ADVANCES IN THE RADIOTHERAPY OF SKIN CANCER

BY

GERALD BLAISE FOGARTY

A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

CENTRE FOR HEALTH TECHNOLOGIES

FACULTY OF ENGINEERING & INFORMATION TECHNOLOGY

UNIVERSITY OF TECHNOLOGY, SYDNEY

2012

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CERTIFICATION

I certify that this thesis has not already been submitted for any degree and is not being submitted as part of candidature for any other degree.

I also certify that the thesis has been written by me and that any help I have received in preparing this thesis have been acknowledged in this thesis.

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Dr G B Fogarty

ACKNOWLEDGEMENTS

I am indebted to my supervisors, Professor Hung Nguyen AM, Dean of Faculty of Engineering and Information Technology,Emeritus ProfessorAG Shannon AMand Emeritus Professor Barry Thornton AM at University of Technology, Sydney. I am also grateful to the many patients and co-researchers who have made this thesis possible, and Dr Helena Jang for her assistance with the typing and formatting of the thesis.

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Dr G B Fogarty

ABBREVIATIONS

3DCRT, 3D	Three dimensional conformal radiotherapy
ASM	Annual Scientific Meeting
BCC	Basal cell carcinoma
CNS	Central nervous system
cSCC	Cutaneous squamous cell carcinoma
CT	Computed tomograph
Dmax	Depth of the maximum dose for a megavoltage beam
DNA	Deoxyribose Nucleic Acid
DSMC	Data safety monitoring committee
EGFR	Epidermal growth factor receptor
eGFR	Estimated glomerular filtration rate
EGFRI	Epidermal growth factor receptor inhibitor
EORTC	European Organisation for Research and Treatment of Cancer
EORTC BN-20	EORTC Quality of Life Questionnaire with Brain module
EORTC QLQ-C30	EORTC Quality of Life Questionnaire
EPI	Electronic portal imaging
ERA	Excellence in Research for AustraliaInitiative
GDS	Global Deficit Scores
HDRBT	High Dose Rate Brachytherapy
HRQOL	Healthrelated quality of life
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiotherapy
IVRS	Interactive voice response system
KPS	Karnofsky Performance Scale
MC1R	Melano Cortin -1- Receptor
MCC	Merkel cell carcinoma
MLCs	Multileaf collimators
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MUs	Machine monitor units
NBCCS	Nevoid basal cell carcinoma syndrome
NCF	Neurocognitive function
NSW	New South Wales
PET	Positron Emission Tomography

PMCC	Peter MacCallum Cancer Centre
PORT	Postoperative radiotherapy
QA	Quality assurance
RA	RapidArc®
RANZCR	Royal Australian and New Zealand College of Radiologists
RCTs	Randomised clinical trials
RHC	Red Hair Colour
RT	Radiotherapy
SCC	Squamous cell carcinoma
SIB	Simultaneous integrated boost
SNP	Single nucleotide polymorphisms
SRS	Stereotactic radiosurgery
UV	Ultraviolet
VMAT	Volumetric Modulated Arc Therapy
WBRT	Whole brain radiotherapy

GLOSSARY OF SPECIALIST MEDICAL TERMS FOR LAY PERSON

- Acute effects – side effects of radiotherapy that occur during treatment delivery or up to 3 months post treatment . These effects are dominated by acute inflammation.
- Adjuvant treatment – a treatment that assists the main treatment in eradicating cancer. Often it assists the definitive or main treatment e.g. chemoradiotherapy – the chemotherapy makes the radiation more effective.
- Axilla – anatomical term for region of the armpit.
- Cancer– a condition whereby cells divide uncontrollably, forming malignant tumours that can invade into other parts of the body.
- Chart – record of patient medical history.
- Definitive treatment – the main treatment being used to eradicate cancer. Adjuvant treatments assist the definitive treatment.
- Immunosuppression–a condition with decreased immunity. This is associated with increased skin cancer risk in older Caucasians living in climates of high ultra violet (UV) exposure.
- Late effects – side effects of radiotherapy that occur at least 6 months after treatment delivery. These effects are dominated by chronic inflammation with the laying down of fibrosis and consequent loss of organ elasticity.
- Megavoltage radiotherapy – radiation for treatment produced by linear accelerators capable of high generating voltages. The possibility of skin sparing is common with this modality.
- Melanoma – type of skin cancer that metastasizes early.
- Metastasis– or secondary; cancer that has spread from the primary and is not continuous with primary.
- Multidisciplinary care – when more than one modality or craft group is employed in treatment , e.g. surgery and radiotherapy.
- Non-melanoma skin cancer – skin cancer that is not melanoma. These include basal cell or cutaneous squamous cell carcinoma. Other more uncommon non-melanoma skin cancers are primary skin lymphomas and merkel cell carcinoma.
- Occult primary – a cancer diagnosed with secondaries that has no identifiable primary lesion.

- Palliative treatment – treatment that aims to increase quality rather than quantity of life. This treatment is usually given for the relief of a specific cancer symptom e.g. pain.
- Primary – the original cancer from which metastases or secondaries arise.
- Radical treatment – when the treatment intent is cure or at least increasing survival. Treatment side effects are tolerated for this end.
- Radiobiology– the study of the action of ionizing radiation on living things.
- Radiotherapy – ionizing electromagnetic energy used in medicine for treating pathology, usually cancer.
- Secondary – or metastases – cancer that has spread from the primary and is not continuous with primary.
- Skin cancer– cancers that have their origin in the epidermis and dermis of skin, the visible covering of the body.
- Skin sparing –property of megavoltage radiation that means that the maximum dose is not at the skin surface.
- Supraorbital – anatomical term for region above the eye.
- Synergistic treatments – when the combination of both treatments gives more tumour control that when the same treatments are used individually.
- Therapeutic ratio – ratio of tumour cell kill to normal tissue side effects. The aim of all cancer treatment is to maximize this ratio – more tumour kill for less normal tissue toxicity.
- Triage – the process by which cases of differing risks are prioritized for treatment.

THESIS PROJECTS BY CODE AND SHORT TITLE IN EACH CHAPTER

CHAPTER 1: Introduction

CHAPTER2: Molecular Advances

2.1 EGFR in skin SCC

2.2 MC1R Skin effects

2.3 Skin Tumour gene.

CHAPTER3: Advances in Radiation Techniques

3.1 Skin Cancer and Axilla

3.2 RT of Supraorbital Nerve

3.3 Eye Toxicity

3.4 Skin RT techniques Spring

3.5 Skin RT techniques Fall

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CHAPTER4: Clinical Advances

4.1 Imaging

- 4.1.1 MRI Brain in Melanoma
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- 4.1.3 PET Occult Primary

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Surgery

- 4.2.1 Melanoma in Brain
- 4.2.2 RT Delay in Skin Cancer
- 4.2.3 RT in recurrent BCC

Chemotherapy

- 4.2.4 Rituximab and skin SCC
- 4.2.5 Radiation Recall

EXECUTIVE SUMMARY

The main purpose of the thesis is to highlight the important role that radiotherapy has in the treatment of skin cancer. This is critically important in Australia which has the highest burden of skin cancer in the world. Twenty four projects were selected from the total works of the candidate, the majority being first in world reports. The projects are groupedaccording to whether their advances are in the molecular area, are a radiation technique, are advances in the clinical area, in quality assurance or guidelines area. Most projects owe their origin to astute observation of unexpected findings in the clinic. Project quality is high as measured by citations, Impact Factor of the journals in which they are published and inclusion in the ERA 2012 Journal List. These projects were either practice changing or confirming in their time. As the thesis develops there is a growing momentum of the underlying importance of the need for communication, for personalized treatment of skin cancer with radiotherapy and for clinical vigilance. This thesis provides a platform for further research and a significant resource for future health workers.

ABSTRACT

Introduction

The main purpose of the thesis is to highlight the important role that radiotherapy has in the treatment of skin cancer. This is critically important in Australia which has the highest burden of skin cancer in the world.

Methodology

Twenty four projects that led to publication over a ten year period by the candidate were selected. They were selected because they were on the subject of radiotherapy of skin cancer and represented a new advance. An essay was written linking them together so as to highlight the findings of each individual project and to investigate and discover common underlying themes.

Results

The quality of the projects is high as they have been published in peer reviewed journals with respectable impact factors. A number have been significantly cited in subsequent articles and open access publications have received significant hits. Most have been published in journals on the ERA 2012 Journal List.

The specific reasons why each project was investigated included:

- the desire for self audit
- to find an association
- to investigate unexpected findings
- to create much needed guidelines
- to compare treatments and techniques.

The specific reasons for publishing included:

- to inform on unexpected results
- to inform on expected but never before published results
- to suggest new guidelines
- to disseminate knowledge on new techniques
- to invite collaboration in a specific trial
- as part of a controversy.

The linking essay comprises six chapters that deals with advances:

- on the molecular level
- in radiation techniques
- in clinical areas
- in quality assurance
- that suggest new guidelines

Significant underlying themes found were:

- the need for communication
- the need for personalized treatment of skin cancer with radiotherapy
- the importance of clinical vigilance.

Conclusions

This thesis shows that radiotherapy in skin cancer has a real place. It describes specifically how the selected projects led to significant advances in the radiation treatment of skin. The thesis provides a significant resource for future health workers. It also provides a platform for further radiotherapy research into improving skin cancer patient outcomes. This thesis will hopefully be a stimulus to other Australian radiation oncologists to engage in this important subspecialty.

OVERVIEW

This thesis is about advances in radiotherapy in skin cancer. The main purpose of the thesis is to highlight the important role that radiotherapy has in the treatment of skin cancer. This is critically important in Australia which has the highest burden of skin cancer in the world.

There are two main components for assessment in this thesis. The first and major component is made up of projects that have led to peer-reviewed publications. Significant work occurred during the candidature. The second component is a reflection on these advances. This reflection is in the form of a linking essay that introduces and integrates the projects. The reflection comments on the advances in the radiation treatment of skin cancerinvestigated and published by the candidate in the last ten years.

Twenty four projects were selected from the total published works of the candidate. The majority are first in world literature reports aiding their successful passage through peer review. These projects were either practice changing or confirming, in their time.
These projects were selected according to the following criteria:

a. They are relevant to the radiation treatment of patients with skin cancer.
b. They represent an advance in skin cancer treatment – they are either a new discovery or new way of integrating current technology in the skin cancer setting.
c. They have been deemed worthy of publication by peers so that this information may be made available to other physicians involved in the care of skin cancer patients

All the projects attempted to enhance the therapeutic ratio of treatment for the benefit of patients in the present and of the future. Most projects owe their origin to astute observation of unexpected findings in the clinic. The projects were usually initiated by the candidate. The specific reasons why each project was investigated included the desire for self audit, to find an association, to investigate unexpected findings, to create much needed guidelines and to compare treatments and techniques. The specific reasons for publishing included: to inform on unexpected results, to inform on expected but

never before published results, to suggest new guidelines, to disseminate knowledge on new techniques, to invite collaboration in a specific trial and as part of a controversy.The quality of the projects is high as they have been published in a peer reviewed journals. A number have been significantly cited in subsequent articles and open access publications have received significant hits. Most have been published in journals on the ERA 2012 Journal List, which have respectable Impact Factors.

