that any therapeutic effect of microwave therapy is related to heating of the tumour cell, either directly or indirectly”. It was noted that these effects were likely to be seen at temperatures higher than those achieved using Dr Holt’s therapy.

Action

Amend sentence on page 14 to state therapeutic effect dependent on achieving increases in the temperature of the tumour; at higher levels than those achieved in WA. Sentence to be correctly referenced.

The Review Committee noted the explanation provided by Dr Holt on his treatment. While this hypothesis was not consistent with current knowledge of cell biology, and is not in line with current research findings, it was agreed to include the statement in the report to clarify Dr Holt’s hypothesis.

Action

Include in Chapter 3:
 “The application of 433-434 MHz UHF results in an increase in the cancer cell growth rate (by a factor of up to 10 times normal growth rate). This is attributable to the fact that cancer cells conduct electricity, so absorb energy at a greater rate than healthy cells, in turn growing faster. This accelerated growth rate is then destroyed by preventing the cancer cell using glucose from the blood at its energy source or by treating with X-ray therapy after UHF. (Ms Pickworth, pers comm)

I.3 CONFLICTS AND DUE PROCESS

Members noted the correspondence from Ms Pickworth on 11 January 2005 in which she wrote:

"Dr Van Hazel's inclusion on the Committee remains of some concern. There is some reason to believe that Dr Van Hazel has criticised Dr Holt's treatments and sought to persuade patients against seeking treatment from Dr Holt. It would be appreciated if you could seek an assurance from Dr Van Hazel that he has not acted in this way. I have checked with Dr Holt's office staff and they advise their records indicate Dr Van Hazel has never referred a patient to Dr Holt. I accept this, of itself, does not necessarily indicate a bias against Dr Holt."

Following receipt of this e-mail, the Chair of the Review Committee discussed this issue with Dr van Hazel. On hearing these unsubstantiated concerns, Dr van Hazel assured the Chair that he had not acted in this way, however recognised that any perceptions of such a conflict could leave the Review Committee open to criticism. In recognition of this concern, Dr van Hazel immediately offered to resign from the Review Committee to ensure the integrity of the review. Dr van Hazel's resignation was reluctantly accepted by the Review Committee.

The Review Committee considered that this matter was an internal administrative matter, and did not consider that it had an obligation to advise Dr Holt's office of the outcome of this process.

Action

No change required to draft interim report.

The Review Committee noted the concerns raised in relation to the distribution of invitation letters to Dr van Hazel and Dr Jefford (members of the Review Committee) seeking their input into the call for submissions. The Review Committee recognised that the call for submissions conducted in October and November 2004 invited response from all oncologists in Australia. This process was managed by a mailing house on behalf of NHMRC, and letters were forward to the two members for quality assurance purposes. No member of the Review Committee made a submission to the consultation.

Action

No change required to draft interim report.

2. SPECIFIC ISSUES

2.1 AVAILABILITY OF DUAL MODALITIES – UHF AND RADIATION

The Review Committee acknowledges that Dr Holt no longer has access to radiotherapy equipment. The Review Committee had previously considered the implications of including a comment in the draft interim report noting that Dr Holt has been excluded from conventional therapies and felt that outlining the reasons for Dr Holt's exclusion from traditional therapies would be prejudicial. In addressing the issues in the response from Ms Pickworth, the Review Committee reaffirmed its previous position that it was beyond its remit to pass comment on the reasons surrounding Dr Holt's exclusion from traditional therapy.

However, the Review Committee previously agreed to include a sentence in the interim report noting that Dr Holt does not have access to traditional equipment.

Action

Previously addressed

The Review Committee noted that Dr Holt has sought access to traditional radiation therapy equipment, however it was either beyond his means, or he failed to gain agreement from local Radiotherapist for access to equipment.

Action

No change required to draft interim report.

The Review Committee reaffirmed the previous response to the inconsistency within the draft interim report in relation to the series of patients to be considered in the patient audit.

Action

Previously addressed

2.2 Bias

The Review Committee had previously agreed to include a statement that Dr Holt does not use UHF in conjunction with radiotherapy because this form of treatment is not available to him.

Action

Previously addressed

The Review Committee recognised that while the findings of the 1974 NHMRC report was considered useful background information, it could be considered prejudicial. The Review Committee agreed to remove reference to the 1974 NHMRC report.

Action

Remove reference to the 1974 NHMRC report from the draft interim report.

The Review Committee reaffirmed its position that it was difficult to interpret the information received through the call for public submissions. Overall, the tenet of the submissions was strongly in support of Dr Holt's treatment however the Review Committee recognised that this was a self-selected group, and as such represented a biased sample, and could not be considered as evidence of the efficacy of Dr Holt's treatment. The Review Committee agreed to include a statement within the report indicating the tenet of the submission, with a caveat that this does not constitute evidence.

Action

Include a statement in Chapter 4, part 2 outlining the tenet of the public submissions.

The Review Committee considered the administration of glucose blocking agents. Members agreed to remove "NB" from the statement "Doses are not titrated to body weight".

Action

Remove "NB" from the statement "Doses are not titrated to body weight".

The Review Committee expressed concern that Dr Holt was treating patients using a chemotherapy drug (cyclophosphamide) even though at homeopathic doses, and continues to claim against Medical Benefits Scheme for chemotherapy. The Review Committee expressed further concern that the other glucose blocking agents used by Dr Holt are "benign because they are present in living human bodies" however Dr Holt continues to claim against the Medical Benefits Scheme.

Action

No change required to draft interim report.

The Review Committee agreed that the statement relating to the lack of Therapeutic Goods Administration approval of the equipment used by Dr Holt is prejudicial, however the statement is accurate.

Action

No change required to draft interim report.

The Review Committee noted the concerns raised in regard to the reporting of deaths associated with the use of this treatment. As the report did not compare the mortality of this therapy against traditional cancer treatment, the Review Committee agreed to reduce the emphasis in the draft interim report.

Action

Chapter 4, Part I to be revised to reduce emphasis of the deaths associated with the use of this therapy.

In relation to comments on the “Safety Summary” and the issuing of warnings to patients, the Review Committee agreed that the warnings and disclosures provided to patients from Dr Holt should be included at page 75 of the report. It was noted that the brochures provided by Dr Holt to his patients was included in the draft interim report at Appendix 8.

Action

Include reference on page 75 to the brochures provided by Dr Holt to patients outlining safety concerns.

The Review Committee noted the statement that “the NHMRC Invitation to Make Submissions did not mention or require comment or input on [safety] issues”. The Review Committee noted that the advertisement clearly stated the terms of reference, and included “safety” as an issue.

Action

No change required to draft interim report.

2.3.1 Accuracy Issues re Description of UHF Treatment

The Review Committee agreed that the waiting time between administration of GBA and radiowave therapy should be between 10-20 minutes.

Action

Amend draft interim report to reflect correct waiting time (10-20 minutes) between administration of GBA and radiowave therapy.

The Review Committee noted that Dr Holt had recently applied for six patents relating to his current treatment regimen, and the concerns raised regarding the inclusion of GBA ingredients and doses in the draft interim report. The Review Committee noted that Dr Holt had previously published information about the ingredients and the doses of the GBA in the open scientific literature, and as such it was appropriate to include the ingredients and doses in this report.

Action

No change required to draft interim report.

The Review Committee noted the request from Dr Holt to include the names of the principals of Health Technology Analysts in the report, and noted that the principals are already included on the verso page of the draft interim report. The principals from Health Technology Analysts are not oncology specialists, rather they are experts in undertaking literature reviews, assessing scientific evidence and preparation of reviews of evidence. The Review Committee recognised that it was important to maintain impartiality and that the review should be undertaken by experts outside the oncology field.

Action

No change required to draft interim report.

2.4 The Non-Referral/Non-disclosure Issues

The Review Committee noted the comments about the Australian public needing to rely on current affairs programs aired on television to learn about UHF therapy provided by Dr Holt. The Review Committee did not consider these comments relevant to this review.

Action

No change required to draft interim report.

3. EXECUTIVE SUMMARY

The Review Committee considered that it had been fair and open in providing Dr Holt an opportunity to comment on the draft report, and confirmed that the Executive Summary had not been included in the draft interim report provided to Dr Holt for comment to allow Dr Holt's comments on the draft interim report to be factored into the summary if necessary. The Review Committee considered the request to provide Dr Holt the opportunity to comment on the Executive Summary, but the Executive Summary simply provides an overview of the report already reported on by Dr Holt.

Action

No action required.

4. DR HOLT'S PREPAREDNESS TO ASSIST/CO-OPERATE WITH CLINICAL TRIALS

The Review Committee noted Dr Holt willingness to be involved in any future clinical trials.

Action

No change required to draft interim report.

APPENDIX 14: MINUTES OF VISIT TO PERTH (APRIL 2005)

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

MEETING WITH DR HOLT

Thursday 7 April 2005

A delegation from the National Health and Medical Research Council (NHMRC) Review Committee on Microwave Cancer Therapy met with Dr Holt on Thursday 7 April 2005 at the Radiowave Therapy Centre, 2nd Floor, 31 Outram Street, West Perth, WA.

The purpose of the meeting was to discuss and clarify the audit of medical records of patients treated by Dr Holt with his current and previous therapies, UHF radiowave combined with radiotherapy, and glucose blocking agents combined with UHF radiowaves respectively. The meeting also provided an opportunity for Dr Holt to raise issues in relation to the interim report.

Present at the meeting were:

NHMRC Delegation

Associate Professor John Boyages	Member NHMRC Review Committee
Mr Phil Callan	Secretary, NHMRC Review Committee

Radiowave Therapy Centre

Dr John Holt	
Dr Michael Holt	
Ms Jenny Pickworth	Legal representation

I. INTERIM REPORT AND EXECUTIVE SUMMARY

Ms Pickworth advised that there was some concern about the tenor of the draft interim report, particularly in relation to discussion on two cases in which male patient died during treatment. Dr Holt indicated that these patients were terminally ill. Prof Boyages indicated that he was also concerned about this section of the draft interim report during Review Committee discussions, and that the report had been redrafted following comments received from Dr Holt.

Dr Holt provided a photo of one of the two patients (entitled: *Whole Body Heating Rates under 12x200 watt moving fields*).

Ms Pickworth asked whether the report had been provided to the Minister for Health, and whether it was possible to obtain a copy of the Executive Summary. Mr Callan advised that the report had been forwarded to the Minister's office in early April 2005. Mr Callan made an undertaking to seek approval to provide a copy of the final Executive Summary to Dr Holt.

[Secretariat Note: A copy of the Final Executive Summary was provided to Dr Holt on Monday 11 April 2005.]

2. PATIENT AUDIT

Prof Boyages indicated that Review Committee's proposed project plan to undertake an audit of the medical records of patients treated by Dr Holt including assessment of

- 31 bladder cancer cases treated with UHF radiowave in combination with radiotherapy between 1973 and 1978;
- Approximately 50 bladder cancer patients treated with UHF radiowave in combination with radiotherapy from the 1980s;
- Approximately 50 bladder cancer patients treated with UHF radiowave in combination with glucose blocking agents (GBA); and
- Approximately 50 bladder cancer patients treated with non-UHF therapies;

Prof Boyages indicated that the Review Committee was also committed to assessing the following groups:

- 100 consecutive cancer patients treated with UHF radiowaves in combination with radiotherapy;
- 100 consecutive cancer patients treated with UHF radiowaves in combination with GBA;
- The 10 best outcomes, any modality

Dr Holt advised that the patients treated with a combination of UHF with radiotherapy were treated by Drs Holt, Nelson and Leckie at the Perth Radiation Oncology Centre, or at the Sir Charles Gairdner Hospital. The medical records are stored at those locations.

Prof Boyages noted that following discussions with Dr Chris Harper, Managing Partner of the Perth Radiation Oncology Centre, medical records are routinely destroyed 10 years after death, consequently some records will no longer be available.

Ms Pickworth undertook to contact Mr Neil Fong, Western Australian Health Department to gain quick access to all medical records.

Dr Holt agreed with the identified series however considered that there was little value in assessing records of bladder cancers from the current practice due to the potentially low number of patients treated and that assessment of the treatment of head and neck cancers should be considered by the Review Committee.

Prof Boyages indicated that the Review Committee was committed to assessing the bladder cancers and that an assessment should be made of as many bladder cancer patients as possible treated with UHF in combination with GBA. Consideration of further patient series, including the head and neck series, would need to be made following completion of these initial series.

Ms Pickworth questioned why the Review Committee were interested in assessing patients treated with UHF and GBA when Dr Holt continues to advise that UHF in combination with radiotherapy is the preferred modality. Prof Boyages advised that the Minister had requested the NHMRC to assess microwave “UHF radiowave” therapies and that this included the treatment currently offered by Dr Holt. Prof Boyages indicated that the Review Committee would be negligent if it were to exclude the UHF/GBA modality from the patient audit.

HISTORY

Dr Holt provided the following brief chronology of his practice:

1961	Private practice opened by Drs Holt and Leckie
1973	Tronado equipment purchased (1 installed at Sir Charles Gairdner Hospital, 1 installed in private practice)
1978	Denied access to public institution
1978-1991	continued to practice at private practice
1991	Left practice

CLOSE OF MEETING

At the close of the meeting, Dr Holt provided copies of the following papers for the consideration by the Review Committee:

- Correspondence from Robert Stanford associates (dated 31 May 1975) 434MHz EMR power absorption in breast cancer and normal breast tissue. Comparison between each breast at corresponding sites.
- Correspondence from Robert Stanford associates (dated 8 June 1979) – A comparative study of the Tronado equipment in use at the private practice of Drs J.A.G. Holt and A.J. Nelson and that owned by Sir Charles Gairdner Hospital
- The UHF X-radiation target
- Hornback NB, Shupe R, Shidnia H, Joe BT, Sayoc E, George R, Marshall C (1979) Radiation and microwave therapy in the treatment of advanced cancer, *Radiology*, 130:459-464
- Dr Holt showed Professor Boyages and Mr Callan his slide collection

APPENDIX 15: MICROWAVE AUDIT FORM

Microwave Audit Form

Data manager _____

Patient factors

1. Case Number _____ 2. Unit MRN _____ 3. Initials _____
 4. Date of birth ___/___/___ 5. Gender Male Female 6. State of Residence _____

Referral

7. Source of referral specialist GP self not known

Name and contact details of surgeon	Name and contact details of GP
-------------------------------------	--------------------------------

8. Patient status prior to commencing study treatment;
- | | |
|---|--|
| <input type="checkbox"/> new patient (no prior treatment) | <input type="checkbox"/> new post-op (surgery before referral) |
| <input type="checkbox"/> new post chemo | <input type="checkbox"/> recurrent (ie loco-regional) |
| <input type="checkbox"/> metastatic | <input type="checkbox"/> other (specify) |
- _____

Tumour factors

9. Date of initial cancer diagnosis _____/___/___
10. Is a pathology report showing cancer in the record? initial subsequent both none
11. Primary site of cancer (ICD-10 code) _____
12. Histology
- | | |
|--|---|
| <input type="checkbox"/> non malignant | <input type="checkbox"/> small cell carcinoma |
| <input type="checkbox"/> carcinoma | <input type="checkbox"/> NHL |
| <input type="checkbox"/> sarcoma | <input type="checkbox"/> Hodgkin's |
| <input type="checkbox"/> melanoma | <input type="checkbox"/> myeloma |
| <input type="checkbox"/> seminoma | <input type="checkbox"/> leukaemia |
| <input type="checkbox"/> non-seminoma | <input type="checkbox"/> not known |
13. Histological grade low grade (1) moderate grade (2) high grade (3)
 not known/indicated
14. Bladders only T1 T2 T3 T4 n/a n/k
15. Degree of spread [stage] at beginning of study treatment localised to the tissue of origin

APPENDIX 15: MICROWAVE AUDIT FORM

- invasion of adjacent tissue or organs
- regional lymph nodes
- distant metastases
- not applicable
- not known
- none or microscopic macroscopic

16. Tumour status prior to commencing study therapy
 not known

17. Please indicate method of determining tumour status. Enter assessment date and where possible tumour size (mm) below.

	SITE	Clinical	Cystoscopy/ Endoscopy	Imaging	Pathology	Other
Lesion 1						
Lesion 2						
Lesion 3						

Treatment factors

18. Treatment intent (re study therapy) curative non-curative prophylactic

Surgery

19. Prior surgery to index site no surgery
 resection – no evidence of macroscopic residual disease
 resection – evidence of residual macroscopic disease

20. Date of surgery / /

Radiotherapy

21. Did the patient receive treatment with radiotherapy? yes no

	Radiotherapy Type	Site	UHF y/n	Start date	Stop date	Gy	No of fractions	No. Fields (spec)
1	Study Therapy							
2	Prior to study therapy – Course 1							
3	Prior to study therapy – Course 2							
4	Prior to study therapy – Course 3							
5	Post study therapy – Course 1							
6	Post study therapy – Course 2							
7	Post study therapy – Course 3							

Comments

Chemotherapy

22. Did the patient receive chemotherapy for index lesion or metastatic disease? yes no
 If 'yes' √ timing of chemotherapy;

Chemotherapy	Yes	No	No of Regimens
chemotherapy prior to study treatment			
chemotherapy concurrent with study treatment			
chemotherapy post study treatment			

UHF factors

23. Did the patient receive treatment with UHF? yes no

24. Date first treatment ___/___/___ Date last treatment ___/___/___

25. Total number of kW _____ 26. Total number of minutes _____

27. No of treatment days _____ 28. Total no of fractions _____

29. Anaerobic glycolytic blocking before UHF yes, (specify) _____ no not known

Outcome – Tumour Response

30. Was tumour response assessed post-treatment? yes no not known

31. If 'yes', please indicate method of evaluation by entering assessment date and where possible tumour size (mm) in the boxes below .

	SITE	Clinical	Cystoscopy/ Endoscopy	Imaging	Pathology	Other
Lesion 1						
Lesion 2						
Lesion 3						

32. Tumour response post-treatment CR PR SD PD n/k

Recurrence

33. If patient CR, PR or SD did they subsequently experience a recurrence? yes no n/a n/k

34. If 'yes', date of recurrence / /

35. Method of assessment clinical cytology pathology imaging
 cystoscopy/endoscopy n/a other (specify) _____

Treatment Post Study Therapy

36. Did the patient receive further treatment post study therapy? yes no n/k

If 'yes' please √ which of the following apply;

No of courses	UHF+RT (no of courses)	UHF+ GBA (no of courses)	RT alone (no of courses)	Chemotherapy (number of regimens)	Surgery (number of surgeries)	Other
1						
2-3						
≥4						

37. Best response to total subsequent treatments CR PR SD PD
 n/a n/k

Outcome Toxicity

38. Was the patient assessed for toxicity during and/or up to 6 weeks post-treatment?
 yes, date / / no
 not known

39. Were there any toxicities during treatment? yes no

If 'yes' specify;

Toxicity	Mild	Moderate	Severe	Life Threatening	Requiring hospital	Requiring termination Rx early
1						
2						
3						
4						
5						
6						

Outcome Symptoms

40. ECOG status; Pre-treatment (circle) 0 1 2 3 4 n/k date __/__/__
 Post-treatment 0 1 2 3 4 n/k date __/__/__

41. Were there any documented symptoms pre-treatment? no yes (specify)

42. Was there a resolution or relief of symptoms at 3 months post-study therapy? yes no n/a n/k

If yes, specify

	Symptom	Date of amelioration/resolution
1		
2		
3		
4		
5		

Comments

Outcome Status

43. Patient status alive dead – cancer related dead – not cancer related not known

44. Disease status at last follow-up, notification or death CR PR SD PD n/k

45. Disease status based on clinical cytology pathology imaging
 cystoscopy/endoscopy n/a other (specify) _____

46. Date of last follow-up or death __/__/__

Comments

Office Use Only

		Study group		Comments	
Group (circle)	Year	Group	Date	Comment	Initials
A	70-91	Bladder RT only			
B+D	70-91	Bladder RT+UHF			
C	'90's	Bladder UHF+GBA			
E	'90's	Any invasive cancer			
F	70-91	Any invasive cancer			
G	Any	10 best Cases			

Verification Documents (indicate if source document verification performed by auditor)

Copy of Pathology Report	Y N	Copy of referral letter	Y N
Evidence of response (eg scan report)	Y N	Evidence of progression	Y N
Evidence of tumour measurements	Y N	Radiotherapy and or UHF report	Y N

Date Entered ___/___/___ Date Entry Checked ___/___/___ Auditor (circle) JB MJ Other (spec)___

APPENDIX 16: PATIENT AUDIT FORM COMPLETION GUIDELINES

Patient Factors

1) Case number

Study number assigned to each patient. Study numbers will be assigned by the data manager completing the case forms. Data managers will also complete a patient log which will link patient number with their name for the follow-up process. Access to this log will only be afforded to the sub-group of the study team responsible for documenting patient follow-up status. The list will be stored under secure conditions.

The study numbers will be derived from the study cohort (A, B, C, D, E, F or G) followed by a sequential number starting from 1. One data manager will assign odd numbers and the other even numbers to ensure no duplication of study numbers.

2) Unit MRN

Medical record number. In some cases more than one record number may exist for a patient (eg, a medical record number plus a radiotherapy file number, etc). In such situations multiple record numbers should be documented with an annotation.

3) Initials

Christian name, middle name, surname with a “-“ if there is no middle name.

4) Date-of-birth

5) Gender

6) State of Residence

NSW, WA, Vic etc for follow-up purposes. If international specify OS.

Referral

7) Source of referral

Document the source of referral, that is the person who made the referral for study therapy. Details of the referring physician, (if applicable) and primary care physician should be provided for follow-up purposes (if necessary).

It is necessary for Medicare purposes to obtain a GP referral and so in some cases of self-referral a GP letter will also be found. However, if a patient has clearly instigated the consultation themselves document this as a self-referral.

8) Patient status prior to commencing study treatment

- a. New patient = newly diagnosed patient, no prior treatment for index lesion; this includes patients with any stage of disease who have had no treatment.

NOTE a newly diagnosed patient presenting with metastatic disease (Stage IV at first diagnosis) would be classified as ‘new’ not ‘metastatic’ as they have had no pre-treatment.

- b. *New post-op*: = presenting for the first time for study treatment but has received prior surgery for index lesion
- c. *New post-chemo*: = presenting for the first time for study treatment but has received prior chemotherapy for index lesion (e.g neo-adjuvant chemo)
- d. *Recurrent – loco-regional* = patient with recurrent disease locoregionally (invasion into local tissue or regional lymph nodes) after a previous treatment
- e. *Metastatic* = patient who has been previously treated and presents with metastatic disease, such as a bone or lung secondary
- f. Other- e.g second opinion

Tumour factors

9) Date of Diagnosis

The date of first histo-pathological diagnosis of disease. This does not necessarily correspond with the date of first symptoms. It is the date of the first diagnosis of cancer. For new patients this is usually in the same year as their primary treatment; for other patients it is in the months (or years) before treatment.

If no pathology has been performed, and if applicable, date of diagnosis may be determined by the date of first imaging. In the absence of imaging, pathology, or any other objective date of diagnosis, then the first clinic date can be used with an appropriate comment.

10) Is the Pathology Report present?

Where possible the primary pathology report which confirms the patient's initial diagnosis should be attached, de-identified as a source document. In some situations the only pathology available will be from a secondary cancer. Please attach this with an explanatory note in these situations.

11) Primary Site of Cancer

See Attachment 1 (of these guidelines) for ICD-10 Codes.

In cases where a patient has two primaries it may be necessary to complete two data forms and attach together, (eg bilateral breast cancer).

12) Histology

As defined by the pathology report.

13) Histological Grade

Low grade ('well differentiated')	= Grade 1,
Moderate grade ('intermediate')	= Grade 2
High grade (or 'poorly differentiated' or 'anaplastic')	= Grade 3

14) T stage

For bladders only please supply the T stage at the time of treatment (See Attachment 2 of these guidelines)

15) Degree of Spread at Beginning of Study Treatment

Refers to spread of the disease prior to starting UHF or RT in the case of the bladder cohort RT alone arm. Only one category should be ticked.

Note, a tumour may be described in the pathology as ‘highly invasive’ but in fact is still localised. Invasion of varying degree into bladder wall is still classified as localised disease. It is only when the tumour extends into the tissue surrounding the bladder or into other organs that it enters the “invasion of adjacent tissue or organs” category.

16) Tumour status

‘None’ or ‘microscopic’ if full surgical excision has been performed, or complete remission achieved from radiotherapy or chemotherapy. ‘Macroscopic’ if disease is detectable on imaging, physical examination or operative report.

17) Tumour Size Prior to Commencing Study Treatment

Where possible an indication of the size of the tumour pre-study therapy should be provided.

Tumour Measurement

- Tumour measurements should be given in mm’s (single longest diameter) will be utilised.
- Enter measurement into the box which relates to the mode of measurement
- Some patients have more than one lesion that can be measured. Cite up to three lesions which can be measured (e.g breast, axillary node, SCF node)

Treatment factors**17) Treatment Intent**

Intention of treatment with study therapy. In the case of radiotherapy, it is classified as ‘curative’ if it is instituted in cases where treatment intention is cure. This includes adjuvant radiotherapy or definitive high dose radiotherapy without prior surgery.

‘Non-curative’ means palliative treatment instituted where there is no reasonable hope of cure. In the case of radiotherapy this usually involves lower doses of radiation (30Gy in 10 fractions; or 20Gy in 5 fractions etc) although sometimes high doses may still be given to patients with “palliative” intent.

‘Prophylactic’ treatment will only apply very rarely and includes such treatment as prophylactic cranial irradiation for patients with certain leukaemias.

Each of the below categories, (surgery, RT, chemotherapy) refers to treatment to the index site prior to commencing study therapy. For the most part study therapy will be UHF, but for the radiotherapy alone arm of the bladder cancer patients (A) it will be radiotherapy.

Surgery**19) Prior surgery to index site**

Some patients may have undergone local excision followed by more complete resection. In this case more than one box will be checked. The date, however, should be for the definitive surgery, (ie the complete resection).

i) No surgery

This includes diagnostic or incisional biopsy.

ii) Resection – no evidence of macroscopic residual disease

This includes excisional biopsy and any excision made with attempt at assessing/achieving clear surgical margins. In the case of bladder cancer it would also include cystoscopically-guided removal of deposits on the bladder wall, (unless it was specified in the urologist's report that residual tumour remained).

iii) Resection – evidence of macroscopic residual disease

Where the surgical intent has been resection of as much disease as possible but for technical reasons, (eg very advanced disease) this has been impossible and the surgery has only removed as much diseased tissue as possible. Includes gross macroscopic disease left behind, "cut-through" of tumour.

20) Date of Surgery

Where there have been multiple surgeries to the index site the date of the definitive surgery should be provided, (ie, the primary attempt at complete surgical resection).

Radiotherapy

21) Radiotherapy administration

Please enter the start and stop dates of radiotherapy administered pre, post and concurrent with study therapy.

Dose should be provided in cGy as per Radiotherapy Treatment Summary.

Note 50Gy = 5000 rads = 5000cGy.

Number of fractions are also given on Radiotherapy Treatment Summary. This is the number of actual treatment attendances. Occasionally patients may have two fractions a day (hyperfractionation) or two or three fractions per week (hypofractionation)

The number of fields is detailed on Radiotherapy Treatment Summary. Arc treatment counts as one field.

Chemotherapy

22) Chemotherapy administration

Chemotherapy may have been administered either to treat the index lesion or metastatic disease from it. If chemotherapy was given please indicate whether it was prior to, concurrent with or post study treatment. Please also indicate the number of different regimens (note, not different cycles).

It may be that multiple chemotherapy regimens have been given at different stages in treatment in which case more than one box would be checked.

Hormonal and immunological therapies are not to be entered in this section including intra-vesical BCG.