The sevenchapters of the thesis include as chapter one an introduction that sets out the purpose of the thesis and sets the scene by a focused literature review. The basis of radiation is explained, especially the ability to conserve in-field normal tissue. The therapeutic ratio has been shown to be a useful tool to evaluate advances.

Chapters two to five describe the contribution to the thesis of projects according to whether their advances are in the molecular area, are radiation techniques, are advances in the clinical area or the quality assurance and guidelines area. This classification is arbitrary but does reflect where the projects impact clinical practice. Chapter six outlines significant ongoing projects that occurred during the candidate's doctoral candidature and concern a randomized trial for Whole Brain Radiotherapy (WBRT) in melanoma and the provision of cutting edge modern technology to the radiotherapy care of skin patients.

Chapter two focuses on the molecular basis of radiation for skin cancer. Molecular changes are the most fundamental in any living system and determine the outcome at more macroscopic levels. The first project (*2.1*) shows it is necessary to confirm the existence of the target in the cells requiring treatment before embarking on a full study of a targeted cancer agent in skin cancer. The second study (*2.2*) found that the difference in frequency of alleles encoding a 'Red Hair Colour' (RHC) phenotype in the cohort of patients with unexpectedly severe acute skin radiation reactions (n=12) was significantly increased compared to the control population (p=0.003) and was especially associated with the R160W variant allele [odds ratio =3.64 (95% CI:1.3-10.27)]. This discovery could potentially contribute to a predictive assay for normal tissue damage from RT. The third project (*2.3*) may have been the first description of a new tumour

suppressor gene syndrome with multiple BCCs in previously irradiated fields, multiple cancers and multiple immunological disorders in the same patient. These projects were all world first reports.

Chapter three comprises techniques developed in an era of three dimensional conformal radiotherapy (3DCRT). They all lead to greater conformality of the radiation dose cloud to the target, often by use of lateral thinking. The axilla project (*3.1*) shows that fields applied with no knowledge of where the tumour is, and what dose to use, leads to poor outcomes. The second project (*3.2*) shows that new technology is not always necessary for better conformality. What is needed is to know the volume requiring radiation and the limits of the current tools. The third project (*3.3*) details how two eyes were saved by thinking laterally about eye position during definitive radiotherapy for skin cancer in cooperative patients. The last three projects (*3.4-3.6*) detail techniques written with radiation therapists from other countries in mind. These projects were all world first reports except the second which was a reply to a previous publication, creating a controversy.

Chapterfour comprises projects relating to clinical advances and these are among the most frequently cited in the thesis. The chapter has two parts. The first is about imaging and comprises three projects about staging. From a study of 100 melanoma patients (*4.1.1*), it was found that staging magnetic resonance imaging (MRI) brain was only needed if patients already had Stage IV disease, had symptoms that may have come from a cerebral secondary, or were contemplating significant treatments for which the finding of an incidental brain metastasis would have made that treatment inappropriate. The next project (*4.1.2*) showed that astute thinking resulted in finding that a PET scan, which diagnosed a melanoma patient as having stage IV disease, actually had a warthin's tumour causing a false positive. The last imaging study (*4.1.3*) found that PET does not add significantly to finding occult primary tumours in 21 cases of patients who presented with cervicallymphadenopathyoverthat given by careful clinical, endoscopic, and radiological examinations. All these projects show that imaging is helpful but not a replacement of the basic clinical skills of proper history taking and examination.

The second part of this chapter consists of projects that examine the interaction of other

anti-cancer treatments with radiotherapy. The initial three projects were about interactions with surgery. The first project (*4.2.1*) describes a case of complete reversal of neurological symptoms following haemorrhage into a cerebral melanoma metastasis with palliative surgery rather than immediate WBRT. The second project (*4.2.2*) found that a delay in postoperative radiotherapy (PORT) for cSCC, BCC and MCC was associated with a worse outcome in ten of 330 patients who had to wait longer than our unit benchmarks. The third project (*4.2.3*) describes what can happen when PORT is not offered for a positive perineural deep margin following resection of a large BCC of the back. The patient developed spinal cord compression that was salvaged by RT. The last two projects concern chemotherapy. The first project (*4.2.4*) describes activation and rapid progression of cSCC in three Caucasians, with long histories of sun damaged skin, following administration of Rituximab. The second project (*4.2.5*) was the third case report in the world literature of a radiation recall reaction with Gemcitabine and the first about radiation recall myositis. The key point of this chapter is that clinicians need to know the relevant place of each diagnostic and therapeutic modality and cannot be just an isolated expert in their own.

Chapter five examines quality assurance (QA) issues and guidelines of radiation treatments for skin cancer. Three QA projects are about the QA of treatment process. The first (*5.1*) is an audit of a chart round review which showed that completion rate of items that were regarded as necessary for effective treatment increased from 80 to 99% with the institution of the chart round. The second project (*5.2*) details a similar audit of a chart round review in a skin radiotherapy unit. The third project (*5.3*) is an invited review of the importance of peer review in QA in the first edition of an international textbook; the candidate was the only Australian contributor. Two projects were presented under guidelines. Guidelines are produced by recognized experts. They are a summary of experience from providers of new advances to new providers of those advances. In project *5.4* the candidate assisted with the updating of the National Guidelines as the evidence-based consensus for skin cancer radiation practice in Australia. Project *5.5* clarified to referrers when referral of a skin cancer patient to a skin multidisciplinary clinic which included radiotherapists was appropriate. Studying how advances are applied through QA completes the journey from idea to safe routine clinical practice. The development of guidelines then makes these advances available

for new practitioners in other departments to apply them safely and in a standard and comparable fashion, an important consideration for dissemination of new advances throughout the industry and for standardization in collaborative ongoing multicenter research.

Chapter six outlines projects that occurred during the candidate's doctoral candidature and are ongoing. Project *6.1* will provide evidence for WBRT in melanoma. At this stage WBRT is given or withheld in melanoma on the basis of no specific randomized evidence. Project *6.2* will strengthen the case to provide cutting edge modern technology to the radiotherapy care of skin patients.

Chapter seven summarises and concludes the thesis, and gives direction for further research.

Recurring themes throughout of the thesis have been:

1. The need for communication within and without the multidisciplinary team.
2. The need for personalized treatment of skin cancer with radiotherapy, given the great variety of patient, tumour and treatment factors.
3. The importance of clinical vigilance.

The contributions of the projects to these themes have been commented on in each chapter. There has been a growing momentum of the underlying importance of these themes in the radiotherapy care of patients with skin cancer as the thesis develops.

This thesis provides a significant resource to health workers involved in the radiation treatment of patients with skin cancer. It also provides a platform for further research into improving skin cancer patient outcomes. It shows that radiotherapy in skin cancer has a real place and this thesis will be a stimulus to other Australian radiation oncologists to engage in this important subspecialty. As Australia has the highest incidence of skin cancer in the world, spends the majority of its cancer budget on skin cancer and has rising incidence and mortality from this group of diseases, it is only fitting that Australia plays a leading role in advancing the radiation treatments available for skin cancer.

CHAPTER 1 Introduction

Part 1.1 About This Thesis

1.1.1 Purpose of this thesis

The main purpose of the thesis is to highlight the important and growing role that radiotherapy has in the treatment of skin cancer, particularly by means of the novel advances described in this thesis. These advances represent the creation of new knowledge in this area. Their publication in peer reviewed journals shows that the skin cancer community deems this knowledge worthy of dissemination for the benefit of skin cancer suffers.

Radiation will continue to have an important role as long as advances in skin radiotherapy are made. Advances will only be made if interested radiation oncologists, trained in the ever increasing advances in general radiotherapy, employ these advances in the care of patients with skin cancer. This is critically important in Australia which has the highest burden of skin cancer in the world.

Other multidisciplinary specialties in Australia, such as dermatologists, plastic surgeons and primary care physicians are open to radiation oncology input. This thesis will hopefully serve as an invitation and challenge to young Australian Radiation Oncologists to take their rightful place alongside their multidisciplinary colleagues in the care of skin cancer patients.

1.1.2 Assessable components of the thesis

There are two main components for assessment in this thesis. The first and major component is made up of projects that have led to peer-reviewed publications undertaken by the candidate in the last ten years. Table 1 lists these projects. This table also breaks down the projects by chapters and identifies each project by a number and short heading for easy reference throughout the thesis. Twenty two publications are in Appendix A at the end of the thesis. Two significant projects done during the candidature comprise chapter six. This component is the prime matter for assessment in the thesis. These projects have never been assessed as part of a higher degree before.

The second component is a reflection on these advances. The reflection is in the form of a linking essay. The purpose of the reflection is to highlight how each of the projects is a unique and important contribution to the role of radiotherapy in skin cancer. The reflection will progressively describe how the projects combine together to contribute to a growing conviction in the mind of the reader that radiotherapy does have a significant role in the treatment of skin cancer, now and into the future. The reflection will show how each project fits into that narrative just as a close examination of a wall shows that each brick is essential for its strength.

This reflection is in the form of a linking document or essay that introduces and integrates the projects under various relevant headings.
This component has three parts:

1. The first part is found in the first chapter and is a general overview complete with literature review.
2. The second part is a commentary on how each of the projects achieves an advance in the radiation treatment of skin cancer. These commentaries form the basis of chapters two to five of the thesis.
3. The third part is chapter six and seven. This part is a conclusion to the whole thesis with a vision of where future research could go based on more projects that the candidate is currently involved in.

A Doctor of Philosophy degree should present new research into a given field. Besides selection and inclusion of these projects into one work, it could be asked what does this collection of already published projects actually add anything to the current state of knowledge of this field? What therefore is new about this thesis is the second component, the linking essay, which defines and characterises the advances made and places them in the context of an evolving therapeutic modality in skin cancer, that is, radiotherapy. The comprehensive comparison of the clinical research and reflection on the associated science is new. Therefore the whole of the thesis does add to the field and is more than just a collection of previously published projects. The critical evaluation of the methodologies and results is considerably more than the sum of the parts. It is said that a doctoral thesis, as assessed by most academics, is of excellent quality if it

generates six publications. This thesis includes twenty four publicationswhich have generated the linking essay.

Table 1: List of projects by short and long titles utilised in thesis

Code	Short title	Long title	Code	Short title	Long title
2.1	EGFR	EGFR in Skin SCC	*4.2.1*	MelBrain	Melanoma in Brain
2.2	MC1R	MC1R Skin Effects	*4.2.2*	Delay	RT Delay in Skin Cancer
2.3	Skin Gene	Skin Tumour Gene	*4.2.3*	RT BCC	RT in Recurrent BCC
3.1	Axilla	Skin Cancer and Axilla	*4.2.4*	Ritux	Rituximab and Skin SCC
3.2	Supra	RT of Supraorbital Nerve	*4.2.5*	Recall	Radiation Recall
3.3	Eye Tox	Eye Toxicity	*5.1*	Chart Round	QA Chart Round
3.4	Tech S	Skin RT Techniques Spring	*5.2*	Skin Chart	Skin Chart Round
3.5	Tech F	Skin RT Techinques Fall	*5.3*	Peer	Peer Review
3.6	Electrons	Skin Electrons	*5.4*	National	National Skin Guidelines
4.1.1	MRI	MRI Brain in Melanoma	*5.5*	Skin Guidelines	Skin Cancer Guidelines
4.1.2	PET	PET in Melanoma	*6.1*	WBRT Mel	WBRT Melanoma
4.1.3	PET Occult	PET Occult Primary	*6.2*	VMAT	VMAT

1.1.3 What does this thesis add to the field?

This thesis adds a reflection on projects already published by the candidate that are relevant to the radiation treatment of skin cancer. This reflection provides a critical description of the impact on practice of these advances and provides a basis for further research. The purpose of the reflection is to show that advances are only truly appreciated when put into the context of the overall field.

The thesis shows in particular that radiation treatment in skin cancer has a real place. The thesis highlights the need for Australian radiation oncologists to engage in this

important field. This is because the role of radiotherapy in skin cancer is undervalued in a global sense(Culleton et al., 2011). Also the Australian radiation oncology community is well regarded by other physicians involved in skin cancer care in this country, which is not the same in every country. The great amount of pathology available for research in this country means that Australian radiation oncologists can make a real difference in terms of world practice in this disease, as has already happened (Burmeister et al., 2006). However Australia could do more. The thesis will also encourage clinicians to have an eye for possible projects to report that come through the clinic. These may otherwise be missed if the clinician does not keep their intellectual curiosity engaged.

1.1.4 Selection of the projects in this thesis

The projects were new additions to the literature in their time. They are based on previously unreported series and cases identified, analysed and treated by the candidate, and also new techniques developed by the candidate. Many were done in conjunction with others of greater skill and experience, fittingly acknowledged as co-authors, to whom the candidate is indebted for their guidance and patience. The main co-authors have written letters of support which can be found in Appendix B.

These projects have been selected according to the following criteria:

a. They are relevant to the radiation treatment of patients with skin cancer.
b. They represent an advance in skin cancer treatment – they are either a new discovery or new way of integrating current technology in the skin cancer setting.
c. They have been deemed worthy of publication by peers so that this information may be made available to other physicians involved in the care of skin cancer patients

These projects are only a selection of those published to date by the candidate. See Appendix C for a complete list of publications. Important publications have also been completed during the candidate's doctoral candidature.

The time during which these projects were generated was when the candidate was a registrar or advanced trainee in radiation oncology, then a radiation oncology fellow,

then a junior consultant in this field, then a senior consultant, and now a Director of a radiation oncology department in metropolitan Sydney, with a known subspecialty interest in the radiation treatment of skin cancer within the skin cancer therapy community of Australia. Table 2 describes the type of study methodology in each, e.g. randomized trial, laboratory study, retrospective series, audit, case study and when they were completed in the candidate's career.

Table 2: Types of study and when study was completed

	Types of Study							**Stage of completion**			
Project code	*Audit*	*Case study*	*Laboratory study*	*Literature review*	*Planning study*	*Retrospective series*	*International multicentre randomised trial*	*Registrar*	*Fellow*	*Junior consultant*	*Senior consultant*
2.1			×						×		
2.2			×						×		
2.3			×					×			
3.1					×	×				×	
3.2		×			×				×		
3.3					×	×					×
3.4					×					×	
3.5					×					×	
3.6					×					×	
4.1.1						×			×		
4.1.2						×		×			
4.1.3	×							×			
4.2.1		×								×	
4.2.2						×			×		
4.2.4						×				×	
4.2.3		×						×			
4.2.5		×						×			
5.1	×							×			
5.2	×								×		
5.3				×							×
5.4				×							×
5.5				×					×		
6.1							×				×
6.2					×						×

1.1.5 Origin of the projects in this thesis

Most projects owe their origin to unexpected findings in the clinic, especially those that the candidate thought may have an important message for clinicians. Some of these have led to truly translational projects that investigated these clinical problems in the laboratory, e.g. *2.1 MC1R*, *2.2 EGFR* and *2.3 Skin Gene*.

The types of study employed in these projects are established and accepted epidemiological techniques in biomedical research. To describe these findings as merely retrospective studies and, therefore, of a low level of evidence and so not greatly important for clinical practice is to underestimate their importance. Unusual events, of course, can only be reported after the event. For example, this is the case in our self audit projects. Our self audit of *3.1 Axilla* showed unexpectedly that our technique was excellent and so reported after the fact. *4.1.3 PET* showed unexpectedly that PET was not indicated in all new head and neck cases. These results could only have been reported after the fact. The case studies are similar. *4.2.5 Recall* describes gemcitabine muscle toxicity and could only have been reported after the event.

Most cases owe their origin to astute observation in the clinic, e.g. *2.1 MC1R* and *4.2.5 Recall*. It is imperative for radiation oncologists to keep their intellect and knowledge, especially of radiobiology, on alert in the clinic. A close eye on the developing literature also ensures publication impact (Thompson, Hong, & Fogarty, 2012).Hopefully this thesis will encourage clinicians to investigate what seems odd in their practice and follow up with a report for the good of other patients.

1.1.6 Initiation of the projects in this thesis

These projects were usually initiated by the candidate and so the candidate is the first author in many of the projects. The only projects not initiated by the candidate are:

- *2.1 MC1R Skin Effects* – the candidate brought to analysis and publication the laboratory work of someone else that otherwise would have remained unanalysed and unpublished;
- *4.2.5 Radiation Recall* and *5.2 Chart Round* – the candidate brought to publication these projects on the suggestions of more senior clinicians;

- *5.3 Peer Review* and *5.4 National Skin Cancer Guidelines* – the candidate responded to an invitation to contribute from a national expert who convened the expert panel.

1.1.7 Motivation for the projects in this thesis

It must be asked "What motivates a clinician to investigate and then publish the finding of that investigation?" In general these reasons could be :

1. Pure scientific enquiry
2. The desire to help the patient(s) in question and future patients.
3. The need to educate the whole skin cancer community.
4. The importance of establishing the proper role of radiotherapy in the skin cancer armamentarium.

These are all worthwhile motivators for a radiation oncologist to investigate and publish.

Specific reasons why each project was investigated and then published is to be found in Table 3. These reasons for investigation include the desire for self audit in six projects, to find an association in four, there are five case studies, four case series, three projects done to create much needed guidelines, one randomised trial, and one comparison trial.

The specific reasons for investigation are differentiated at the project level. Among the self audit projects, *3.1 Axilla* was done as we were concerned that our technique was inferior, but the audit vindicated our practice. The same applied to *3.2 Supraorbital*. *4.1.1 MRI* confirmed with hard data our suspicion that MRI brain was not mandatory for staging every melanoma patient. *4.1.3 PET* showed the same result for unknown primary of head and neck. The self audit done in *5.1 Chart Round* and *5.2 Skin Chart* confirmed the increase in clinical outcomes with the addition of quality assurance exercises as expected.

Among the projects done to find an association *2.1 EGFR, 2.2 MC1R* and *2.3 Skin Gene* all were of interest as they showed unexpected results. *4.2.2 Delay* found an association that until then had been clinical suspicion only. Of the five case studies, three case studies reported unique cases for the first time (*4.2.1 MelBrain, 4.2.3 RT BCC* and *4.2.5*

Recall).*4.1.2PET* was the second world report. The case study *3.6 Electrons* reported for the first time a new technique. Of the four case series, three reported new techniques for the first time (*3.3 Eye Tox, 3.4 Techs S, 3.5 Techs F*) and the last, *4.2.4 Ritux*, reported an unexpected finding. The reason to investigate *5.3 Peer*, *5.4 National* and *5.5 Skin Guidelines* was to create much needed new guidelines. The reason for the randomized trial (*6.1 WBRT*) is to answer a controversial question on radiotherapy of melanoma, the reason to investigate the comparison trial (*6.2 VMAT*) was to analyse the efficacy of one radiation modality above another.

The specific reasons for publishing are also differentiated at the project level. The majority are first in world literature reports or a publication of an unexpected result, hence their successful passage through peer review.

Other specific reasons include:

- Eight projects were published to inform on unexpected results (*2.1 EGFR*, *2.2 MC1R*, *2.3 Skin Gene*, *4.1.2 PET*, *4.2.1 Mel Brain*, *4.2.3 RT BCC*, *4.2.4 Ritux* and*4.2.5 Recall*);
- Five projects were published to inform on an expected but never before published result (*4.1.1 MRI*, *4.2.2 Delay*, *5.1 Chart*, *5.2 Skin Chart*, *6.2 VMAT*).
- Four projects were published to suggest as new guidelines (*3.1 Axilla*, *5.3 Peer*, *5.4 National*, *5.5 Skin Guidelines*);
- Four projects were published to disseminate knowledge on new techniques (*3.3 Eye Tox*, *3.4 Skin Tech Spring*, *3.5 Skin Tech Fall*, *3.6 Electrons*);
- One project was published to invite collaboration in an important area (*6.1 WBRT Mel*);
- One project was published as part of a controversy started by the publishing of what we thought was an improper technique (*3.2 Supraorbital*);
- One project was published was published as a confirmatory study(*4.1.3 PET Occult*).