UHF Factors**23) Did the patient receive treatment with UHF?****24) UHF Factors**

Date of First Treatment, (ie date of commencing therapy – not first consultation date). The patient may have received multiple cycles of UHF. Details of only the first course should be entered here. Subsequent courses are accounted for in Q36.

25) Total Number of Kilowatts

Total number of kilowatts. Generally four generators are used per dose, A, B, C, and D. Each delivers a wattage which is usually (but not always) the same, therefore this must be multiplied by four to obtain watts per dose. (If fewer generators are used then just add up the total dose).

The total kilowatts for the whole treatment schedule should be entered here.

26) Total number of Minutes

The number of minutes for each treatment sometimes varies a little and so a total time for the whole course in minutes should be entered.

27) Number of Treatment Days

Number of days of treatment. Will not include weekends, but only the actual days treatment was administered.

28) Number of Fractions

This is the number of treatments. It is generally the same as total number of treatment days but not always.

29) Anaerobic Glycolytic Blocking Agent (GBA)

Some patients received intra-venous medication of a GBA pre-treatment to potentiate the effect of the therapy. Please specify the drug(s) given if possible.

Outcome Tumour Response**30) Was Tumour Response Assessed Post Treatment?**

This necessitates imaging or some mode of assessment within a reasonable temporal period post the end of treatment, (eg in the case of ca bladder the post treatment cystoscopy is generally performed 3 months after treatment).

31) Tumour measurements

Please enter the post treatment tumour measurements into the relevant boxes as in Q17.

32) Tumour Response Post Treatment

CR = complete response

PR = partial response

SD = stable disease

PD = progressive disease

Where possible these response criteria should comply with RECIST definitions (Attachment 3 of these guidelines). In the case of bladder carcinoma, bladder-specific criteria are applied (Attachment 4 of these guidelines).

Where it is impossible to comply strictly with these criteria because of lack of information, a determination of response should be made on the best available evidence and an annotation added.

Recurrence

33) Recurrence

For patients who achieved any response – even stable disease – details of date of recurrence should be entered where possible in order to be able to determine disease-free survival.

34) Date of Recurrence

Please enter the recurrence date. Where possible this date should coincide with the clinical investigation at which recurrence is diagnosed, even though the symptoms of recurrence may pre-date this. Sometimes a pathological diagnosis is not achieved in which case a clinical diagnosis of recurrence is acceptable.

35) Method of assessment

Indicate the imaging or tumour evaluation modality utilized.

36) Further Treatment

The patient may have received multiple treatment modalities for recurrent disease. In the table below please enter all the treatments the patient received between recurrence and last follow-up/death.

Subsequent treatments may be to the index site or to sites of metastatic disease;

- 1) **UHF + RT**
The number of courses should be entered. A patient may receive multiple courses of UHF/RT treatment separated by weeks, months or years.
- 2) **UHF + GBA**
Please enter the number of courses.
- 3) **RT**
Similarly the number of courses of radiotherapy should be entered. Sometimes this will simply be an isolated, palliative fraction, on other occasions it will be a whole course. In both instances, a 'course' or 'single fraction' counts as a separate episode.
- 4) **Chemotherapy**
Enter the number of different regimes (not different cycles) employed. Immunotherapy and hormonal therapy should also be entered here.
- 5) **Surgery**
Enter the total number of subsequent surgeries for primary and metastatic disease. These may be major such as a salvage total cystectomy, or minor such as palliative excision of a troublesome metastatic lesion. Each episode counts as a separate event.

37) Best Response

This applies to the sum of the treatments administered for metastatic disease. The best status the patient reached post recurrence should be entered into this field; complete response, partial response, stable disease, progressive disease, or unknown.

Outcome - Toxicity**38-39) Was the patient assessed for Toxicity?**

Please document any treatment-related toxicities, ie signs and symptoms occurring during study treatment or during the 6 weeks subsequent to study treatment. Indicate whether these symptoms were mild, moderate or severe. Pre-existing symptoms should not be included unless they have significantly worsened during study treatment.

The grading of 'mild', 'moderate' and 'severe' is based on the Common Terminology Criteria (<http://ctep.cancer.gov/forms/CTCAEv3.pdf>) and correspond with grades 1, 2, 3 and 4 on this scale.

Please also indicate whether the toxicities necessitated hospitalisation or early termination of study treatment.

Outcome - Symptoms**40) ECOG status**

Please enter the ECOG status of the patient pre-treatment (see Attachment 5 of these guidelines). If not provided in the notes an evaluation of status can sometimes be made from the clinical information provided. However, in some cases this will not be adequate to make an accurate judgement in which case the response should be 'unknown'.

41) Were there any Symptoms present pre-treatment?**42) Was there any improvement in Symptoms?**

Please document whether any symptoms pre-dating study therapy were documented as resolving post study therapy. Post-treatment symptom response should allow for treatment-related toxicity and therefore the post-treatment determination of symptom response should be made greater than 6 weeks post therapy.

Retrospective assessment of symptom response is difficult. Please enter any comments that may be necessary to clarify symptom response to treatment.

Outcome - Status**43-46) Date of and Patient status at last follow-up**

Patient status should correspond with the last documented entry in the patient record. If the patient was alive at this time, (even if it is likely that their status has now changed) they should be entered as alive pending more accurate data from the Cancer Registry.

44) Disease status

The best assessment possible should be made from the patient record of disease status at time of follow-up or death. Sometimes the information for this is limited and if necessary a comment should be made in cases where there is lack of clarity.

Office Use Only

Comments Box

Here the data manager can assign the patient to the relevant study cohort and enter any comments pertinent to any section of the form.

Verification Documents

The data entry person should indicate whether the records were available in the patient record.

- 1) Copy of the original referral letter
- 2) Evidence of response refers to objective evidence of response such as a scan report or cystoscopy report.
- 3) 'Evidence of tumour measurements' should only be checked if there are good, objective measurements provided pre- and post treatment.
- 4) Copy of the referral letter
- 5) Copy of any documentation of disease progression once again refers to objective evidence of progression or a clear entry in the medical record of clinical evidence of progression.
- 6) Please indicate if the radiotherapy treatment summary and UHF report is available in the record.

Data of data entry is completed by the data manager and the date of data checking by the auditor who also identifies themselves at the bottom of the form.

Glossary of Terms

Bladder symptoms

Bladder-related symptoms occurring after six weeks post completion of therapy.

Bladder toxicities

Bladder-related symptoms occurring during or within 6 weeks of treatment that were not present prior to treatment

Index Site or lesion

'Index site' refers to the principle treatment site, i.e. the site causing the symptoms and the site having the study treatment.

Study Treatment

'Study treatment' refers to the investigational treatment, ie UHF+/- GBA+/-RT. In one cohort of bladder cancer patients (the RT alone cohort), the RT is the study treatment. If the patient has had surgery this is the post-operative tumour status.

Attachment 1 to Appendix 16

ICD Codes	Sites	ICD Codes	Sites
	Unknown	C01	Base of tongue
C80	Malignant neoplasm without specification of site	C10.0	Valleculae
	1. Skin	C10.9	Oropharynx, unspecified
C43	Malignant melanoma of the skin	C11	Nasopharynx
C44	Other malignant neoplasms of the skin	C12	Piriform sinus
	2. Lymphoreticular System	C13.0	Post Cricoid
C85.9	Non Hodgkins lymphoma	C13.2	Subglottis
	Unspecified type	C32.1	Supraglottis
C81	Hodgkins disease	C32	Glottis
C90	Multiple myeloma	C32.9	Larynx, unspecified
C95.90	Leukaemia unspecified without mention of remission	C31	Accessory sinuses
C90.2	Plasmacytoma, extramedullary	C30	Nasal cavity and middle ear
C47.0	Histiocytic and mast cell tumours of uncertain and unknown behaviour	C08.9	Major salivary gland, unspecified
	3. CNS	C77.0	Secondary neoplasm of lymph nodes of head, face and neck
C69	Eye and adnexae	C76.0	Head, face and neck
C70	Meninges		5. Breast
C71.0	Cerebrum	C50	Breast
C71.5	Ventricles nos		6. Lung/Thorax
C71.7	Brain stem	C34	Bronchus and lung
C71.6	Cerebellum	C39	Other respiratory and intrathoracic sites
C72.4	Nerve, acoustic	C38.4	Pleura
C75.1	Pituitary		7. Alimentary Tract
C72.0	Spinal cord	C15	Oesophagus
C72.1	Cauda equina	C16	Stomach
C72.9	CNS unspecified	C18	Colon
	4. Head and Neck	C20	Rectum
C00	Lip	C21	Anus and anal canal
C02	Tongue other than base	C24.9	Biliart tract nos
C04	Floor of the mouth	C25	Pancreas
C06.2	Retromolar trigone	C22	Liver and intrahepatic bile ducts
C06.0	Cheek mucosa	C26	Other digestive organs
C03	Upper and lower gum		8. Urinary Tract
C05.0	Hard palate	C64	Kidney
C06.9	Mouth unspecified	C65	Renal pelvis
C09	Tonsil	C66	Ureter
C05.1	Soft palate	C67	Bladder
C10.2	Oropharynx, lateral wall	C68	Other urinary organs
C10.3	Oropharynx, posterior wall		

Continued over page ►

APPENDIX 16: PATIENT AUDIT FORM COMPLETION GUIDELINES

ICD Codes	Sites	ICD Codes	Sites
	9. Female Genital		12. Musculo-skeletal
C53	Cervix uteri	C40	Bone and articular cartilage of the limbs
C54	Corpus uteri	C41	Bone and articular cartilage of other (non limb) sites
C52	Vagina	C49	Other connective and soft tissues
C56	Ovary	C46	Karposis sarcoma
C51	Vulva	C47	Peripheral and autonomic nerves
C57	Other female genital organs		13. Endocrine
	10. Testis	C73	Thyroid
C62	Testis	C74	Adrenal gland
	11. Male Genital	C75	Other endocrine glands
C61	Prostate		
C60	Penis		
C63	Other male genital organs		

Attachment 2 to Appendix 16
T staging for bladder cancer

Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall or abdominal wall
T4a	Tumour invades prostate, uterus, vagina
T4b	Tumour invades pelvic wall, abdominal wall

American Joint Committee on Cancer (2002). Urinary bladder. In *AJCC Cancer Staging Manual*, 6th ed., pp. 335–340. New York: Springer-Verlag.

Attachment 3 to Appendix 16

RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)

Quick Reference: <http://imaging.cancer.gov/clinicaltrials/imaging/>

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of “Target” and “Non-Target” lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

- * *Complete Response (CR)*: Disappearance of all target lesions
- * *Partial Response (PR)*: At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
- * *Progressive Disease (PD)*: At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
- * *Stable Disease (SD)*: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

- * *Complete Response (CR)*: Disappearance of all non-target lesions and normalization of tumor marker level
- * *Incomplete Response/ Stable Disease (SD)*: Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
- * *Progressive Disease (PD)*: Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

- (1) Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/ biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

Attachment 4 to Appendix 16

Bladder Specific Response Criteria (per TROG 02.03)

Complete Response (CR)

Requires, at three or more month post randomisation, the absence of any invasive tumour in the tumour-site biopsy specimen or elsewhere and a bimanual exam that does not indicate the presence of a tumour mass. For a primary tumour response following treatment, a urine cytology specimen that is not positive is also required (in the absence of CIS/dysplasia elsewhere in the bladder urethelium).

Partial Response (PR)

Requires all the response criteria of a CR except that the urine cytology remains positive (in the absence of CIS/dysplasia elsewhere in the bladder urithelium).

No response/ Stable Disease (SD)

Requires continued presence of tumour in the tumour-site biopsy specimen, or elsewhere.

Progressive Disease (PD)

Requires an increase of 50% or more in the largest diameter of the endoscopically appreciable tumour and the continued presence of tumour in the tumour-site biopsy specimen.

Attachment 5 to Appendix 16**ECOG status**

Grade	ECOG
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg light office work, house work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.
5	Dead.

APPENDIX 17: SITE OF PRIMARY CANCER

Site	Tumour site					
	Bladder			Any invasive		Any – 10 best
	RT alone (A)	RT + UHF (B)	UHF + GBA (C)	UHF + RT (D)	GBA + UHF (E)	UHF + GBA ± RT (F)
	N=34	N=11	N=18	N=56	N=49	N=10
C00 lip				1		
C02 tongue					1	
C08 salivary glands				1	1	
C11 nasopharynx				1		
C15 oesophagus					1	
C16 stomach				1	1	
C18 colon					5	
C20 rectum/anus				2	1	
C32 larynx				5		
C34 trachea, bronchus, lung				6	6	1
C38 pleura					4	2
C40-C41 bone/articular cartilage					1	1
C43 melanoma				1	4	
C44 skin cancer				2	3	
C49 connective/soft tissue				2		1
C50 breast				21	6	1
C53 cervix					2	
C61 prostate				6	2	
C64 kidney				2	2	
C67 bladder	34	12	18			2
C70, C72 other & unspecified nervous system					2	1
C71 brain				1	3	
C73 thyroid gland					2	
C39, C77, C80 unknown primary site				2	1	
C85 non-Hodgkin's lymphoma				2	1	1

APPENDIX 18: BRIEF SYNOPSES OF PUBLICATIONS BY DR JOHN HOLT

Yoffey JM, Ancill RJ, Holt JAG, Owen-Smith B, Herdan G (1954) The Effect of Compounds E, F, and A on the Bone Marrow of Normal Guinea Pigs. *J Anat* 88 (2): 115–132

Relevance to current review: Not relevant, no patients treated with microwave therapy.

This paper reports the result of daily intraperitoneal injections of various steroid hormone (5 mg of cortisone, hydrocortisone or compound A) in guinea pigs. Specifically, the paper reports the impact of the interventions upon the bone marrow.

Hadfield GJ, Holt J (1956) The Physiological Castration Syndrome in Breast Cancer. *BMJ* 27: 972–973

Relevance to current review: Not relevant, no patients treated with microwave therapy.

This short paper reports clinical observations for a case series of patients with metastatic breast cancer with a view to providing information on factors affecting the course of the disease.

Methods

The paper states that all patients in the case series were diagnosed before the menopause and all had progressed to metastatic disease. The patients received various treatments, but the paper focuses on the patients' responses to natural menopause, oophorectomy (referred to as castration = removal of the ovaries) and adrenalectomy.

The paper reports three series of patients: a) those with oestrogen-dependent tumours (n=19); b) those with oestrogen-independent tumours (n=11); and a small group treated with stilboestrol^a (n=7).

No information is provided regarding the diagnosis of hormone-dependent cancer or how tumour regression was measured.

Results

The paper reports that women with hormone-dependent tumours experienced temporary regression of their metastases after oophorectomy, ranging in duration from 2 months to 4 years. Similarly, after subsequent adrenalectomy these patients' metastases regressed for between 2 and 22 months. In contrast, patients with tumours that were not hormone-dependent had no regression. The authors state that stilboestrol administration generally aggravated metastatic growth (data and number of patients not reported), although they list seven patients who experienced some regression on stilboestrol (but appropriate denominator not reported).

The authors conclude that the behaviour of metastatic breast cancer during natural or artificial menopause indicates the probability of hormone-dependence.

^a Di-ethyl-stilboestrol (DES) is a synthetic form of the female hormone oestrogen, prescribed to women from 1938 until the early 1970's mainly during pregnancy. In 1971, a link between the use of DES and a rare form of cancer found in the daughters of women who had taken the drug was discovered. Consequently, the FDA banned the use of DES during pregnancy. DES has since been linked to a number of health problems in women who were given the drug during pregnancy and children born to women who took DES during their pregnancy.

O'Donnell JM, Bremner J, Joyce PR, Holt JAG (1964) From ?Epidermal Naevus to Mycosis Fungoides to Sarcoma. *Med J Aust* 1:642-646

Relevance to current review: Not relevant, patient not treated with microwave therapy.

This case study reports a patient with a skin lesion of the thigh with the clinical appearance of naevus verrucosus. The condition was subsequently diagnosed as mycosis fungoides. The patient ultimately developed large masses in the inguinal region and their histopathology was indistinguishable from reticulum-cell sarcoma. The patient received surgical and radiation therapy, and responded well.

Holt JAG (1964) The Acute Radiation Pneumonitis Syndrome. *J Coll Radiol Aust* 8:40-47

Relevance to current review: Not relevant, patient not treated with microwave therapy.

This paper reports a retrospective case series of all patients who had received radiotherapy of the thorax at the authors institution in the previous five years (n=102). The paper describes an acute condition caused by radiation therapy that the author labels 'acute radiation pneumonitis'. The author makes a case that this is distinct from late radiation-induced fibrosis of the lung.

Methods

This paper reports the findings of a retrospective review of 102 lung cancer patients treated with radiotherapy at the Institute of Radiotherapy in Western Australia.

Results

Fifteen of the 102 patients had radiographic evidence of lung reactions that occurred within 12 weeks of radiotherapy. Seven cases appeared within five weeks of therapy and all died of pneumonitis.

The author discusses the lack of physical signs of acute radiation pneumonitis syndrome and the radiographic distinction from fibrosis. The author proposes that the reaction is an acute necrotizing desquamative lesion of the lung that is equivalent to an acute moist skin lesion.

The author states that the development of acute radiation pneumonitis syndrome is related to dose rate rather than total dose. It is fairly common at more than 1,000 rads TD of 4 MeV X-rays per week. It is stated that patient with Hodgkin's disease are particularly susceptible.

The author concludes that acute radiation pneumonitis syndrome is responsible for considerable morbidity and mortality amongst patients undergoing radiotherapy of the lungs.

Vaughan BF, Holt J (1964) Lymphography. *J Coll Radiol Aust* 8:59-77

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This paper describes the visualisation of the lymphatic vessels and glands of the limbs, pelvis and abdomen using an intra-lymphatic injection of iodised oil. The technique had been adopted by the Royal Perth Hospital and the paper describes 10 illustrative cases.

Holt J (1964) The Management of Patients suffering from Bronchial Carcinoma. *J Coll Radiol Aust* 8 (3):237-242.

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This symposium review discusses the management of bronchial cancer. The author states that there is acrimony between the surgical and radiation teams that causes confusions, however makes the argument that a standard approach can be formulated for these patients.

The author discussed the value of post-operative X-ray therapy, stating that its value increases the smaller amount of tumour that remains after surgery. However, this logical assumption is incorrectly evidenced by retrospective survival data from four cohorts of patients who had had varying levels of surgical intervention - with no regard to the fact that the disease status (including likelihood of metastatic disease) would clearly have been different between these cohorts. The author then goes on to contradict the previous statements arguing for uniformity of approach depending on the size of the post-surgical remnant, to state that even cancers of the same size, situation and shape would all respond differently to exactly the same X-ray treatment.

In the group of patients with 'incurable' lung cancer, the author argues that 'words are more valuable and more valued than actions and visits and discussions are more important than treatments'. He states that the clinicians treatment plan for these patients is further complicated as 'family personalities, preconceived ideas learnt from the Press, previous doctors, relatives with the disease, and so on, make for a multitude of possibilities to which only experience will give any help in the management'.

The author believes that chemotherapy should be limited to patients who cannot have X-ray therapy and who have superior vena caval obstruction; patients with multiple skin secondaries too extensive for X-ray therapy; patents with severe osteoarthropathy not relieved by X-ray; and patients with effusions.

The paper concludes by discussing the promise of hyperbaric treatment of cancer, stating that "the evidence at present is that under full oxygen saturation almost 100% of cancer cells are destroyed by present accepted maximum safe dose levels" (of X-ray). To conclude, the author speculates that the results of clinical trials of hyperbaric treatment in lung cancer "might be startling and send all radiotherapy departments into a fever of development".

Holt JAG (1965), The place of radiotherapy in the management of laryngeal cancer. *The Nisbet Symposium* pp. 199-203.

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This symposium review is similar to the previous publication in that it discusses the relative merits of surgery and radiotherapy, however in this case relating to laryngeal cancer.

Holt J (1965) A Trial of Thiethylperazine (“Torecan”) in Patients Suffering from Radiation Sickness. *Med J Aust* 9(3): 199-203

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This report describes the incidence and severity of radiation sickness symptoms in patients, and compares two difference radiation sickness treatments.

Methods

The publication reports data from two retrospective cohorts of patients; approximately half of the patients treated between May 1961 to May 1962 and approximately half of the patients treated between May 1962 and Sept 1963. Differences in the X-ray treatment regimens between the two groups are not reported.

Patients in the early cohort (Group 1) had radiation sickness treated with dimenhydrinate 100 mg three time daily (with or without intramuscular pyridoxine), whilst those in the latter cohort (Group 2) received thiethylperazine (variable dose ranging from 6.5 mg tablet 1–5 five times daily).

Results

The rates of nausea and vomiting were similar in the two groups. Thiethylperazine provided nausea relief to 78% of affected patients, compared to 47% amongst the dimenhydrinate-treated patients. Vomiting was relieved in 76% and 54%, respectively. Some side effects were present with thiethylperazine.

The thiethylperazine-treated patients were then analysed according to the radiation dose they received (low, medium, high). The following results were obtained:

	Low dose radiation (n=37)	Mid dose radiation (n=34)	High dose radiation (n=20)
Complete relief	65%	50%	35%
Fair relief	22%	18%	50%
Poor relief	13%	32%	15%

The author’s interpretation of these data are that they “confirm the impression that the severity and difficulty in relieving radiation symptoms are proportional to the daily integral dose of radiation used”. The author selectively refers only to the complete relief data, as this is not the picture if one considers complete + fair relief together. These data do not support such a statement.

Holt J (1965) The Biological Effects of Ionizing Radiations at very low dose rates. *Aust Dent J* 10(1): 38-40

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This publication is the transcript of a conference paper describing known or possible biological effects of low dose ionising radiation to a dental conference.

Holt J, Woodliffe HJ, Davis RE, Neal JR (1967) Radiation and Marrow Infusion in Leukaemia. A patient with CGL Treated with Whole Body Irradiation and Infusion of Isogenic Marrow. *Aust Radiol* 11:63-66

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This publication reports a case study of a patient with chronic granulocytic leukaemia who was treated with radiation and an infusion of isogenic marrow from his monozygotic twin. The patient developed pneumonitis and died two months later. The value of marrow infusion, the radiation dosimetry and the problem of radiation pneumonitis are discussed.

Holt JAG (1971) The Value of Chemotherapy in Ovarian Cancer. *Aust Radiol* 15(2):160-163

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This publication reports a retrospective review of patient records of the radiotherapy departments and public hospitals of Western Australia, for 1955–1965 (although patients treated outside this time period are also discussed).

A total of 162 primary ovarian malignancies with appropriate histology were discovered in these hospitals during these years. The author states that these patients fall into two categories. Category 1 originally had suspected ovarian malignancy, followed by laparotomy and removal of all or most of the primary disease was possible. These patients had no ascites or evidence of spread beyond the pelvis. Category 2 have their diagnosis made by the presence of ascites together with evidence of malignancy in and outside of the pelvis. In the series under consideration, the author states that 53 patients would fall into category 1, whilst the remaining 109 patients would fall into category 2. The paper reports the treatment and five year survival of these two groups of patients.

Category 1:

The first group were predominantly treated with surgery (hysterectomy and bilateral salpingo-oophorectomy) with post-operative radiotherapy.

After 5 years, 30/53 (57%) were still alive, although seven had had a recurrence retreated within this time.

Category 2:

It is difficult to determine the treatment of the second group as this is poorly reported. To add to the confusion, the paper suddenly refers to an additional 39 patients' records retrieved from pre-1955, then sub-divides the patients into pre-1961 and post-1961.

With respect to the pre-1961 group, the paper states the “survival of the majority of these patients... was approximately 10 weeks”. The author states there was no evidence at all that large-field X-ray therapy had appreciably altered the average survival, although their survival was longer (~14 weeks), they were more likely to have had a better prognosis when the decision was made to treat with X-ray therapy (ie., selection bias).

In the post-1961 group, various chemotherapy regimens replaced radiotherapy in this group. Patients were often treated with sequential trials of cyclophosphamide, chlorambucil and thio-tepa (dose regimen information is poorly reported, if at all). These drugs were used in that order, but starting with a different drug for each patient as they turned up in sequence. The length of time in remission on the drug on which they started was noted. This was then repeated for the next two drugs. The author states that “it is my opinion cyclophosphamide is the best of these three drugs”. The paper states that 41 of 53 patients “have a clinical remission of their disease with reduction their ascitic fluid, and in the case of 28... the abdomen has apparently returned completely to normal”. The average time to recurrence was 9 months, and the average survival for the entire group was 27 months.

No data is tabulated in this publication, and it is difficult to determine imbalance between the subgroups of patients who received each chemotherapy treatment first line, without the impact of cross-over treatments.

Toward the end of the paper, the author makes reference to an additional five patients with late ovarian cancer, massive ascites and secondary deposits throughout the abdominal cavity, who were treated with chemotherapy. The author states the response of these patients to cyclophosphamide was dramatic, “and within a few weeks the patients were apparently back to normal health”. However on closer examination, all had residual abdominal tumours, which were then surgically removed, with or without post-surgical radiotherapy. “These patients remain alive four, three, two and one year after their second laparotomy or the radiotherapy following it.”

In summary, the author concludes ovarian cancer is one cancer “for which chemotherapy has, in my opinion, offered an extremely effective method of palliation”.

Holt JAG (1971) The Results of Treatment of Carcinoma of the Cervix in WA. *Aust Radiol* 15(2): 164-176.

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This publication is similar to the preceding report, although it refers to cervical cancer. The paper is a retrospective review of the treatments of cervical cancer in Western Australia between 1953 and 1965, although the report also includes a selection of patients treated between 1965 and 1968.

The authors presents the patients in groups, by disease stage and treatment received.

Results for patients treated Jan 1953–Feb 1962

Stage, number of pts	Treatment	Outcome
T1, n=32	Radiation alone	75% 5 yr disease-free survival
T1, n=28	Radiation then surgery	50% 5 yr disease-free survival
T2, n=46	Radiation alone	27% 5 yr disease-free survival
T2, n=32	Radiation then surgery	22% 5 yr disease-free survival
T3, n=22	Radiation + "occasionally surgery"	27% 5 yr disease-free survival
T4, n=15	No treatment information provided	13% 5 yr disease-free survival

Results for patients treated Feb 1962–June 1965

Stage, number of pts	Treatment	Outcome
T1, n=39	Radiation alone	69% 5 yr disease-free survival
T1, n=8	Radiation then surgery	38% 5 yr disease-free survival
T2, n=58	Radiation alone	59% 5 yr disease-free survival
T2, n=9	Radiation then surgery	44% 5 yr disease-free survival
T3, n=22	Radiation +/- surgery	23% 5 yr disease-free survival
T4, n=23	No treatment information provided	13% 5 yr disease-free survival

Results are also presented for a highly selected sub-set of surgically-treated patients who were later referred to RT departments. This takes no account of the outcome of patients who received surgical treatment alone.

Once again the investigator makes no allowance for the fact that patients with different prognoses may have been candidates for different treatments (ie., selection bias) which is likely to have had considerable impact. For example, patients who received treatment with both radiation and surgery may have had more extensive disease.

The investigator concludes that the results "lead me to the conclusion that in Western Australia the natural history of carcinoma of the cervix is such that primary surgery should not be performed for a T1(in situ), T1 and T2 carcinoma". Such a conclusion is certainly not supported by a retrospective review such as this, that is likely to suffer from inherent selection bias.

Herrmann RP, Dougan L, Holt JAG, Jackson JM, Matthews MLV, Nelson AJM, Stenhouse NS, Woodlife HJ (1972) Chronic Granulocytic Leukaemia - Comparison of Uracil Mustard and Busulphan. *Med J Aust* 1:789-791

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This publication reports 22 patients with chronic granulocytic leukaemia, who received alternating courses of intermittent busulphan and uracil mustard therapy. Remission criteria were i) total white cell count falling to 20,000/ μ l or less; ii) splenic size reduced by 50%. It is not clear whether either or both of the criteria had to be met.