Table 3: Reasons for project investigation and publication – place in world literature

Project code and short title	Why investigate?	Why publish?	Report Novelty
2.1.EGFR	Find association	Unexpected new result	1st in world

2.2 MC1R	Find association	Unexpected new result	1st in world
2.3 Skin Gene	Find association	Unexpected new result	1st in world
3.1 Axilla	Self audit	Suggest as new guidelines	1st in world
3.2 Supra	Self audit	Correct other technique	2nd in world
3.3 Eye Tox	Case series	Show new technique	1st in world
3.4 Tech S	Case series	Show new technique	1st in world
3.5 Tech F	Case series	Show new technique	1st in world
3.6 Electrons	Case study	Show new technique	1st in world
4.1.1 MRI	Self audit	Expected new result	1st in world
4.1.2 PET	Case study	Unexpected result	2nd in world
4.1.3 PET Occult	Self audit	Expected new result	Confirmatory
4.2.1 MelBrain	Case study	Unexpected result	1st in world
4.2.2 Delay	Find association	Expected new result	1st in world
4.2.3 RT BCC	Case study	Unexpected new result	2nd in world
4.2.4 Ritux	Case series	Unexpected new result	1st in world
4.2.5 Recall	Case study	Unexpected new result	1st in world
5.1 Chart Round	Self audit	Expected new result	1st in world
5.2 Skin Chart	Self audit	Expected new result	1st in world
5.3 Peer	Create new guidelines	Suggest as new guidelines	Review
5.4 National	Create new guidelines	Suggest as new guidelines	Review
5.5 Skin Guidelines	Create new guidelines	Suggest as new guidelines	1st in world
6.1 WBRT Mel	Randomised Trial	Invite collaboration	1st in world
6.2 VMAT	Comparison Trial	Expected new result	1st in world

1.1.8 Quality of projects included this thesis

This thesis is based on a total of 24 separate projects which were published. This represents a significant and substantial contribution to this field. A fundamental question to ask is how one is convinced that these projects are of a high quality? Fortunately in medicine there is a long tradition of statistics-based investigation as a way of testing whether advances should become standard treatments. However in certain scenarios this is not possible due to rarity of the clinical situation, lack of resources or inability to do a comparative test. Other levels of published evidence are then used, e.g. the retrospective study, case report, etc. These may be all that exist in the literature to guide clinicians confronting a similar problem. Some of these projects presented here fall into these latter categories. The fact that these projects have been

published in a peer reviewed journal means that at least the profession as represented by the reviewers considers the projects worthy of a public forum.

Systems to measure quality of publications include the number of times the work has been cited in subsequent articles. This is a citation index and the citations so far for each of these projects with citation over three are detailed in Table 4. Citations are time dependent. A more dated article may attract more citations because of lead time bias as compared to a newer article that will eventually have more impact on the field. The year of publication is therefore included in the table to show this effect.

Another way of measuring the impact of a publication is for those published in open access journals is the number of times the article has been accessed. This is available for *6.1 WBRT Melanoma* which was published in open access journals and also detailed in Table 4.

Table 4: Citations of projects with over three citations

Code and long title	Year of publication	No of citations as at January 2012
4.1.3 PET Occult Primary	2003	57
2.1 EGFR in Skin SCC	2007	21
5.1 QA Chart Round	2001	10
4.2.4 Rituximab and Skin SCC	2006	9
4.1.1 MRI Brain in Melanoma	2006	9
3.1 Skin Cancer and Axilla	2007	4
2.2 MC1R Skin effects	2009	4
6.1 WBRT Melanoma (open access)	2011	1433 web hits from 17/04/2011- 01/09/2011

Another way to assess the quality of the articles is to ascertain the quality of the journals in which they have been published. Fortunately there is another way this can be done in the Australian context. Reference is now made to the current gold-standard for research publications in Australia. The Australian Research Council, a federal government sponsored agency administers the Excellence in Research for Australia (ERA) initiative which assesses quality within Australia's higher education institutions using a combination of indicators and expert review. The main indicator is the ERA Journal

List which is updated yearly. The ERA 2012 Journal List defines the journals which are eligible for Australian universities' 2012 submissions for assessing research quality.

To be listed the journals needed to:

- Be active during the ERA 2012 reference period for research outputs (1 January 2005 – 31 December 2010)
- Be scholarly
- Have peer review policies acceptable to the discipline
- Have an ISSN

Table 5 displays the journals in which the different projects have been published. Shown is the name of the journal, the journal ERA Identification Number (ERAID), the ERA fields of research (FoR), the number of projects per journal, and the projects by thesis code number. It is clear from the table that the published research in this thesis is, therefore, of considerable depth.

Table 5: Thesis projects, Impact Factors and the ERA 2012 Journal List

Journal title	Impact factor	ERAID no.	For divisions	No. of projects in the journal	Project code
Acta Oncologica	2.27	15589	Oncology and Carcinogenesis	1	*4.1.2*
ANZ Journal of Surgery	1.34	15704	Clinical Sciences	2	*4.2.1, 4.2.3*
British Journal of Dermatology	4.35	15829	Clinical Sciences	1	*2.1*
Clinical Oncology	2.4	15937	Oncology and Carcinogenesis	3	*2.3, 4.1.1, 4.2.4*
Head and Neck	2.18	42238	Oncology and Carcinogenesis	1	*4.1.3*

International Journal of Radiation: Oncology – Biology – Physics	4.81	16268	Clinical Sciences	1	*2.2*
Lung Cancer	3.26	16576	Clinical Sciences	1	*4.2.5*
Journal of Medical Imaging and Radiation Oncology	0.95	40470	Clinical Sciences	5	*3.1, 3.2, 5.1, 5.2, 5.5*
BMC Cancer	3.15	15804	Oncology And Carcinogenesis	1	*6.1*

(Commonwealth, 2012)

(NB: Not all projects were published in ERA 2012 Journals.ie 3.3-3.6; 4.2; 5.3; 6.2)

Another way of assessing a journals importance is by the Impact Factor. The Impact Factor is a measure reflecting the average number of citations of recent articles published in science and social science journals. It is an indication of the relative importance of a journal within its field. Journals with higher impact factors are deemed to be more important than those with lower ones. The Impact Factor for the journals in which the projects are published are also shown in Table 5. The journals all have respectable Impact Factors. (Garfield, 2006)

For some projects the ERA journal list is not relevant. Projects *5.3* and *5.4* are published as chapters in books. The journal "Radiation Therapist" in which are published projects *3.3*, *3.4*, *3.5* and *3.6*, was specifically targeted as a journal outside Australia that addressed radiation therapists of another country (USA). This journal, even though it satifies the ERA criteria, is not found in the ERA 2012 List.

1.1.9 Detailed structure of the thesis

The thesis is presented in seven chapters. Chapter one is an introduction that sets out the purpose of the thesis and sets the scene by a focussed literature review. The literature review orientates the reader as to the nature of the problem of skin cancer in Australia, and defines the terms of the thesis. These terms include the name of the thesis and the therapeutic ratio. This ratio is that between tumour cure and normal tissue toxicity. The aim of all cancer therapy is to maximize the therapeutic ratio. It acts as a guide to assess the real benefit of any cancer intervention upon the cancer patient.

Chapters two to six describe the contribution to the thesis of projects according to whether their advances are:

- in the molecular area;
- a radiation technique;
- the clinical area; or
- the quality assurance/guidelines area.
- ongoing research that occurred during the candidature

This classification is arbitrary but does reflect where the projects fit in clinical practice. The chapters include an overview of the projects then a detailed synopsis of the contribution and then a conclusion. The actual publications of the projects are in Appendix A.

The projects in the chapters are discussed in a narrative setting. There are common themes in the discussions of the projects. These themes include:

- Background – the specific setting of the study, why it was done etc.
- Study progress – the progress of the study, especially unusual happenings.
- Study findings – a summary of the new advance.
- Impact on practice – how the findings impacted on practice at least in our unit.
- Candidate's contribution– This will describes the contribution of the candidate into this project.
- Notes on the investigating, reporting and publishing of the articles.
- Contribution of the project to the thesis as a whole.

Of most importance is the relevance of the project to the thesis. As discussed previously, all projects are relevant to radiation treatment of skin cancer, all projects are about a specific advance, and all projects have had a positive impact on the therapeutic ratio.

Chapter two details projects that focus on the molecular area. It is fitting that this be the first detailed chapter as what happens at every other level is a reflection of this most fundamental stage. Molecular studies look precisely at sub cellular aspects and can be considered the most important as they eventually explain all that happens at a more

macroscopic level.

Chapter three analyses advances in radiation techniques. These techniques were developed in an era of 3DCRT. There are now more modern techniques available like intensity modulated radiotherapy (IMRT). These techniques all led to greater conformality of the radiation dose cloud to the target, often by use of lateral thinking. They all contributed to the therapeutic ratio as normal tissues were excluded from the field more effectively and therefore not irradiated.

Chapter four focuses on projects that are clinical in their nature. This chapter is further divided:

- 4.1 – Imaging Advances are important as imaging becomes more a part of cancer staging.
- 4.2 – Advances in understanding the impact of other modalities of treatment.

Chapter five examines quality assurance (QA) issues of radiation treatments with a focus on skin. Better treatments are only effective if they can be properly delivered. QA measures how effectively treatments are delivered (L. J. Peters, Browning, D., & Potocsny, A.S., 1991). New advances may be ineffective if delivered incorrectly, and a worse therapeutic ratio may be unfairly inferred(L. J. Peters et al., 2010). QA is, therefore, essential in treatment delivery. QA programs are in themselves a new advance and are growing in number and importance, especially in areas such as medical credentialing, the setting of minimum requirements for licensing, and the refining and generalization to other departments of the treatment process. This chapter examines some examples of effective QA programs developed by the candidate that have helped in the delivery of the advances described in the previous chapters. They form the backbone of some of the guidelines then described.

Chapter five also deals with guidelines. Guidelines are produced by recognized experts in different fields to assist others in prescribing safe and effective treatments. They are essential to the creation of industry standards and benchmarks. They can be seen as a summary of experience from providers of new technologies to new providers of that technology. Guidelines ensure that new treatment techniques are applied with the

concept of maximizing the therapeutic ratio in mind. Chapter five describes guidelines that the candidate has been involved in generating.

Chapter six outlines projects that occurred during the candidates doctoral candidature and are ongoing. Project *6.1* will provide evidence for WBRT in melanoma. At this stage WBRT is given or withheld in melanoma on the basis of no specific randomized evidence. Project *6.2* will strengthen the case to provide cutting edge modern technology to the radiotherapy care of skin patients.

Chapter seven summarises and concludes the thesis, and gives direction for further research.

Part 1.2 Literature Review

1.2.1 Advances

To advance means to improve. As a noun, advance means a forward movement, an improvement. These words adequately describe the contribution of the projects detailed in this thesis to the care of patients with skin cancer. They have been investigated and written up by the candidate, and accepted by the peer review process to be a forward movement in the field. They have been therefore considered worthy of publication so that the whole skin cancer community can have access to specific new ways of doing things.

Advances include new discoveries or new ways of integrating current treatments to reach a better outcome. Both kinds are detailed in the projects presented. Advances in general radiotherapy are happening at an accelerating pace(Fraass & Moran, 2012). It is important that those who care for skin cancer patients bring these advances into the field.

Advances can play a significant role in decreasing skin cancer related mortality, morbidity and cost. They can be considered by whether they involve molecular (Chapter 2), technical (Chapter 3) or clinical (Chapter 4) pathways. Their implementation can be measured by the use of quality assurance programs and guidelines (Chapter 5). These divisions can seem artificial; all worthwhile advances should lead to better patient

outcomes anyway. However, they reflect the different fields of medical specialization. Molecular advances are of interest primarily to the scientist, technical advances to the radiation therapy team, clinical to the clinician. However, the whole team want a better outcome and so any advance in any area is of interest to all. Quality assurance and guidelines are of interest to all embarking on the application of new advances.

1.2.2 Skin cancer in Australia

Cancer is a condition whereby cells divide uncontrollably, forming malignant tumours. These can invade into nearby parts of the body. They can travel to distant sites in the body. Skin cancers have their origin in the epidermis and dermis, the visible covering of the body. It is the most common malignancy in the human person and the incidence is increasing(Rogers et al., 2010). Skin cancer can be considered as melanoma or non melanoma skin cancer (NMSC) the latter being usually basal cell (BCC) or cutaneous squamous cell carcinoma (cSCC). Other more uncommon primary non-melanoma skin cancers are lymphomas and merkel cell carcinoma.

Australia has the highest incidence of skin cancer in the world, at nearly four times the rates in Canada, the United States and the United Kingdom. The incidence of skin cancer is five times that of any other cancer in the country(Staples et al., 2006). On an annual basis, over 10,600 Australians will develop a melanoma(AIHW, 2010).

The incidence of skin cancer in Australia is rising. From 1985 to 2002, age-standardised incidence rates of BCC and SCC had increased by 35% and 133% respectively(Staples et al., 2006). The mortality is also increasing. From 1984 to 2005, the number of deaths in Australia per year increased for melanoma from 640 to 1,273; and for NMSC from 228 to 405 (AIHW, 2008).As the number of patients who are immune suppressed rises, so do the number of skin cancers, causing morbidity and mortality(Ong, Keogh, Kossard, Macdonald, & Spratt, 1999).

Skin cancer is the most expensive Australian cancer. Most Australian Government funding allocated to cancer care is spent on skin cancer. In 2001, it was estimated the

treatment of non-melanoma skin cancer cost $264 million and melanoma $30 million("Cancer Council Australia - Skin Cancer Facts and Figures," 2011).

Treatment of skin cancer is usually at an early stage as it the most visible cancer. Therapies include local ablative therapies such as surgery, freezing, diathermy, and cytotoxic or immunogenic skin lotions. Later stage skin cancer may require more significant treatment such as significant surgery, chemotherapy and megavoltage radiotherapy(G. Fogarty, 2012).

1.2.3 Therapeutic ratio

A fundamental concept in cancer management is the therapeutic ratio(Marcu & Bezak, 2011). This concept will be used extensively in this thesis. The therapeutic ratio is that ratio between tumour cure and normal tissue toxicity. The aim of all cancer therapy is to maximise the therapeutic ratio, that is, to achieve maximal tumour cell kill for the minimum of normal tissue toxicity. It guides all cancer disciplines. The therapeutic ratio offers a way of assessing the relative merits of advances particularly in terms of a holistic approach to patient management.

The ideal therapeutic ratio ensures durable tumour control and a high quality of life post treatment. A technique that develops a better cure rate may not be embraced because it delivers significant normal tissue toxicity. Another that produces equivalent cure rates may become standard treatment because of its better normal tissue side effect profile. Often the concept of maximising the therapeutic ratio is expressed more simply as improving patient outcomes; hence the statement that an advance has been made because it delivers a better outcome. It is a measure of the usefulness of the advance.

1.2.4 Radiation treatment

Radiation is also an effective treatment modality in many scenarios of the treatment of skin cancer (Matthiesen et al., 2011). Radiation works by denaturing the Deoxyribose Nucleic Acid (DNA) by a process of ionization. DNA makes up the genetic material of the cell. The cell is then unable to divide and so dies. Death can occur immediately or at cell division. Normal cells are able to repair the small amount of DNA damage

following a small dose of radiation. Tumour cells cannot. Therefore, when radiation is given as a fractionated treatment the normal cells within the field can repair the damage done between the fractions and can survive; the tumour cells die. Therefore radiotherapy is excellent for normal tissue preservation within the radiation field. This is demonstrated in Figure 1 below a case treated by the candidate and detailed in the publication *3.4 Skin Techniques Spring*.

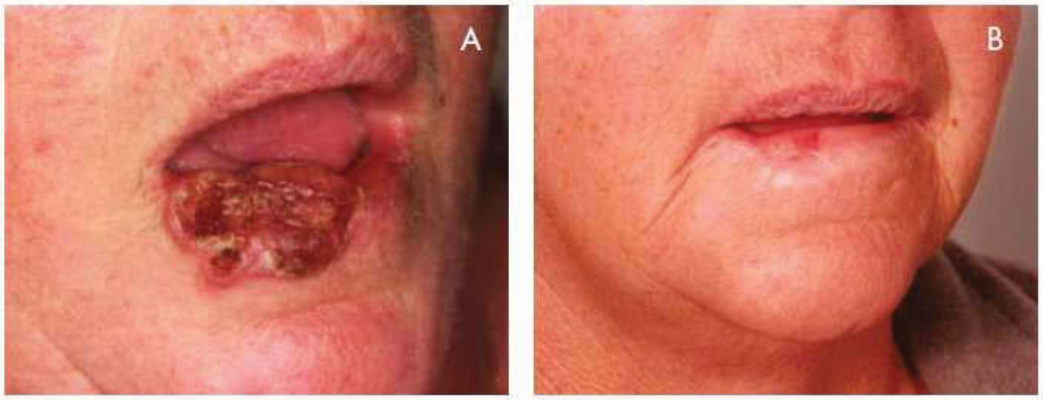

Fig. 8. This 50-year-old patient with a large squamous cell carcinoma of the lip was treated with a combination of external beam and brachytherapy. Treament consisted of 6 MV parallel-opposed lateral fields and a boost to the gross tumor using an iridium-192 implant. A. Original lesion. B. Outcome at 6 months.

Figure 1. A case treated by the candidate in the publication *3.4Skin Techniques Spring*

The alternative treatment for this lady would have been excision with a graft or flap repair, and she would then have had to have post operative radiotherapy anyway as this was a tumour invading muscle. Radiotherapy has cured her cancer but with preservation of the normal tissue within the field. This has maximized her quality of life post treatment. She not only has a competent and continent mouth, but also she has preserved her own mouth.

There are particular ways in which radiation techniques can lead to a better therapeutic ratio. One is by the ability radiation has to selectively kill tumour cells and preserve normal cells within an irradiated volume when appropriately delivered. This causes tissue conservation within the field as detailed above. The paradigm situation is breast conservation, now the most common reason for prescribing radiation on a world

scale(Haberer et al., 2011). Tissue conservation plays a role in other tumour types such as head and neck (larynx preservation) (Foote et al., 2006), SCC anus (sphincter preservation) (Northover et al., 2010),and also skin cancer, with preservation of normal skin within the treatment volume(G. B. Fogarty, & Porter, B., 2006). Oftentimes this is why radiation is selected instead of surgery for definitive treatment or is used as adjuvant to more limited surgery with less tissue being sacrificed.

The second way in which radiation can augment the therapeutic ratio has been the increasing conformality of radiation dose to the volume requiring treatment. Radiotherapy treatment modalities are becoming more and more conformal as better technologies evolve. This allows for improved conformality of radiation dose to the volume at risk of disease yet sparing the unnecessary irradiation of surrounding normal tissue in the entrance and exit beams, so reducing toxicity(Du et al., 2011). This is not always easy as external beam radiotherapy often needs to enter and exit the body through normal tissues in order to cover internal tissue at risk of tumour. Increased evolution of hardware such as multileaf collimators (MLCs) and electronic portal imaging (EPI) to allow image guided radiotherapy (IGRT) and software to enable delivery of IMRT and volumetric modulated arc therapy (VMAT) has accelerated the adoption of increased conformality of dose in the clinic.

Part 1.3 Conclusions of Introduction

This introduction outlines the purpose of this thesis which is to highlight the important role that radiotherapy has in the treatment of skin cancer, particularly by means of the novel advances described in this work. It outlines what is put up for assessment – the content of published projects and the integrating essay that unites them in fulfilling the purpose of the thesis. It describes in general the projects – how they were selected for inclusion, how initiated, why they were published, the quality of the projects, the presentation, the criteria for grouping them into chapters. It describes the thesis structure in detail.

The introduction also contains a literature review that defines and describes the terms of the thesis including the nature of advances, skin cancer in Australia, and radiation

treatment. It also describes the therapeutic ratio, an important concept in cancer therapy. The introduction sets the scene and begins the narrative that will outline how these projects have contributed and will continue to contribute to the radiation treatment of skin cancer.

Recurring themes throughout the thesis will be:

1. The need for communication within and without the multidisciplinary team delivering care for skin cancer patients.
2. Another theme will be the need for personalized treatment of skin cancer with radiotherapy, given the great heterogeneity in molecular make up of tumour and host, histological type of tumour, site in skin, patient characteristics and radiotherapy techniques available.
3. A further theme is the importance of clinical vigilance. Many of the projects owe their origin to astute observation and reliance on the foundational medical skills of history taking and examination rather than relying on investigations alone.

All of the projects address something unique within these themes, hence their acceptance by peer reviewed publications.

CHAPTER 2 Molecular Advances in the Radiation Treatment of Skin Cancer

Projects discussed in this section are:

- *2.1 EGFR in Skin SCC* Fogarty, G. B., Conus, N. M., Chu, J., & McArthur, G. (2007). Characterization of the expression and activation of the epidermal growth factor receptor in squamous cell carcinoma of the skin. *Br J Dermatol, 156*(1), 92-98. doi: 10.1111/j.1365-2133.2006.07603.x
- *2.2 MC1R Skin Effects* Fogarty, G. B., Muddle, R., Sprung, C. N., Chen, W., Duffy, D., Sturm, R. A., & McKay, M. J. (2010). Unexpectedly severe acute radiotherapy side effects are associated with single nucleotide polymorphisms of the melanocortin-1 receptor. *Int J Radiat Oncol Biol Phys, 77*(5), 1486-1492. doi: 10.1016/j.ijrobp.2009.07.1690
- *2.3 Skin Tumour Gene* Fogarty, G. B., & McKay, M. J. (2005). Multiple malignancies and immunological diseases after radiotherapy: a new tumour suppressor gene disorder? [Case Reports Letter]. *Clin Oncol (R Coll Radiol)*, 17(8), 668.

Part 2.1 Introduction to Chapter 2

Molecular changes are the basis for all other changes in biological systems. Molecular advances are examined in a laboratory setting and include technologies that bring new understanding to how things work at a fundamental biochemical level. Changes at the molecular level underlie different technical and clinical advances. When these technologies have an impact on clinical management they can be considered as translational. A translational project is one where there is a laboratory and clinical interaction that leads to better patient outcomes (Cao et al., 2011). It is, therefore, appropriate to reflect on projects that investigate molecular advances in this first core chapter.