Patients received sequential alternate courses of the two drugs, and all courses were included in the analyses - ie., irrespective of whether an initial and subsequent course.

Time to induction of remission and duration of remission were the same with the two treatments, as were side effects.

Holt JAG (1973) The detection of breast abnormalities by thermography. *Australasian Radiology* 17: 453-463.

Relevance to current review: Not relevant, patients not treated with microwave therapy.

This publication describes two years of use of the AGA Thermovision Unit in Western Australia for the thermographic examination of female breasts. A total of 1,512 women were screened with 1,025 read as 'normal' and 487 'abnormal'. None of the former group were found to have breast carcinoma, although the follow-up period was too short to confirm this. Only 35 of the 487 patients with abnormal actually had carcinoma. In summary, thermography in isolation has poor sensitivity with an unacceptably high false positive rate.

Holt JG (1974) The Cure of Cancer. A Preliminary Hypothesis. *Aust Radiol* 18: 15-17.

Relevance to current review: Not a clinical study, opinion piece.

The author presents a list of opinions relating to various treatments for cancer (eg. surgery, x-ray radiation therapy, cytotoxic chemicals and microwave radiation therapy).

This publication postulates that: "Cancer can be cured when the method of treatment specifically kills cancer cells only without damage to the normal. Microwave radiation therapy complies with both criteria and can thus cure cancer."

The author presents a list of factors that, in his opinion, will stop patients being cured from cancer by microwave radiation therapy. The author states:

"Therefore one cannot cure patients:

- a) who cannot stand erect for a few minutes
- b) whose cardiac physiology is insufficient to tolerate moderate stress
- c) in whom uptake of microwave energy does not occur. To date all patients have shown uptake and include carcinomata of tongue, pharynx, larynx, oesophagus, skin, stomach, pancreas, colon, rectum, cervix, ovary, vagina, lung and sarcomata such as chondrosarcoma, rhabdomyosarcoma, fibrosarcoma, reticulum cell sarcoma, lymphosarcoma and all the lymphoma tried. The glioma also takes up energy and appears curable. Metastases are equally sensitive.
- d) in whom the necrosis of their cancer will cause major calamity...."

The author presents a list broad ranging and largely unsubstantiated implications that in his opinion will occur due to the introduction of microwave radiation therapy. The author states:

"The implications of this discovery are tremendous.

- 1) **No patient will ever become a chronic cancer nursing problem again if treated correctly with microwave radiation.**
- 2) Inpatient accommodation for microwave radiation patients will be much less than required for all other types of therapy.
- 3) **Cytotoxic therapy is "dead" in its present form.** Perhaps it may occasionally survive in association with other methods for some rare cancers.

- 4) X-ray therapy is of value for pituitary adenomata, artificial menopause, intracranial arterio-venous malformations, syringo-myelia, rheumatic diseases, pterygia and warts, etc.
- 5) **Cancer surgery will be revolutionised.** It will be needed to make diagnosis and perform such operations as are essential to prevent complications which will arise from tumour necrosis. **Radical cancer surgery is therefore unnecessary. Surgery need only remove the primary and microwave therapy will be able to kill the metastases.**

The author concludes that: "All current cancer research in the world becomes pointless, except that relating to experiments relating to human cancer and microwave therapy."

The author states: "There is therefore no need to wait five or ten years to predict that this type of microwave radiation therapy can cure cancer. The author can predict without fear or favour that this will be found to be correct in due course."

Holt JAG (1975) The Principles of Hyperbaric and Anoxic Radiotherapy. *Brit J Radiol* 48: 819-826.

Relevance to the current review: Excluded, not a microwave therapy study.

Describes a number of factors that the author believes require exact control if hyperbaric therapy is to be used to full advantage. These factors are as follows:

- 1) Rate of pressurisation of the chamber
- 2) Soaking time
- 3) Decompression rate
- 4) Gas temperature
- 5) Humidity
- 6) Type of anaesthesia
- 7) Treatment planning and patient set up
- 8) Optimum dose
- 9) Contradictions for treatment

The author discusses anoxic therapy and where he believes the therapy can only be rationally used, the essential features of the treatment and the essential steps, which he believes, must be taken after the tourniquet is put in place.

The author presents a number of case studies of patients treated with x-ray therapy and anoxia. The author also presents a case series of patients treated with hyperbaric therapy.

The author concludes on the basis of these uncontrolled case studies that: "These two methods [anoxia and hyperbaric radiotherapy] have produced such excellent clinical responses that those malignancies which experience has taught can be best treated must indeed be so managed if the patient is to be given the best chance of cure or palliation. No other ethic or moral decision is possible."

Holt JAG (1975) The Use of V.H.F Radiowaves in Cancer Therapy. *Aust Radiol* 19(3): 223-241.

Relevance to the current review: Portions of this publication were included in the safety section of the systematic review.

Initially the publication describes the equipment used to generate V.H.F. radiation for cancer therapy. The author describes the apparent effect of V.H.F. radiation in a series of case reports. These case reports include patients with: astrocytoma; carcinoma of the breast with multiple metastases; primary pancreatic carcinoma; squamous carcinoma of the neck. The publication then details the death of one child treated with V.H.F. for a glioma in the left posterior parietal region.

The author states: "It is our opinion, however, that the best results come from using V.H.F. synchronously with x-ray therapy. Under such circumstances it is our experience that V.H.F. is a radio-sensitiser without equal."

The author describes, in brief, the first 363 patients treated in the first 9 months of the microwave facilities operation. The publication then presents 13 separate case reports of patients with a variety of cancers treated with V.H.F. (eg. Squamous cell carcinoma of the pyriform fossa, papillary adenocarcinoma of the thyroid, carcinoma of the descending colon, etc).

Holt JAG, Nelson A. (1976) Four Years of Microwaves in Cancer Therapy. *J Belge Radiol – Belgisch Tijdschr Radiol* 62: 467-476.

Relevance to the current review: Included in the safety portion of the systematic review. The relevant patient data has been extracted from the publication and is presented in the systematic review. Excluded from systematic review of efficacy as wrong study design to address research question (or duplicate data).

The publication presents a collection of previously reported case series of patients treated with combinations of VHF, radiotherapy and cytotoxic compounds. The case series include patients with: 1) head and neck cancer; 2) breast and axilla cancer; 3) bone metastases; 4) liver metastases; 5) primary or metastatic brain cancer lesions; 6) lung cancer; 7) abdomen cancer; 8) rectal cancer; 9) bladder and prostate cancer; 10) sarcomata; and 11) lymphoma.

The authors conclude that: "VHF constitutes a non-toxic form of therapy applicable to all cancers, in all stages and all sites, even after conventional methods have failed. It has proven to bet the best radio-sensitiser so far."

Holt JG. (1977) Increase in X-ray Sensitivity of Cancer After Exposure to 434 MHz Electromagnetic Radiation. *Journal of Bioengineering*. 1: 479-485.

Relevance to the current review: Included, contains duplicate patient data. Relevant patient information has been extracted from the publication and is presented in the accompanying systematic review.

The publication presents a series of 52 patients with head and neck cancer treated with 434MHz electromagnetic radiation and x-radiation. This group of patients was

compared with two selected historical control groups, one treated with x-irradiation alone, and the other treated with x-irradiation under 3 atmospheres hyperbaric oxygen at 37 degrees Celsius. It should be noted that these types of comparisons are prone to high levels of bias. Despite this, the authors conclude that: "The use of 434 MHz H-wave electromagnetic waves has been shown to be an 'exquisite radiosensitiser' in our preliminary clinical experiences. This appears to be partly non-thermal."

Nelson AM, Holt JG (1977) The problem of clinical hyperthermia. *Aust Radiol* 21: 21-30.

Relevance to the current review: Included, the relevant patient data has been extracted from the publication and is presented in the accompanying systematic review.

The authors discuss the historical origins of hyperthermia usage. The researchers then discuss in vitro and animal model cancer cell responses to radiation and heat. The publication presents different methods of heating tumours (eg. whole body heating and VHF) and the variation of response different tissues have to VHF radiation. The authors then detail the results of a number of whole body hyperthermia experiments conducted in Perth and why the researchers decided to use VHF to induce hyperthermia instead. The next section of the publication describes the Tronado equipment used to generate the VHF for cancer treatment. The researchers also discuss the putative benefits of heat on cytotoxic drug action.

The authors present a case series of 27 patients with secondary cancer in the bone treated with a combination of VHF (via the Tronado machine) and various combinations of 'cytotoxic drugs' and radiotherapy. The authors state that all patients were relieved of pain after the first course; nineteen patients lived 11-26 months; seven died after 7-20 months.

The publication presents a case series of 12 cancer patients with a large painful liver (in 10 patients a liver scan showed large deposits) that were treated with radiotherapy and VHF and injections of cyclophosphamide. The author states that all patients had complete and fairly rapid pain relief; five deaths occurred at 2-13 months; seven other cases survived 3-18 months; and one other patient died in the subsequent five months.

A previously reported case series of 52 patients with ENT cancers treated with 434MHz electromagnetic radiation and x-radiation are presented. This group of patients was compared with two selected historical control groups, one treated with x-irradiation alone, and the other treated with x-irradiation under 3 atmospheres hyperbaric oxygen at 37 degrees Celsius. It should be noted that these types of comparisons are prone to high levels of bias. Despite this, the authors state that: "... in all respects the hyperthermia combination is almost twice as effective as hyperbaric therapy, or three to four times as effective as conventional therapy."

The authors state: "It was clear to us that except in a few rare cases, the microwave form of hyperthermia used alone would not provide a cure for cancer."

The researchers conclude that: "... hyperthermia is to be considered as a powerful adjuvant to conventional cancer treatment methods. It would be unethical to conduct a controlled trial to test hyperthermia alone against other modalities, as it is clear that used alone it is unlikely to cure or do more than temporary objective palliation."

Nelson AM, Holt JAG. (1978) Combined Microwave Therapy. *Med J Aust.* 2: 88-90.

Relevance to current review: Included, patients with head and neck cancer.

The publication describes 52 cases of advanced head and neck cancer treated with 434MHz radiowave hyperthermia combined with cobalt radiotherapy and/or gold grain implant. The authors compare these results with the results of: 1) 52 patients treated with radiotherapy and hyperbaric oxygen over two years, and; 2) 52 patients treated with super-voltage therapy alone, before 1970.

The authors state: “No local cures could be obtained by this microwave hyperthermia alone, but where radiation was added, a marked sensitivity was seen, ...”

It should be noted that these types of comparisons are prone to high levels of bias. Despite this, the authors state that: “According to every parameter, the combined microwave treatment was two or three times better than conventional treatment...” And, “microwave hyperthermia appears to be a superior and effective adjuvant to treatment with ionising radiation for advanced cancer of the ear, nose and throat group.”

Holt JG. (1979) The Cause of Cancer: Biochemical Defects in the Cancer Cell Demonstrated by the Effects of Electromagnetic Radiation, Glucose and Oxygen. *Medical Hypotheses.* 5: 109-143.

Relevance to the current review: Included in the safety portion of the systematic review.

Note about this journal: *Medical Hypotheses* is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. *Medical Hypotheses* takes a deliberately different approach to peer review. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. *Medical Hypotheses* will publish radical ideas, so long as they are coherent and clearly expressed. In *Medical Hypotheses*, the authors' responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a “chooser”, and not a “changer”.

The publication lists various theories regarding VHF, glucose metabolism and carcinogenesis.

The author discusses 380 patients with a wide variety of primary cancers (eg. lung, breast, prostate etc) treated with VHF alone (“after they had been unsuccessfully treated by all other appropriate conventional methods”). The researcher also discusses 322 seemingly unrelated patients with vertebral collapse due to metastatic cancer that were treated with x-ray therapy and/or cytotoxics. The author makes the following statement based on his comparison: “In contrast, [to the group treated x-ray therapy and/or cytotoxics] VHF can not only palliate the disease by killing cancer cells but in addition influences the normal tissue to regenerate in their former shape and appearance.” The researcher presents various histological photographs and radiographs of case studies to attempt to support these hypotheses.

In Appendix A the author presents the methodology used for temperature measurements in 41 of the 380 patients treated. Photographs of a patient with malignant Schwannoma treated with x-ray and VHF are also presented.

In Appendix B the author postulates that VHF has non-thermal effects on cancer. Previously reported data on patients with head and neck cancer and patients treated by whole body heating are presented to attempt to support this hypothesis. The author concludes: “VHF has non specific thermal and specific thermal effects on cancer.”

In Appendix C the author argues that VHF at 434MHz is cancericidal. The author attempts to support this hypothesis by presenting three patient case studies.

Appendix D discusses a number of hypothesised effects of low intensity 434MHz radiation on cancer.

Appendix E discusses temperature increases and power consumed by the VHF apparatus when it was used in: 50 patients with widespread cancer, 22 volunteers with no cancer and saline phantoms. The deaths of two patients during VHF therapy are also discussed.

In Appendix F the researcher postulates that 434 MHz VHF therapy at an intensity of 11 m w/sq cm increases cancer-doubling time unless patients are anoxic and hypoglycaemic, in which case the ‘stimulant effect’ of VHF on cancer colonies is prevented. The researcher attempts to support this theory by comparing a small series of patients that received VHF to various parts of the body to another group of patients that had cancer metastases to their forearms. The patients in the latter group had a tourniquet applied to their forearms and were instructed to gently exercise their forearm prior to VHF therapy to induce anoxia or were treated with systemic insulin to induce severe hypoglycaemia.

The author states that: “Most patients expressed their interest [in the study] and said that they were prepared to undergo any simple experimentation to try and find the cause of cancer.”

In Appendix G the author presents a crude study to support the hypothesis that the application of VHF appears to accelerate normal skin healing processes and improve the cosmetic appearance of biopsy scars.

Appendix H presents additional patient data on the 380 patients discussed in the body of the publication.

Holt JG. (1980). Alternative therapy for recurrent Hodgkin’s disease. Radiotherapy combined with hyperthermia by electromagnetic radiation to create complete remission in 11 patients without morbidity. *Brit J Radiology* 53: 1061-1067.

Relevance to current review: Excluded from systematic review as wrong study design to address research question.