These three projects were all truly translational studies. They were done to find an association between clinical and laboratory findings. All led to unexpected answers.

2.1 EGFR in Skin SCC

The first project had its origins in wanting to find a better way of treating those with widespread cutaneous squamous cell carcinoma. This scenario is becoming more common with the increase in successful transplants(Ong et al., 1999). The Peter MacCallum Cancer Centre (PMCC) in Melbourne, Victoria, Australia, is a tertiary referral centre for locally advanced cSCC from that state. This paper was the result of the candidate's laboratory fellowship at PMCC.

This study is the characterization of the epidermal growth factor receptor (EGFR) in cSCC. EGFR is up regulated in many cancers. Epidermal growth factor receptor inhibitor drugs (EGFRI) were being trialed at that time in mucosal, that is, non-cutaneous squamous cell carcinoma (SCC) of head and neck in combination with radiotherapy. The candidate thought that EGFRI may also play a role in the radiation treatment of cSCC. For example the addition of concurrent EGFRI may allow radiation dose reduction. The candidate applied for and received a grant from a drug company for $50,000 Australian dollars to do a Phase one clinical study of radiation plus EGFRI in patients with this problem.

The supervisor (Professor Grant MacArthur) and the candidate thought we should first of all characterize the expression and activation of EGFR in tissue-banked cutaneous SCC to ensure that the target was present in the tumours before committing patients to a trial. For the study we used a quantitative western block technique called the LiCor system that was new to our laboratory. The candidate compared these results to immunohistochemical and clinical outcomes. This study found, counter to intuition, that EGFR was present and activated only in a minority of cSCC evaluated. EGFR was not related to activation of downstream events or clinical outcomes. This result was not expected. The planned clinical study did not go ahead.

This paper lead to recognition in PMCC that it is necessary to confirm the existence of the target in the cells requiring treatment before embarking on a full study of a targeted cancer agent. Based on this result future EGFR targeted therapy trials in skin will need to do a confirmatory test for target presence as an inclusion criterion. The negative finding of the study ensured that these patients would not be subjected to a trial of a new agent that for the majority would have been useless in terms of disease control. The new drug may perhaps even harm as the patients would have experience the side effects in normal tissues, usually a significant rash. The therapeutic ratio for these patients was therefore improved by not being subject to an unnecessary treatment.

The candidate was responsible for the concepts, design, laboratory experimentation, data collection, analysis and interpretation of data; drafting, revision and submission of the article. The publishing of this article ensured that this result was available to the skin cancer community. The investigation and reporting of this important study confirms the necessity of ensuring the target is present prior to targeted drug administration.

This project contributes significantly to the thesis. We found that EGFR was not up regulated in all cSCC as initially thought. Therefore it is logical to deduce that EGFRI given concurrently with radiotherapy would only benefit a minority of tumours, those that expressed the target. This is actually an advance in the radiotherapy of skin cancer, to realize that proper patient selection, starting at the molecular level, is essential. This

project is about bringing a new paradigm in medicine, personalized medicine, to the radiotherapy of skin (Hirst & Robson, 2010).

2.2 MC1R Skin Effects

The second project was based on anecdotal evidence that fair skinned patients have more severe radiotherapy reactions. Single nucleotide polymorphisms (SNPs) of the melanocortin-1-receptor gene (MC1R) had already been found to be the main driver of skin colour. The group investigated the relationship of SNPs of MC1R and their relationship with unexpectedly severe radiation reactions. The candidate discoveredthis project while doing a skin radiotherapy fellowship at PMCC. It had lapsed due to a change of personnel. The candidate organized a re-analysis of the date. It involved several collaborations across the country of scientists and statisticians. We did not think it would show a positive result but surprisingly it did.

The project was the following. The MC1R genotype of a cohort of Australians with unexpectedly severe acute and/or late skin reactions from radiotherapy for cancer (n=30) was analysed. The findings were compared to control data from a previous study of *MC1R* representative of the general Australian population (n=1787). The difference in frequency of alleles encoding a RHC phenotype in the cohort of patients with unexpectedly severe acute skin radiation reactions (n=12) was significantly increased compared to the control population (p=0.003). Acute radiosensitivity was especially associated with the R160W variant allele [odds ratio = 3.64 (95% CI: 1.3-10.27)]. The corresponding comparison of MC1R controls with unexpectedly severe late skin radiation reactions (n=18) was not significant. R160W as a part of the genotype in the patients with unexpectedly severe acute skin radiotherapy side effects as compared to the control group was also significant (p=0.043). This significant result was reported in the leading world journal in radiation oncology.

The impact of this project on future practice is important. The discovery that SNPs of MC1R are associated with worse acute skin reactions could potentially contribute to a predictive assay for normal tissue damage from RT. This has long been sought in RT. This result was hoped for but not expected. More studies are needed to verify this

finding. If verified, this study may enhance the therapeutic ratio by allowing patients with a certain skin type, who test positive for the R160W MC1R allele could be offered treatment other than radiotherapy, thereby decreasing normal tissue toxicity from radiotherapy. The candidate's contribution was responsibility for the analysis, interpretation of data, drafting, submission and revision of the manuscript. The publishing of this article ensured that this result was available to the skin cancer community so that a verification study could be started.

This project contributes significantly to the thesis. Understanding at a molecular level the causation of radiotherapy side effects leads to proper treatment selection. This project is another example of how to bring personalized medicine to the radiotherapy of skin.

2.3 Skin Tumour Gene

The third study reports the molecular analysis of a patient we suspected of having a relatively rare but well described genetic syndrome. This is known as the nevoid basal cell carcinoma syndrome (NBCCS). Individuals with this syndrome have a tendency to multiple BCCs in skin that had previously been exposed to radiation. This syndrome is based on a dysfunction in a tumour suppressor gene. It is important to know if this syndrome is present as radiation should not be given to these people for fear of inducing further cancer.

The candidate identified this patient through his regular attendances at clinic for treatment of basal cell carcinoma (BCC). He was treated previously with surgery but this was the first time he had been referred for consideration of radiation treatment of his multiple BCCs. The candidate noted that he was a young man with recurrent BCC, mainly within previous radiation fields. He had been treated as a younger person with radiation alone for Hodgkin's Disease. This alerted to the possibility that his previous radiation may have been a cause of his BCCs. The initial impression was that this could have been a new case of NBCCS as he had several morphological features that suggested this syndrome. However, the history was not entirely typical of NBCCS, given the incidence of significant immunological phenomena as well.

Our molecular analysis found that this patient was not positive for the NBCCS genetic test. This was an unexpected result. We postulated that he may represent a new tumour suppressor gene mutation that impacts on immunity as well as malignancy and development. This patient continues to be closely watched in our unit and is treated with surgery, not radiotherapy, when new BCCs develop.

The project helped maximize the therapeutic ratio as this patient was spared further possible cancer inducing radiation. The project also encourages physicians to have a high index of suspicion for possible genetic problems when young patients with several cancer presentations are discovered in the routine clinic situation.

The candidate was responsible for discovering the patient, the project concept, data collection, interpretation of data; drafting, revision and submission of the article. The publishing of this article ensured that this result was available to the skin cancer community so that a similar individual may be identified. The next laboratory step of trying to find out the causative gene has not been done yet for resource reasons.

This project contributes significantly to the thesis. The advance is that of the possible detection of a new genetic problem that predisposes patients with the gene to radiation induced cancer and, in this case, with an association with immunity problems. This can alert other clinicians to the confirmation of a new syndrome. It has led to better triaging of treatment options for our affected patient. This project is yet another example of how to bring personalized medicine to the radiotherapy of skin.

Part 2.2 Conclusions of Chapter 2

These projects demonstrate that understanding molecular changes are important to ensuring best care in the radiation treatment of patients with skin cancer. The successful conclusion of the first project (*2.1*) demonstrated an important step in the evolution of targeted therapies. It is necessary to confirm the existence of the target in the cells requiring treatment before embarking on a full study of a targeted cancer agent. Proven presence of the target should be an inclusion criterion in skin EGFRI trials. The second

study (*2.2*) found that the difference in frequency of alleles encoding a RHC phenotype in the cohort of patients with unexpectedly severe acute skin radiation reactions (n=12) was significantly increased compared to the control population (p=0.003). Acute radiosensitivity was especially associated with the R160W variant allele [odds ratio =3.64 (95%CI: 1.3-10.27)]. The discovery could potentially contribute to a predictive assay for normal tissue damage from RT, which has not been found yet. Interestingly, this skin type is also associated with an increase in skin cancer incidence. The third project (*2.3*) may have been the first description of a new tumour suppressor gene syndrome with multiple BCCs in previously irradiated fields, multiple cancers at a young age and with multiple immunological disorders. This case was discovered because of vigilance in the clinic.

These projects were all world first reports. They emphasize the importance of addressing radiation effects at the molecular level to enhance the therapeutic ratio. The projects all contribute significantly to the thesis. They increase understanding at a molecular level of the important of patient and treatment selection in order to avoid radiotherapy side effects including radiation induced skin cancer.

These projects reinforce the recurring themes of the thesis:

1. The need for communication – the first project only came about by communication between radiation and medical oncology leading to an unexpected result.
2. Personalized treatment of skin cancer with radiotherapy– the second project brought anecdotal clinical suspicion of increased radiosensitivity in fair skinned people to the laboratory to find an unexpected significant result based on SNPs of MC1R.
3. Clinical vigilance – the third project was discovered only by this and could be a new tumour suppressor gene.

CHAPTER 3 Advances in Radiation Techniques for Skin Cancer

Part 3.1 Introduction

Advances in radiation techniques are essential to maximizing the therapeutic ratio. These techniques were developed in an era of 3DCRT. 3DCRT was a considerable advance in megavoltage radiotherapy. However, the problem of 3DCRT is that the intensity of the beam cannot be finely conformed to the volume needing treatment.

A conceptual way of thinking of this is that 3DCRT radiotherapy comes in "blocks". Unfortunately tumour volumes, as with most biological structures, come in curves. Planning is then all about trying to fit "the round peg into the square hole". It is difficult to achieve perfect conformality of the radiation dose cloud to the target volume requiring radiation treatment. The projects presented here all represent important advances in the techniques of radiation in skin cancer using 3DCRT, the only modality available at the time. There are now more modern techniques available like IMRT.