This publication describes the methods used and the results obtained when 11 patients with recurrent Hodgkin’s disease were treated with various doses of combined radiotherapy and hyperthermia.

The author also describes two separate pieces of equipment used to deliver hyperthermia treatment (ie. 12 dipole x 200W device and a 4 dipole x 0.1 – 2 kW device). Additionally, the publication briefly describes temperature measurement studies

using these hyperthermia devices on a phantom of agar jelly. These studies showed significant rises at axial points in the phantom up to 20 cm outside the radiation space. They also indicated the existence of hotspots in cross-sections of the phantom.

The author also discusses the use of streptokinase therapy in conjunction with hyperthermic therapy.

Nelson AM and Holt JG. (1980) Microwave Adjuvant to Radiotherapy and Chemotherapy for Advanced Lymphoma. *Med J. Aust.* 1: 311-313

Relevance to the current review: Excluded from systematic review as wrong study design to address research question.

This publication describes the treatment of 40 patients with recurrent Stage IV lymphoma. The patients received a combination of a wide variety of cytotoxic drugs, radiotherapy and 434MHz microwave therapy. The author states: "A complete remission, represented by total disappearance of masses, a good health, and a normality of blood count, occurred in 34 (85%) of patients after the first definitive treatment. Twelve of these developed some evidence of disease after six or more months, and received appropriate treatment with further remission."

The author provides theories regarding the thermal and non-thermal effects of VHF. The author also discusses theories regarding glucose metabolism and cancer treatment.

The author concludes that: "...VHF microwave hyperthermia therapy is a powerful synergist to conventional agents with a considerable potential for treatment of advanced and recurrent malignant tumours."

Holt JAG (1980) The Extra Nuclear Control of Mitosis and Cell Function. A Theory of Cellular Organisation. *Medical Hypotheses.* 6: 145-192.

Relevance to the current review: Excluded from the systematic review, wrong outcomes reported.

Note about this journal: Medical Hypotheses is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. **Medical Hypotheses takes a deliberately different approach to peer review.** Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. **Medical Hypotheses will publish radical ideas**, so long as they are coherent and clearly expressed. In Medical Hypotheses, the authors' responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a "chooser", and not a "changer".

The author postulates many theories regarding mitosis, cell division, glucose metabolism, cell growth, and VHF, etc.

The author describes around 700 cancer patients who were treated with VHF alone or in combination with x-ray therapy and/or cytotoxics. The author describes the two forms of equipment used to generate VHF. The author presents measures of 'reflected power' in 7 selected patients.

The researcher discusses clinical observations (primarily 'reflected power measurements') of patients treated with VHF and various other agents. These other agents included: 1) Ethanol; 2) D-fructose; 3) L-glucose ; 4) 'Glucose analogues'; 5) D- and L-mannose;

6) D- and L-Fucose; 7) Azaserine and DON; 8) Insulin; 9) Biguanides/Sulphonyl Ureas; 10) Streptokinase; and 11) Steroids. From these observations the author draws conclusions about glucose metabolism in cancer and normal cells.

The author states: “patients with advanced widespread cancer treated whilst they were clinically inebriated achieved long term remission of their cancer ...” The author then presents a list of theories to explain his observation.

The author expounds a theory that the cell has a CEO (Chief Executive Officer) and this ‘CEO’ “has an existence as the entity which controls every cell’s destiny.” The researcher explains that this ‘CEO’ “Interprets the nuclear blueprint and builds the adult cell and whole body to its genetic information.” The author believes that the ‘CEO’ resides in the ENCC (extra nuclear cell constituents) and has “two ‘foremen’ which whilst interconnected probably supervise the two distinct areas of (a) maintenance of normal, cellular perfection and (b) supervision of function of the cell.”

The publication presents theories on the following topics: 1) VHF induced resonance in compounds in cancer cells; 2) the interaction between VHF and cytotoxic compounds; 3) the metabolic requirements of cancer cells; 4) mechanism of spontaneous remission in cancer; 5) oxygen’s effect in radiotherapy; 6) insulin tolerance of patients with cancer; and 7) cytotoxic chemicals.

The author states: “The place of conventional cytotoxics is thus seen (with very few exceptions) to be as agents for euthanasia rather than for therapy.”

Holt J (1982) 434MHz as an Adjuvant in Cancer Therapy: A Survey of Results Obtained and the Biochemical Knowledge Derived from the Use of this Therapy. *Progress in Radio-Oncology II*. 425-433.

Relevance to the current review: Portions of this publication were included in the systematic review.

The publication describes the two pieces of equipment used by the researchers to generate VHF for cancer treatment.

The authors present a collection of case series some of which have been reported previously. The relevant patient data has been extracted from the publication and is presented in the accompanying systematic review. In summary, the patients in these case series were treated with various combinations of VHF, radiotherapy, ‘glucose analogues’, hypoglycaemia and streptokinase. The case series include patients with: 1) Hodgkin’s disease; 2) Non-Hodgkin’s lymphoma; 3) rectal cancer; 4) breast cancer; 5) head and neck cancer; 6) bladder cancer; 7) prostate cancer; 8) primary brain cancer; and, 9) other cancers.

The publication revisits a hypothesis reported in Holt (1979) where the researcher states that 434 MHz VHF therapy at an intensity of 11 m w/sq cm increases cancer-doubling time unless patients are anoxic and hypoglycaemic, in which case the researcher believes the ‘stimulant effect’ of VHF on cancer colonies is prevented. The researcher attempts to support this theory by comparing a small series of patients that received VHF to various parts of the body to another group of patients that had cancer metastases to their forearms. The patients in the latter group had a tourniquet applied to their forearms and were instructed to gently exercise their forearm prior to VHF therapy to induce anoxia or were treated with systemic insulin to induce severe hypoglycaemia.

The researcher concludes that: “Under VHF stimulation cancer cells lose all their characters of differentiation and function, i.e. they become ‘primitive’, yet without the potential of embryo cells to form more adult structures.”

The author also presents various theories on glucose metabolism and carcinogenesis.

Holt JG. (1983) Cancer, a Disease of Defective Glucose Metabolism. The Energy for Mitosis Appears to Come From a Glutathione Mediated Glycolysis. *Medical Hypotheses*. 10: 133-150.

Relevance to the current review: Excluded, not peer-reviewed, not a clinical study, opinion piece.

Note about this journal: *Medical Hypotheses* is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. *Medical Hypotheses* takes a deliberately different approach to peer review. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. *Medical Hypotheses* will publish radical ideas, so long as they are coherent and clearly expressed. In *Medical Hypotheses*, the authors’ responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a “chooser”, and not a “changer”.

The author postulates various theories regarding the interplay between glucose metabolism, cell cycling, carcinogenesis, mitosis, glutathione and VHF radiation.

The author also presents theories regarding the radiosensitising effects of VHF on cancer.

Holt JG. and Nelson AM (1985) Squamous-cell carcinoma treatment. *Med J Aust*. 142: 79-80.

Relevance to the current review: Excluded not a peer reviewed clinical study, letter to the editor.

This letter to the editor requests more information regarding a publication on the response to combination cytotoxic treatment of squamous cell carcinoma conducted by Woods *et al.* (1984).

The author states: “However, our own work suggests that a microwave adjuvant with radiotherapy results in a striking clearance of these advanced tumours, and with a lower than usual radiation dose.”

Holt JG. and Nelson AM (1985) Combined Microwave Therapy. *Med J Aust*. 142: 707-708

Relevance to current review: Non peer-reviewed letter presenting previously described patient data.

The publication presents the crude 3 and 5-year survival rates of a series of ENT patients treated with microwave therapy and/or conventional therapy.

The authors discuss other centres that have been involved in similar research. They believe that 16 major US oncology centres are using apparatus similar in concept to the Tronado machine. The authors also discuss a Japanese company that has developed an 8MHz hyperthermia device, which is to be used as an adjuvant to radiotherapy or chemotherapy.

The authors conclude that it is time to conduct some “serious randomised controlled trials”. The researchers believe that in their experience adjuvant 434MHz hyperthermia is more effective than other wavelengths or whole-body hyperthermia.

Holt JG and Stanford RW (1986) The synergism between hyperthermia and ionising radiation. *The British Journal of Radiology*. 59: 795-796.

Relevance to current review: Excluded, previously reported patient data.

The author discusses the use of Electromagnetic non-ionising radiation (EMR) in combination with x-ray therapy. The author postulates that EMR induced hyperthermia has the potential to “shield” normal tissue while maintaining its increased cell kill ratio per x-ray dose applied. The author also believes that there is no categorical evidence, which indicates X-irradiation sequelae are deleteriously enhanced by the use of EMR.

The publication presents previously published crude survival data for three series of patients treated for head and neck cancer (Nelson and Holt, 1978). The first group was treated with EMR and ionising radiation, the second was treated with ionising radiation and hyperbaric oxygen and the third was treated with ionising radiation alone.

The author also presents previously reported crude survival rates for two later series of patients treated with combination therapy or conventional therapy (Holt and Nelson, 1985).

The author compares these case series of patients treated with combination therapy (ie. EMR and ionising radiation) and those treated with ionising radiation alone. It should be noted that these types of comparisons are prone to high levels of bias. Despite this, the author concludes that the most beneficial treatment regimen “has to be” some combination of EMR and ionising radiation.

Holt JG, (1986) The Fundamental Chemistry of Life. *Medical Hypotheses*. 12: 359-367.

Relevance to current review: Excluded, not a clinical study, opinion piece.

Note about this journal: *Medical Hypotheses* is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. *Medical Hypotheses* takes a deliberately different approach to peer review. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. *Medical Hypotheses* will publish radical ideas, so long as they are coherent and clearly expressed. In *Medical Hypotheses*, the authors’ responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a “chooser”, and not a “changer”.

This publication presents a list of hypotheses regarding life's creation and evolution. In addition the publication presents theories on: control of exponential growth, carcinogenesis, the Pasteur effect etc.

The author advocates the now discredited evolutionary mechanism, Lamarckism. The publication states: "In theory, Lamarckism would appear to be the only effective possible method of preserving survival in any species ..."

Lamarckism argues that traits that are acquired (or diminished) during the lifetime of an individual organism can be passed on to the offspring (for example: a blacksmith, through his work, strengthens the muscles in his arms. Lamarckism theorises that this blacksmith's sons will have similar muscular development when they mature).

Holt JG (1986) Clinically derived dose-effect relationship for hyperthermia given in combination with low-dose radiotherapy. *The British Journal of Radiology*. 60: 100-101.

Relevance to the current review: Excluded, not a clinical study, letter.

The author notes that they (Holt and Nelson) have treated in excess of 6000 patients with combined therapy using non-EMR heating or EMR as an ionising radiation adjuvant. The researchers note that they measured the temperature "in most of the first 1000 or so patients" treated. The authors have "abandoned routine temperature measurements in 1977 and now solely use the regime [regimen] of 434MHz EMR delivered before 150-180cGy (rads) X-ray therapy on two or three occasions per week."

The author states: "Irradiation at 434 MHz quickly followed by X-ray therapy produces responses so different from any other regimen as to suggest a non-thermal mechanism." The author supports this statement by referring to a low level of evidence, poor quality 'historically controlled' trial of patients with head and neck cancer. These types of comparisons are prone to high levels of bias. Regardless of this fact, the author states: "If 434MHz (frequently inducing a low temperature rise, often well below 41.8 degrees C) plus x-ray therapy produces a survival three times as good as that from x-rays alone or from an identical (or larger) dose of X-ray therapy proceeded or succeeded by simple hyperthermia to 41.8 degrees C, then only a non-thermal EMR induced sensitisation could account for the difference."

Holt JG and Nelson JM (1988) Synchronous Radiation and Chemotherapy. *Med J Aust*. 148:370

Relevance to the current review: Excluded not a clinical study, letter

This letter contains a response to a review of synchronous radiation and chemotherapy for locally advanced cancer by Dr Denham of Newcastle Mater Misericordiae Hospital. Dr Denham concludes that most results are not decisively better than are those of the existing treatments and he urges further large-scale trials. Dr Holt and Dr Nelson disagree.

A previously reported case series of 52 patients with otolaryngological cancers treated with 434MHz electromagnetic radiation and x-radiation is presented. This group of patients was compared with a historical control group. It should be noted that these

types of comparisons are prone to high levels of bias. Despite this, the authors conclude that: “The three-year apparent cure rate [of those patients treated with 434MHz] was three times that of historical control subjects.”

Dr Denham replies by stating: “The letter by Dr Holt and Nelson contains a mixture of facts, supposition and innuendo which potentially is confusing to the reader and has little to do with the substance of my review article.”

Holt JG. (1988) Microwaves Are Not Hyperthermia. *The Radiographer*. 35 (4): 151-161

Relevance to current review: Included in the review. Some patient data reported previously.

This publication postulates that microwaves at 433-434MHz radio-sensitises cancer without having to induce hyperthermia. This hypothesis is largely based on the author’s assertion that cancer ‘fluoresces’ when treated with microwaves at 434MHz. The author also presents a previously reported historically controlled series of 52 patients with head and neck cancer treated with 434MHz electromagnetic radiation to ‘prove’ that 434MHz “must have specific non-thermal effect on cancer.” It should be noted that these types of comparisons are prone to high levels of bias and the benefits the author has perceived to be due to 434 MHz may be due to the inherent bias present in these types of studies. However, even if this were considered adequate evidence of clinical effect, this would in no way provide evidence to support the author’s putative mechanism of action.

The author describes the equipment originally used to deliver microwave therapy (Tronado machine, 12 x Erbe UHF 200 W generators) and a redesigned version of the equipment (4 x 1-2kW generators).

The publication presents various groups of cancer patients treated with microwave therapy. These groups include patients with: 1) head and neck cancer; 2) oesophageal cancer; 3) gastrointestinal cancer; 4) rectal cancer; 5) bladder cancer; 6) hodgkin’s disease; 7) lymphoma and non-hodgkins lymphoma; 8) other cancers; and 9) skin cancer.

The author concludes that: “In the author’s opinion UHF is the greatest advance in cancer therapy since the discovery of radioactivity by Madame Curie.”