One way around this 3DCRT limitation is to try to fit the modalities available to the clinical situation. This includes lateral thinking and also the use of different types of megavoltage radiation. The first type is photons. Megavoltage Photon beams are "skin sparing". The entry dose, the depth of the maximum dose (Dmax) and the attenuation in tissue after the maximum dose point are dependent on the generating energy. This beam gradually attenuates in tissue after the Dmax. Electrons are another megavoltage radiation modality. They have a surface dose and also a depth dose in tissue that both increase as the generating energy is increased. The energy deposition of electrons suddenly decreases at a depth that is usually one third of the generating energy in centimetres. Planning with these beams is usually done with the aid of computed tomography (CT). CT does not image the skin surface well. Special care needs to be taken with respect to beam characteristics when planning radiation skin cancer treatment, especially when matching fields. Wire and other devices are used to capture skin cancer characteristics onto the CT data at planning.

Knowledge of what volume to irradiate is fundamental to successful radiotherapy in skin cancer. Improving the therapeutic ratio in the radiotherapy of skin includes accurate radiation volume delineation. When dealing with increasing tumour control, this requires knowledge of tumour type, patterns of spread, the presence of nearby dose limiting normal tissues, details of interaction with other modalities, e.g. surgery. It also requires knowledge of the possibilities and limitations of different radiation modalities. Experience and communication between oncologists, physicists and radiation therapists, especially at planning, are vital. This collection of techniques is an attempt to pass on the experience gained to others involved in skin cancer radiotherapy through the use of publications. The last three articles are especially aimed at radiation therapists, the staff that actually plan and treat the patients. The therapists are a necessary part of the multidisciplinary team involved in skin cancer treatment with radiation along with the physicists and oncologists. The techniques exemplify the great variety of situations that are found in treating skin cancers. Some are included to give salutary lessons to clinicians in how we need to respect these tumours which can cause morbidity and mortality.

Projects presented in this section:

- *3.1 Skin Cancer and Axilla* — Fogarty, G. B., Cassumbhoy, R., Martin, J. M., Fay, M., & Ainslie, J. (2007). Technique for axillary radiotherapy using computer-assisted planning for high-risk skin cancer. [Evaluation Studies]. *Australas Radiol, 51*(3), 267-275. doi: 10.1111/j.1440-1673.2007.01729.x
- *3.2 RT of Supraorbital Nerve* — Fogarty, G. B., & Cassumbhoy, R. (2005). RE: Another technique for radiation treatment of the supraorbital nerve. [Comment Letter]. *Australas Radiol, 49*(6), 522-525. doi: 10.1111/j.1440-1673.2005.01511.x
- *3.3 Eye Toxicity* — O'Dea, N., & Fogarty, G. (*in press for* 2012). A technique to minimize eye toxicity using megavoltage photon radiotherapy for skin cancers involving the orbit in cooperative

	patients.*Radiation Therapist (in press)*.
• *3.4 Skin Techs Spring*	Fogarty, G. B., & Porter, B. (2006). Techniques for Skin Cancer Treatment in Australia. *Rad Therap, 15*(2), 57-63.
• *3.5 Skin Techs Fall*	Fogarty, G. B. (2006). Techniques for Skin Cancer Treatment in Australia – Letter. *Rad Therap, 15*(2), 1-2.
• *3.6 Skin Electrons*	Fogarty, G. B. (2007). Electron Technique for Treating Skin Cancer *Rad Therap, 16*(1), 1-4.

3.1 Skin Cancer and Axilla

This paper grew out of the need for standardisation of radiotherapy axillary field planning and treatment in an international phase III trial investigating the role of adjuvant radiotherapy following lymphadenectomy for clinically apparent nodal metastasis of melanoma in the axilla. The heterogeneity of how different clinicians outlined the volume requiring treatment became obvious when the QA was being done on the first few trial cases. There could be a wrong conclusion to the trial if there was not uniformity of treatment between the different centres involved in the trial. This trial, ANZMTG 01.02 A randomised clinical trial of surgery versus surgery plus adjuvant radiotherapy for regional control in patients with completely resected macroscopic nodal metastatic melanoma, has been presented at international meetings and the manuscript has been submitted for publication.

We decided to publish our technique of irradiating the axilla to aid with quality assurance in the trial. The candidate thought that doing an institutional audit of historical patients would add to the weight of evidence. These patients were treated before the trial was opened and they were not all melanoma. While searching through the records the candidate did notice that there were some cases treated in our institution with axillary fields not consistent with our skin unit policy. These patients had not done well.

The paper describes the technique used at PMCC skin unit. This group of patients treated with this technique had more than a 90% (10/11) regional control after a follow up of over 2 years. Both of the radical patients who were not treated according to the technique had regional failure by that time.

The impact on practice was that axillary radiation fields in the postoperative setting was standardized in many institutions, adding to the rigor of the trial and to better patient care. The candidate was responsible for the concepts, design, data collection and analysis and interpretation of data; drafting, revision and submission of the article.

This project is relevant to the thesis as it directly relates to the radiation therapy of skin, represents a significant advance and leads to a better therapeutic ratio. This was the first time that radiation planning of the axilla in skin cancer had been described in the literature. This is also first time that computer assisted planning for the axilla had been described in the literature.

3.2 RT of Supraorbital Nerve

This paper arose out of a controversy conducted in the literature about how to effectively treat the supraorbital nerve when involved with cutaneous squamous cell carcinoma. This is not a rare occurrence with locally advanced carcinomas of the upper face and scalp. Another Australian department had described an IMRT technique that aimed to spare the lacrimal gland in an effort to make sure the eye did not become dry post treatment. However, the technique as described in that paper was inappropriate as the dose allowed to the brain could be as high as 60 Gy, a dose associated with a risk of neurotoxicity. IMRT uses more resources than 3DCRT.

The candidate wanted to point out in the literature that the previouslyreported technique was both inappropriate and used unnecessary resources, and he also offered a solution that was better. The candidate was treating a similar patient at the time with less dose to the brain with the technique describedbutalso without needing the use of resource-draining, high-end technology. The technique is described in the paper with a case study to demonstrate its efficacy and low side effect profile. The technique irradiates the

supraorbital nerve, while keeping brain dose to well within tolerance – much less than that with the resource-intensive technique. It helps to have an understanding of how the eye is lubricated so that radiation field placement can effectively treat the tumour but minimize the long-term risk of dry eye.This is an example of how knowledge of disease, normal tissue function and available radiation modalities can target tumour and yet spare normal tissues, maximising the therapeutic ratio. The candidate was responsible for the concept, design; drafting, revision and submission of the article.

This project is relevant to the thesis. It applies to patients with skin cancer involving the supraorbital nerve. The technique comparatively decreases normal tissue toxicity and so is less dangerous, thereby enhancing the therapeutic ratio. It is an advance even though it utilizes older technology. It is alsoless resource intensive than the other published technique.

3.3 Eye Toxicity

Skin cancer involving the orbit requires specialist care when using radiotherapy, as there are several radiation sensitive normal tissue structures in the orbit. This project details how a technique of rotating the iris out of the beam in co-operative patients can be used to decrease morbidity when treating skin cancer involving the orbit. Our technique worked very well to save two eyes. The only surgical option for these two patients was orbital exenteration. Our technique should be considered when treating such patients, especially those for whom surgery is too morbid or who are inoperable or decline operation.

The candidate was the senior author. He was responsible for the concept, the project design and revision of the article

This project is relevant to the thesis. It is specifically for patients with orbitalinvolvement with skin cancer to effect organ conservation. This is an advance, and an increase in the therapeuticratio, as normal tissue, that is, eyes, are conserved.

3.4Skin Techs Spring, 3.5 Skin Techs Fall, and 3.6Skin Electrons

Practical radiation techniques for radiation therapists for skin cancer treatment

This is a collection of three projects of radiation techniques for radiation therapists forskin cancer treatment. These papers arose after a team of radiation therapists visited our unit from another country. They were amazed at how much skin cancer was treated with definitive radiotherapy in Australia. The candidate realized there was a need and a duty to inform other units, especially from overseas, about our home grown techniques. Hence the publications are all in an international journal.

Our techniques were well accepted. Other units did implement some of our techniques. We knew this because of the feedback which led to the second paper in this section. Further enquires after the publication of the first article led to the publication of the third. The last paper describes a particular technique for treating a unilateral neck for skin cancer. This particular technique saves linear accelerator time, which is important in departments where there are waiting lists for treatment. In the papers, clinical considerations were stressed. Also included were ways to get the best out of 3DCRT,and how to be aware of the important of the physical beams and the volume requiring treatment, especially as pertains to cancers involving skin.

The candidate was responsible for the concepts, design, data collection; drafting, revision and submission of the articles.

These projects are relevant to the thesis. These techniques are all designed for patients with skin cancer. The advances include:

- increasing conformality of the radiation dose cloud to volume requiring treatment with particular attention to field junctions.
- use of customized bolus to ensure full dose to skin only where needed
- different beam arrangements.

These techniques ensure an increase in the therapeutic ratio as patients suffer less with less normal tissue irradiated. There is better workflow in the department with technique *3.6*.

Part 3.2 Conclusions of Chapter 3

These techniques were developed in an era of 3DCRT. They all lead to greater conformality of the radiation dose cloud to the target, often by use of lateral thinking. They all contributed to the favourable therapeutic ratio as normal tissues were excluded from the field more effectively and therefore not irradiated. Improving the therapeutic ratio in the radiotherapy of skin includes accurate radiation volume delineation. It is paramount to know what volume to irradiate based on tumour characteristics.

The axilla project(*3.1*) shows that fields applied with no knowledge of where the tumour is, and what dose to use, leads to poor outcomes with two patients having local failure due to inadequate cover. The second project(*3.2*) shows that new technology is not always necessary for better conformality. What is needed is to know the volume requiring radiation and the limits of the current tools. The third project(*3.3*) details how two eyes were saved by thinking laterally about eye position during radiotherapy in cooperative patients. The last three projects (*3.4-3.6*) detail techniques written with radiation therapists from other countries in mind, hence the international journal used. In these techniques experience and communication within the multidisciplinary craft groups (radiation therapists, physicists and oncologists) is essential to good outcomes.

One characteristic of all of these techniques is that they represent a personalized approach to skin cancer. No two skin cancers are the same. Even if the lesions were the same histology, size and shape, there is great heterogeneity also in patient factors, and site of disease. Treatments need to be tailored to each case. Hence there are no class solutions to skin cancer, unlike other cancers where radiotherapy indices can be defined by consensus and applied effectively across the board [e.g. volume definitions in prostate cancer; (Michalski et al., 2010)].

These projects were all world first reports except the second, which was a reply to a previous publication that the candidate thought was misleading in treating supraorbital disease. The first is the only one to have been extensively cited. It was also written offering guidelines for treatment. The others have still been influential judging from the feedback from other institutions.

Radiation oncologists need to be up to date with new advances in radiation delivery so they can bring new techniques to the care of skin cancer patients. These techniques are expanding (Fogarty et al, 2011). These techniques will only be effective if all the multidisciplinary team is well trained, interested and communicating well with each other and other departments. These projects were a result of this dialogue.