Holt JAG (1991). Untitled letter to the editor, *The Journal of Microwave Power and Electromagnetic Energy* 2(3): 126-127.

Relevance to current review: Excluded from systematic review as non-peer reviewed letter only. Refers to his hypotheses of non-thermal effects of microwaves. A peer-review of the letter was sought by the journal’s editor-in-chief.

This letter to the editor is a response to an Editorial that discussed the question of whether or not there are any athermal effects of microwave on food spoilage organisms. The response by Dr Holt is accompanied by a reply by Dr John Osepchuk (requested by the Editor), which is also referred to here.

Dr Holt commences the letter by referring to two of his publications relating to the non-thermal effects of 434 MHz radiation on cancer (Holt 1986 - actually Holt and Stanford; Holt, 1988). The hypotheses put forward in these publications are largely based on 1)

the author's assertion that cancer 'fluoresces' when treated with microwaves at 434MHz, and; 2) that the results of a previously reported **historically controlled** series of 52 patients with head and neck cancer treated with 434MHz electromagnetic radiation were so impressive that they 'prove' that 434MHz "must have specific non-thermal effect on cancer." It should be noted that these types of comparisons are prone to high levels of bias and the benefits the author has perceived to be due to 434 MHz may be due to the inherent bias present in these types of studies. (Even if this were considered adequate evidence of clinical effect, this would in no way provide evidence to support the author's putative mechanism of action.) Despite this, the author believes that the radiosensitivity of cancer cells can be two or more decades higher following exposure to this type of radiation than it is after heating the cancer to the maximum tolerable body temperature (41°C). He states that "the non-thermal effect on cancer is not present at any of the other frequencies that I have tested and has resulted in my abandoning these frequencies for practical clinical purposes".

Dr John Osepchuk of the Raytheon Research Division in USA responds by pointing out that the diathermy exposure at 434 Mz reported in Holt & Stanford 1986 can be characterised as 8 times the whole body limit of 0.4 watts/kg specified by ANSI C95.1-1982 standard. The exposures used in Holt 1988 were up to 80 times the C95 limit - and therefore if there is any athermal effect it is unlikely to be of relevance to lower exposure limits.

Dr Osepchuk states that "whether or not there is an athermal effect in Dr Holts work is debatable". He states that the simple comparison of the UHF effect with that obtained when a similar temperature is created by non-electromagnetic waves (eg. hot bath) ignores a) differences in temperature-time history and b) differences in heating and distributions throughout the tissue volumes. He states that Dr Holt's claims that athermal effects are site-specific, frequency-specific and that one can not expect to discover any non-thermal effect in a target which displays uniform absorption are "**sweeping generalities not likely to be endorsed by many at either end of the spectrum of believers to skeptics**".

Dr Osepchuk also points out that there is no evidence of measurements to support Dr Holt's claim of a 'fluorescence' that is peculiar to his irradiation with the Tronado machine.

Holt JAG (1993). The glutathione cycle is the creative reaction of life and cancer. Cancer causes oncogenes and not vice versa. *Medical Hypotheses* 40(5): 262-266.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

Note about this journal: *Medical Hypotheses* is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. *Medical Hypotheses* takes a **deliberately different approach to peer review**. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. *Medical Hypotheses* will **publish radical ideas**, so long as they are coherent and clearly expressed. In *Medical Hypotheses*, the authors' responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a "chooser", and not a "changer".

This paper contains a diverse range of ideas, that have not been subject to peer-review. The deviate quite considerably from accepted medical knowledge and from accepted understanding of biology. The paper makes several extreme and selective leaps of logic between various hypotheses, without evidence.

The following points are made by the author:

- The glutathione cycle (oxidation and reduction) is the creative reaction of life and cancer.
- 434 MHz microwave radiation (and 434 MHz alone) stimulates cancer growth rate by forcing this cycle into activity
- Cancer causes oncogenes and not vice versa
- Genetic material will only reproduce if placed within an immortal cell in which all controls of the glutathione system have been lost, as in a cancer cell.
- All life forms die if any or all of their chemical reactions are reversed.
- Comparative photograph of a biopsy pre- and immediately post UHF treatment is presented. On the basis of one pathologist's review of these pre- and immediately post-UHF biopsies, "UHF had altered the microscopic appearance so grossly that one cancer had changed into a different one". NB. This patient was treated with 20 mW/cm² - approximately 20 times the ANSI C95.1 1999 maximum permissible exposure limits.
- The authors argues that the increase in the mortality rate for chronic myeloid leukaemia in the late 1960s was due to the advent of television ("3 high powered TV transmitter, radiating 90% of the population"). He does not presented mortality from any other cancers for the same time period. He cites this as evidence supporting "the hypothesis that cancer can be influenced by factors which do not influence genetically controlled situation".
- Brief clinical details of 11 highly selected patients in listed in an Appendix. Most of these patients have been presented elsewhere in Dr Holts clinical papers.

Holt JAG (1995) Some characteristics of the glutathione cycle revealed by ionising and non-ionising electromagnetic radiation. *Medical Hypotheses* 45(4) 345-368.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

Note about this journal: *Medical Hypotheses* is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. *Medical Hypotheses* takes a deliberately different approach to peer review. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. *Medical Hypotheses* will publish radical ideas, so long as they are coherent and clearly expressed. In *Medical Hypotheses*, the authors' responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a "chooser", and not a "changer".

This publications expands upon the glutathione cycle hypotheses presented in the *Medical Hypotheses* publication above (Holt, 1993).

In addition the author states:

- The glutathione reaction produces the energy for mitosis and is kept in controlled inactivity until needed to maintain perfection of form and function by energising mitosis.
- UHF changes the glutathione reaction from inactive to active and in doing so causes resonance and/or fluorescence of the glutathione cycle.
- The glutathione reaction is intelligent compared with non-exponential reactions but cannot be the basis of intellectual brain functions which must be based on non-exponential chemical processes.
- One's brain mutates to increase its learning (referred to by the author as chemical evolution). The author provides a discussion about the increases in intelligence within an individual and also the inheritance of intelligence.
- Evolution therefore cannot be by chance and the Darwinian theories must be incorrect. Adaptation to environment as it is exemplified by the automatic combination of the glutathione cycle and Pasteur reaction controlling it indicate that evolution is automatic and of Lamarckian form.
- The author introduces the concept of electrical evolution (the glutathione cycle) and states this is the "direct cause of the evolution of the species".
- It is proposed that Alzheimer's disease is due to an excessive chemical reaction leading to the overgrowth of neuronal proteins, thus producing the classic 'tangles' of neural tissue.
- Simple heating (ie., achieved by means other than UHF) doubles the radiosensitivity of cancer, but UHF may increase it by up to 20 times.

The author commences the Discussion with the statement "Cancer does not have the characteristics of an inherited disease and cannot be recognised as can all genetically-controlled life eg. elephants, tigers etc". The publication concludes with the statement "Life is an atheistic phenomenon of the electrochemical reactions of glutathione".

Holt J (1996) Cancer therapy by immobilizing mitotic energy sources. *Journal of Orthomolecular Medicine* 11(2): 100-111.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

Note about this journal: This is the quarterly journal of the Orthomolecular Society. Orthomolecular medicine is a branch of complementary medicine that describes the practice of preventing and treating disease by providing the body with optimal amounts of substances which are natural to the body. In the orthomolecular view, the provision of vitamins, amino acids, trace elements or fatty acids in amounts sufficient to correct biochemical abnormalities will be therapeutic in preventing or treating diseases such as atherosclerosis, cancer, schizophrenia or depression.

This is a further publication referring to the importance of the glutathione reaction in the creation of life, cancer and the treatment of cancer.

The Methods section of the paper lists treatment information for seven patients treated seven different ways, but makes no reference to histopathological investigation or cell culture procedures. However, then the Discussion section proceeds to discuss the rate of cell kill that appears to be purely theoretical speculation. This is misleading for the reader as it implies that cellular measurements were actually made.

Holt, J. (1997) A theoretical biochemical basis of cancer: confirmation by electromagnetic radiation. *Journal of Orthomolecular Medicine* 12(3): 149-163.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

Note about this journal: This is the quarterly journal of the Orthomolecular Society. Orthomolecular medicine is a branch of complementary medicine that describes the practice of preventing and treating disease by providing the body with optimal amounts of substances which are natural to the body. In the orthomolecular view, the provision of vitamins, amino acids, trace elements or fatty acids in amounts sufficient to correct biochemical abnormalities will be therapeutic in preventing or treating diseases such as atherosclerosis, cancer, schizophrenia or depression.

This paper is a purely theoretical paper that expands upon the previous hypotheses the Dr Holt has presented. The author presents a system “to explain the non-chaotic basis of all life in contrast to the chaotic basis of everything inanimate in the universe”.

The author states:

- that he has the ability to cure HIV infections through application of these principles
- that radiowave pollution is the most likely cause of the demise of certain types of animal life and the reduction of sperm counts in humans
- that schizophrenia can be successfully treated with vitamin B3
- that "in a survey of 50,000 patients with cancer treated in Western Australia over a 40 year period the radiotherapists have only treated one patient who was diagnosed with schizophrenia. This is the basis of teaching the students that to avoid cancer one should become a schizophrenic".

Holt J & Nelson A (1997). Letter responding to “Adjuvant VHF therapy in locally recurrent and primary unresectable rectal cancer (Trotter *et al*, 1996)”. *Aust Radiol* 41(3): 317-318.

Relevance to current review: Excluded non-peer reviewed letter. A reply letter from Dr Trotter appeared in the same edition, and is also referred to here.

This is a letter to the editor in response to the Trotter *et al* 1996 paper in the same journal. Drs Holt and Nelson contend that the Trotter rectal cancer study should not have been published without the “correct historical perspective” - meaning that the authors should have referred in more detail to the poorly controlled head and neck cohorts from the 1970s.

They also state that the rectal cancer study (which Dr Holt was actually involved in as a principal investigator) was agreed to under duress as rectal cancer was not their cancer of choice for the trial. They state this is “why we have refrained from having one or both of our names on the paper”.

In his reply, Dr Trotter points out that Dr Holt was involved on the management committee of the rectal cancer trial and that indeed it was he who recommended the doses of VHF therapy and radiation for the combined treatment arm. He clarifies that Dr Holt endorsed the choice of rectal cancer, and that Dr Holt had at the time drawn attention to a survival advantage observed in rectal cancer in a retrospective comparison of radiotherapy vs VHF plus radiotherapy that had been undertaken in Perth (Cassidy, 1990) - indeed similar in design to much-reported head and neck series.

The fact that the early rectal cancer observations were not able to be replicated in a randomised controlled trial reiterates the need for caution to be exercised when assessing studies with consideration selection, intervention and measurement bias.

Holt JAG (2001). The metabolism of sulphur in relation to the biochemistry of cystine and cysteine: Its fundamental importance in biology. A cyclic interchange between their mono- and di-sulphides is the unique reaction creating life and intelligence. *Medical Hypotheses* 56 (5): 658-676.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

Note about this journal: *Medical Hypotheses* is a forum for ideas in medicine and related biomedical sciences. It will publish interesting and important theoretical papers that foster the diversity and debate upon which the scientific process thrives. *Medical Hypotheses* takes a deliberately different approach to peer review. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. *Medical Hypotheses* will publish radical ideas, so long as they are coherent and clearly expressed. In *Medical Hypotheses*, the authors' responsibility for integrity, precision and accuracy of their work is paramount. The editor sees his role as a "chooser", and not a "changer".

The author presents various theories about the creation of life and intelligence. The author again advocates the now discredited Lamarckian evolutionary mechanism. The author states: "Evolution is therefore 'pushed' by an intelligent ER_{ex} [a theorised 'exponential reaction that creates life from non-life'] and must be of Lamarckian form."

And,

"Physical evolution is thus pushed by ER_{ex} and is Lamarckian and automatic. Any block to the evolutionary progress will be overcome and chance Darwinian response can play little or no part in such a system."

And,

The author discusses, "Life in another solar system." He states: "Starlings' would automatically evolve to survive on star world like all life on earth and would certainly be totally different in physical form but have identical ability to adapt to star world environment. Evolution there would also be Lamarckian."

Lamarckism argues that traits that are acquired (or diminished) during the lifetime of an individual organism can be passed on to the offspring (for example: a giraffe, by continuing to stretch his neck will pass down to its offspring an increased stretching ability and the long neck that goes with it).

The author postulates that three unique characteristics create life. "These are: exponential growth proportional to time; the irreversibility of this exponential growth; and the transference of these two features to create generations of life from non-life." The author states that cancers obey all these three criteria of life. The author also states cancer can only arise from stem cells.

The author reiterates various theories about glutathione, glucose metabolism and the Pasteur reaction.

The author believes that heat treatment (hyperthermia) does not generate a clinical response in any patient except relief from bone pain. The author believes 434MHz selectively kills cancer cells, the author states: "... this selective lethality to cancer cells is unique to 434MHz radiation amongst every other cancer therapy." The author postulates that cancer uniquely 'resonates' and 'fluoresces' when subjected to 434MHz radiation. The author also reiterates his theory that 434MHz has a non-thermal radiosensitising effect on cancer. The author believes that "ERex [a theorised 'exponential reaction that creates life from non-life'] must be the only primary target of ionising radiation." The author concludes: "... 434MHz before X-ray therapy converts disaster to triumph!"

The author discusses the use of hyperbaric oxygen and anoxic radiotherapy for cancer treatment.

The author believes that every: multiple sclerosis, scleroderma, herpes zoster, hepatitis, amyotrophic lateral sclerosis, ankylosing spondylitis, and systemic lupus erythematosus patient has benefited and most have had their disease eliminated by treatment with 434MHz therapy.

The author also believes 434MHz can cure Alzheimer's disease.

The author states that 434MHz can unequivocally cure AIDS. The author states: "A patient with seroconversion in 1988 progressed to AIDS in 1992 and had four courses of therapy over the next three years ... He appears unequivocally cured of his infection."

The author also believes it is possible that Creutzfeld-Jakob disease (a Prion disease) should be eminently treatable by 434MHz.

The author presents a number of theories on crocodile populations and the war's effect on population growth and compares these to the biology of cancer.

The author presents theories on virology, neurones and cancer.

The author postulates theories on overcrowding, starvation, 'the creed of greed', consciousness, and the suppression of consciousness.

Holt J (2003) Ultra high frequency radiowave cancer therapy. *Reviews in Clinical Oncology*. 1 (2): 16-17.

Relevance to current review: Excluded non-peer reviewed letter.

The author states: "In 1973 I discovered that Ultra High Frequency Radiowaves (UHF) would increase the radiosensitivity of otherwise unresponsive cancers by any factor up to 10,000 times the cancer cell kill, when used before a dose of radiotherapy compared with the effect of a similar or greater dose used in isolation."

The author presents the results of a ‘phase I trial’ of patients with mesothelioma (see table below).

Group	Site	Treatment	No patients	Survival (weeks)		
				Average	Maximum	
1	A	Lung	Cytotoxics before UHF	27	12	20
	B	Lung	UHF before Cytotoxics	16	7	13
2	A	Lung	X-ray therapy before UHF	28	43	57
	B	Lung	UHF before X-ray therapy	24	87	2 at 260+
3	A	Abdomen	X-ray therapy before UHF	7	12	23
	B	Abdomen	UHF before X-ray therapy	7	34	65

It is very important to note that no details regarding the staging of these patients’ disease were presented in this letter and no description of how the patients were assigned to treatment groups were shown. Therefore, it is unclear if ‘UHF before X-ray therapy’ had any beneficial treatment effect in these patients or if the apparent difference in average survival was simply due to biased patient allocation or the patient populations simply being different at baseline.

The author states: “In 1986 the radiotherapy was abandoned in favour of anaerobic ‘glycolytic blocking agents’ (oxidised glutathione, cystine - disulphide form and other disulphide amino acids) before UHF therapy.”

The author presents information about 14 mesothelioma patients treated with UHF and ‘glycolytic blocking agents.’ The author lists a series of Australian patent numbers that cover this therapy and states: “Anyone interested in this method can apply to me for a franchise on the method ...”

Holt J (2004). The unique exponential growth of life is powered by anaerobic glycolysis. *J Molecular Liquids* 114: 193-206.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

The author postulates various theories regarding:

- Ionising radiation, normothermic, normobaric therapy
- Non-electrical hyperthermia
- Anoxic, normothermic, normobaric and radiation therapy
- ‘Synergism between 434MHz UHF and X-rays’
- ‘Anaerobic glycolytic blocking before UHF’
- The importance of the glutathione reaction in the creation of life, cancer and the treatment of cancer.
- Pasteur’s reaction
- ‘Exponential growth of life and cancer’
- Putative ‘athermal effects of non-ionising radiation / 434MHz UHF’
- Neurones, glial cells and cancer
- Nanobug life ‘peppered’ throughout the universe

The author believes that: “The epidemics of influenzas appear to be directly correlated with the amount of radiowave pollution in the atmosphere. The influenza virus will not only be electrically conductive and stimulated by radiowave pollution but will have a decreased mutation time such that a lethal new disease can be created readily at any time. The first epidemic of influenza occurred when Faraday was commencing his experiments on electromagnetic induction.” The author continues by stating: “It is tempting to suggest that the enormous radiowave pollution generated by massive naval and military installations was responsible for the 1918 epidemic of influenza.”

The author also states: “In NSW where chronic lymphatic leukaemia figures were analysed, there is an increased incidence of this disease proportional to the radiowave pollution levels associated with TV transmitters ...” The author concludes that: “... radiowave pollution will increase the rate of growth of both chronic myeloid leukaemia and chronic lymphatic leukaemia but that it is also a causative agent in chronic lymphatic leukaemia.”

The author concludes: “ionising radiation is the only biological killer of cancer available in the universe.”

Holt J A G (2004), The energy system creating life and cancer from inanimate compounds. *Journal of Orthomolecular Medicine*. 19 (3): 141-161.

Relevance to current review: Excluded from systematic review as a publication containing non-peer reviewed hypotheses relating to biological process, rather than peer-reviewed clinical trial data.

Note about this journal: This is the quarterly journal of the Orthomolecular Society. Orthomolecular medicine is a branch of complementary medicine that describes the practice of preventing and treating disease by providing the body with optimal amounts of substances which are natural to the body. In the orthomolecular view, the provision of vitamins, amino acids, trace elements or fatty acids in amounts sufficient to correct biochemical abnormalities will be therapeutic in preventing or treating diseases such as atherosclerosis, cancer, schizophrenia or depression.

The author postulates various theories regarding:

- Glutathione and glycolysis
- Cancer and neurones
- Cancer ‘resonating’ and ‘fluorescing’ when subjected to 434MHz radiation
- Pasteur’s reaction
- Non-thermal effects of 434MHz
- Out of body experiences
- Out of life experiences
- Anoxic therapy versus UHF therapy

The author advocates the now discredited Lamarckian evolutionary mechanism and rejects Darwinian evolution. The author states: “Evolution is pushed by ER_{ex} [a theorised ‘exponential reaction that creates life from non-life’] and must be of Lamarckian form, rather than according to Darwin’s chance theory.”

Lamarckism argues that traits that are acquired (or diminished) during the lifetime of an individual organism can be passed on to the offspring (for example: a giraffe, by continuing to stretch his neck will pass down to its offspring an increased stretching ability and the long neck that goes with it).

APPENDIX 19: SYNOPSES OF RECENT *IN VITRO* PUBLICATIONS BY UNSW RESEARCH GROUP

Harvey C, French PW (1999) Effects on protein kinase C and gene expression in a human mast cell line, HMC-1, following microwave exposure, *Cell Biology International*. 25(11): 739-748

This publication describes an *in vitro* study investigating the effect of microwave exposure (864.3 MHz) on the human mast cell line (HMC-1). The cells were treated with three 20 minute exposures each day for a seven day period. Another group of cells were treated in an identical fashion without the application of microwave to act as a control group. The researchers did not actively control the temperature of the cell cultures but temperature measurements of the cell cultures were made.

The temperature was different in the electromagnetic radiation exposed culture and the unexposed cell cultures however this difference did not reach statistical significance (control: 25.8°C; exposed group: 26.5°C).

The researchers found no significant morphological differences between the control (unexposed) and the exposed cells at any time point in the exposure period. The authors note that there was only a small number of cells available for morphological assessment.

The researchers note that in four experiments there was “a consistent trend” for an increase in the amount of immunoreactive protein kinase C in the membrane fraction of the exposed cells and a concomitant decrease in the cytosolic fraction. However, the researchers do not provide details of the number of experiments where no difference between the exposed cells and the control group occurred.

In two experiments changes in expression between the exposed and control HMC-1 cells were seen in only three genes out of a total of 588 genes screened (0.5%). The researcher notes that this indicates that such exposure does not have a broad effect on gene expression and indeed the effects on specific genes are moderate rather than substantial. Again, the researchers do not provide details of the number of experiments in which no difference between the exposed cells and the control group was found.

The researcher note that there was some variability between the experiments. **Some genes were altered in one experiment but not the other, and some genes were altered in different directions between experiments.** The authors note that this may have been due to differences in cell passage number, stage of the cell cycle, or physical variations within the exposure chamber.

The researchers state: “This indicates that for this exposure set up, the effect of athermal exposure is quite small.” Despite the discussion of an ‘athermal effect’ the authors discuss the possibility that localised ‘hot spots’ within the culture vessel may have given rise to the modest effects observed.

French PW, Penny R, McKenzie DR (2000) Mobile phones, heat shock and cancer. *Differentiation*. 67:93-97

This publication presents the **hypothesis** that mobile phone radiation is not physiologically inert and primarily acts to induce the heat shock response in the brain tissue of phone users.

The authors discuss the role of heat shock proteins in cancer.

The authors then postulate that if chronic RF exposure induces the heat shock response, which leads in turn to increased cancer proneness, this could explain the significant increase in lymphoma seen in transgenic mice exposed to 900 MHz at low SARs (specific absorption rates).

The authors present the theory that non-thermal RF radiation may induce heat shock response in cellular targets. They discuss, in brief, some experimental results obtained in a study of *C. Elegans* (a nematode model) that showed a significant difference in the expression of heat shock proteins between control and RF exposed nematodes. The researchers state: "Our own recent work has indicated that Hsps [heat shock proteins] are induced by chronic non-thermal exposure of rat mast cells to pulsed RF radiation", however, this data is not shown.

The researchers also discuss a report in which RF microwave radiation at much larger SARs failed to induce the heat shock response in HeLa (a breast cancer cell line) cells and CHO (Chinese Hamster Ovary) cells.

French PW, Donellan M, McKenzie DR (1997) Electromagnetic radiation at 835MHz changes the morphology and inhibits proliferation of a human astrocytoma cell line. *Biochemistry and Biogenetics*. 43:13-18

This publication describes an *in vitro* study of astrocytoma cell line that was exposed to electromagnetic radiation at 835 MHz at a power density of either 40 mWcm⁻² or 8.1 mWcm⁻² for 20 minutes, 3 times a day for 7 days. A control group of cells were handled in an identical fashion except that they were not exposed to electromagnetic radiation. The researchers did not actively control the temperature of the cell cultures but the temperature of the cell culture medium was measured at the conclusion of exposure with a thermocouple temperature probe. The exposed and unexposed cells were then subjected to a proliferation assay (³H-thymidine uptake) and confocal scanning laser microscopy.

In both electromagnetic radiation exposed cultures the temperature was higher than recorded in the unexposed cell cultures (control: 26.2 ± 0.6°C; low power group: 27.0 ± 0.9°C; high power group: 34.0 ± 0.1°C).

There was no difference in the rate of proliferation between the exposed cells and the cells treated with 40 mWcm⁻². The proliferation rate of the cells treated with 8.1 mWcm⁻² was significantly different from both the control cells (p = 0.019) and the cells irradiated at 40 mWcm⁻² (p = 0.018) using the students t-test.

After 7 days the cells exposed at 8.1 mWcm⁻² showed a marked alteration in cell shape. The cells normal spherical morphology had disappeared, and instead the cells had adopted a flattened, spread shape. At the same time, the cells lost the actin-containing cell surface projections observed in the control cells. Similar results were seen for

the 40mWcm⁻² exposure, the difference being that the flattened cells exhibited actin aggregates (blebs) localised at specific sites on the cell membrane.

The authors postulate that the changes in morphology of the cell lines detected in cells exposed to microwave energy at 40 mWcm⁻² were presumably due to thermal effects of the microwave irradiation on either the culture medium or the cells. The authors state: “At lower power, no significant heating is detectable, and the actin blebs are not present.” The authors discuss the hypothesis that the reduction in the proliferation of the astrocytoma cell line treated at 8.11 mWcm⁻² was due to an effect on the mitogen-activated protein kinase (MAPK) cascade.

The authors do not discuss the possibility that localised ‘hot spots’ within the culture vessel may have given rise to the effects observed. This possibility is raised in a subsequent paper published by in Harvey and French in 1999.

The authors acknowledge the contribution of Dr J.A.G Holt of the Microwave Therapy Centre, Perth, Western Australia, who initiated the project, provided funding, most of the consumables, the exposure tank and associated materials.

Laurence JA, French PW, Lindner RA, Mckenzie PW (2000) Biological effects of electromagnetic fields – mechanisms for the effects of pulsed microwave radiation on protein conformation. *J Theor Biol.* 206: 291-298.

This publication presents a **theoretical model** in which pulsed microwave radiation causes a triggering of the heat shock or stress response by altering the conformation of proteins through transient **heating** of the protein and its close environment.

The researchers hypothesise that:

“At low power levels, a partial unfolding of specific target protein(s) occurs, which will be insufficient to induce the stress response, but sufficient to alter protein function. A biological effect (eg. on cell proliferation) will be observed.”

“At higher power levels a more unfolded (molten globule) conformation is induced. The stress response will be activated, protecting the protein, and preventing an observable biological effect.”

“At very high power levels, protein aggregation and precipitation occurs, and despite the activation of the entire stress response, a catastrophic biological effect (eg. cell death) will be observed.”

Donnellan M, McKenzie DR, French PW (1997) Effects of exposure to electromagnetic radiation at 835MHz on growth, morphology and secretory characteristics of a mast cell analogue, RBL-2H3. *Cell Biology International*. 21(7): 427-439.

This publication describes an *in vitro* study of a mast-cell line, that was exposed to electromagnetic radiation at 835 MHz for 20 minutes, 3 times a day for 7 days at a power density of 8.1 mW/cm². A control group of cells were handled in an identical fashion except that they were not exposed to electromagnetic radiation. The researchers did not actively control the temperature of the cell cultures but temperature measurements of the cell cultures were made. The exposed and unexposed cells were then subjected to a proliferation assay (³H-thymidine uptake) and an assay of B-hexosaminidase (a marker for granule secretion). Immunofluorescence and confocal microscopy were used to determine the effect of 835 MHz exposure on F-actin distribution and cell morphology.

The exposed cell cultures were found to be on average $0.8 \pm 0.4^{\circ}\text{C}$ greater in temperature than the unexposed cultures.

For the first five days of exposure the rate of ³H-thymidine uptake was similar. After the first five days the rate of ³H-thymidine uptake in the control cells declined due to the cells reaching confluence. This decline was not seen in the exposed cells.

After seven days of exposure the appearance of actin-containing cell surface ruffles which were not detected in the control cells appeared.

When the researchers averaged data from three separate experiments they detected a difference in B-hexosaminidase secretion from stimulated cells that had been exposed to electromagnetic radiation for greater than 4 days compared with the un-irradiated cells.

The authors hypothesise that the effects of exposure to an electromagnetic field at 835 MHz may be mediated via a signal transduction pathway.

The authors conclude: "Which, if any, of the above mechanisms are operating to produce the effects reported above of electromagnetic field-associated cellular changes requires further detailed study."

The authors acknowledge the contribution of Dr J.A.G Holt of the Microwave Therapy Centre, Perth, Western Australia, who initiated the project, provided funding, most of the consumables, the exposure tank and associated materials.