These projects reinforce the recurring themes of the thesis:

1. The need for communication – publication of the first project ensured some standardization of radiation volumes in our trail.
2. Personalized treatment of skin cancer with radiotherapy– the second to sixth projects outline just how varied the presentation of skin cancer can be, requiring a personalized approach.
3. Clinical vigilance –the second to sixth projects are about using lateral thinking to conform radiotherapy fields to tumour volumes with the best outcomes in terms of disease control yet acceptable normal tissue toxicity in the 3DCRT era when radiotherapy dose conformality was more problematic.

CHAPTER 4 Clinical Advances in the Radiation Treatment of Skin Cancer

Part 4.1 Introduction

Clinical advances refer to advances that are implemented in the clinic. The clinic is thatincredibly human and practical place where the patients' symptoms and signs lead health professionals to make the diagnosis, give treatment and conduct follow up. Many lessons can be learnt by careful observation and examination in the clinic.

Clinical implementation usually refer to drugs that have already gone through the rigorous pre clinic testing that is required to ensure safety, tolerability and efficacy. However, the clinical advances in this section refer more to different clinical factors that shed light on the biology and radiobiology of skin cancer, often described in the literature for the first time. These arise often by serendipity and are noticed by clinicians with an interest.

This section is divided into two parts. The first part (*4.1*) comprises three projects that have to do with the advent of new imaging modalities in the radiation treatment of skin cancer. Imaging is important in radiotherapy. The main uses for imaging in radiation oncology are for staging, delineation of tumour volumes and measuring response to treatment. These three projects all have to do with staging. Staging means looking for metastatic disease. Staging ensures that treatment is given with the correct intent. Giving radical treatment to a patient with undiagnosed metastatic disease means that the patient will suffer treatment side effects for no increase in quantity of life. Staging prior to treatment ensures the appropriate treatment is delivered.

The second part (*4.2*) is comprised of projects that examine the interaction of other anti-cancer treatments like chemotherapy and surgery with radiotherapy. These interactions are important to know about in these days of multidisciplinary care when one treatment may have an effect on another. For radiotherapy this may require a reduction in radiation dose or of volume treated. The interaction may be synergistic so that a reduction in RT dose or volume may be possible to avoid the side effects of over treatment. These projects reveal a lot about effective communication, or lack of

it,between radiation oncologists and other oncologists. Communication can affect the logistics of treatment, in this case their timing. The danger of multimodality specialization is that patients can fall “between the stools” if effective mechanisms are not in place to ensure timely treatment.

Section 4.1 Imaging

Projects presented in this section:

- *4.1.1 MRI Brain in Melanoma* Fogarty, G. B., & Tartaguia, C. (2006). The utility of magnetic resonance imaging in the detection of brain metastases in the staging of cutaneous melanoma. *Clin Oncol (R Coll Radiol), 18*(4), 360-362.
- *4.1.2 PET in Melanoma* Fogarty, G. B., Mok, M., Taranto, A., & Murray, W. (2005). Positron Emmission Tomography in Cutaneous Melanoma Staging – a False Positive with Warthins Tumour. *Acta Oncol, 44*(1), 87-89.
- *4.1.3 PET Occult Primary* Fogarty, G. B., Peters, L. J., Stewart, J., Scott, C., Rischin, D., & Hicks, R. J. (2003). The usefulness of fluorine 18-labelled deoxyglucose positron emission tomography in the investigation of patients with cervical lymphadenopathy from an unknown primary tumor. *Head Neck, 25*(2), 138-145. doi: 10.1002/hed.10191.

4.1.1 MRI Brain in Melanoma

This paper arose out of a controversy in our PMCC melanoma unit. Treatment was being delayed because of a systematic delay outside our control of obtaining a staging MRI scan of brain for every patient with high risk disease e.g. thick primary, node positivity. I thought that this was not needed. We performed an audit of MRI brain in the unit. This was the first published audit of MRI brain in staging melanoma done in the world.

A radiology trainee colleague and I performed this retrospective analysis. The radiology request forms and hospital records for one hundred consecutive eligible patients were reviewed. No patients were upstaged by MRI. Of a total of 33 patients already graded as stage IV by prior staging, 11 (33%) were found to have brain metastases. No patients graded less than stage IV were found to have brain metastases on MRI. Six out of 12 patients with incidental symptoms had metastases. Five patients graded already as stage IV had asymptomatic brain metastases.

This impacted our practice. From this we developed a protocol for when to persist with staging the brain with MRI scan. MRI brain was only ordered if patients already had Stage IV disease, had symptoms that may have come from a cerebral secondary, or were contemplating significant treatments for which the finding of an incidental brain metastasis would have made that treatment inappropriate. The candidate was responsible for the concept, design, data collection, analysis and interpretation of data; drafting, revision and submission of the article.

This project is relevant to the thesis. The study was directly relevant to cutaneous melanoma patients. It was an advance as patients did not get an unnecessary MRI of brain. They began treatment sooner, not having to wait until the MRI was done to start treatment. Those with asymptomatic metastases had radiation treatment to the brain before becoming symptomatic.

4.1.2 PET in Melanoma

This project owed it origin to a patient of the candidate who was staged for melanoma using PET. Seven months after a wide local excision for a melanoma on the left cheek, he was found to have left cervical lymphadenectomy that was FNA positive for melanoma. Staging PET prior to operation showed a contralateral avid right sided neck masswas found on PET, presumably an involved lymph node. He was staged as having distant disease and, therefore, was triaged for palliation only. This result did not seem to follow a normal lymphatic drainage path even with melanoma which is known to metastasize in a unique fashion. The candidate insisted that a biopsy be done of the mass. A warthin's tumour was found on histopathology. This was the second report in the world of warthin's tumour causing a false positive on PET in melanoma staging. The patient was subsequently treated with curative intent. It is now widely accepted in the imaging world that warthin's tumour is a well-known false positive in PET staging. Thecandidate was responsible for the concepts, design, data collection and analysis and interpretation of data; drafting, revision and submission of the article.

This project is relevant to the thesis. It concerns a skin cancer patient, it shows that one still needs a high clinical acumen and a quality assurance mentality and not just believe the technology without question.

4.1.3 PET Occult Primary

This paper was the result of controversy arising in our skin and head and neck unit. We did not know the true utility of PET in finding the primary in the case of patients who presented with cervical lymphadenopathy and occult primary of head and neck. This is particularly pertinent in Australia where many occult primaries of head and neck involving cervical lymph nodes can come from a previously treated and perhaps forgotten skin cancer. The candidate performed a retrospective review of 21 patients in our head and neck unit with occult primary tumour of the head and neck regionwho had had a PET scan performed to look for an occult primary. The candidate found that PET does not add significantly to the yield of finding occult primary tumours above that given by careful clinical, endoscopic, and radiological examinations. It was of some

usefulness in finding further occult disease in patients with nodal disease that was N2 disease in the TNM staging (i.e. a single lymph node between three and six cm in size or multiple lymph nodes) (Sobin, 2009). It also helped with delineating regional disease for more accurate radiation planning, and in finding distant disease in patients with undifferentiated nodal histology. The candidate was responsible for the concepts, design, experimentation, data collection and analysis and interpretation of data; drafting, revision and submission of the article.

This project was relevant to the thesis. Many patients with cervical lymphadenopathy from unknown primary in Australia have had a skin primary, often forgotten. The discovery of the lack of utility of PET in patients already thoroughly worked up is a new discovery.

Section 4.2 Other Treatment Modalities

Projects presented in this section:

- *4.2.1Melanoma in Brain* — Tran, P., Fogarty, G., Phillips, C., & Tange, D. (2005). Worthwhile palliation with surgery for symptomatic haemorrhage from brain metastasis. [Case Reports Letter]. *ANZ J Surg, 75*(5), 366. doi: 10.1111/j.1445-2197.2005.03360.x
- *4.2.2 RT Delay in Skin Cancer* — Fogarty, G. B., Burt, J., & Ainslie, J. (2006). Delay of post operative radiotherapy in high risk skin cancer can be associated with recurrence. [Letter].*J Plats Reconstr Aesthet Surg, 59*(2), 203-205.
- *4.2.3 RT in Recurrent BCC* — Fogarty, G. B., & Ainslie, J. (2001). Recurrent basal cell carcinoma causing spinal cord compression. [Case Reports]. *ANZ J Surg,* 71(2), 129-131.
- *4.2.4 Rituximab and Skin SCC* — Fogarty, G. B., Bayne, M., Bedford, P., Bond, R., & Kannourakis, G. (2006). Three

cases of activation of cutaneous squamous-cell carcinoma during treatment with prolonged administration of rituximab. [Case ReportsLetter]. *Clin Oncol (R Coll Radiol), 18*(2), 155-156.

- *4.2.5 Radiation Recall*

Fogarty, G.B., Ball, D., & Rischin, D. (2000).Radiation recall reaction following gemcitabine. *Lung Cancer*, 33:299-302.

4.2.1 Melanoma in Brain

This paper describes a case of complete reversal of neurological symptoms following haemorrhage into a cerebral melanoma metastasis with palliative surgery. The team were asked to see this patient for consideration of Whole Brain Radiotherapy after he presented with a sudden symptomatic cerebral metastases of melanoma. However, on viewing the scan, the significant mass effect was due to a haemorrhage into the lesion.

We thought decompressive surgery would have a better chance of helping reverse his immediate symptoms because of the patient's young age, previously good performance status and rapidity of his decline. We encouraged our neurosurgeons to take on this case. This patient was able to return home and be independent in the activities of daily living after his neurosurgical treatment. He then went onto radiation treatment.

This case eloquentlyshows the need for multidisciplinary care and communication in the palliative situation as well as in the radical situation of caring for patients with skin malignancies. Better liaison with our neurosurgical colleagues resulted from this case. The candidate was responsible for the concept, drafting, and revision of the article.

This project is relevant to the thesis. The case concerns a common event in the progression of cutaneous melanoma is brain metastases, and it is not uncommon for these to haemorrhage. Radiotherapy is made more efficacious by the addition of surgery

to debulk. The advance is actually a human one, of being clinically astute in history taking and viewing all the relevant investigations and knowing the strength and weaknesses of each treatment modality. The therapeutic ration was maximised by multidisciplinary care.

4.2.2 RT Delay in Skin Cancer

Due to factors outside our control, a waiting list developed for treatment of skin cancers with radiotherapy in our department. We noted that several patients who had a delay in starting postoperative radiotherapy (PORT) treatment had an adverse outcome. The timing of radiotherapy is becoming increasingly important in these days of multidisciplinary care and resource allocation. There is significant literature which shows that delay in radiotherapy is associated with worst outcomes in most cancer types as is detailed in the discussion of the publication. Unlike other cancers, there was a lack of evidence at the time in skin cancer that delay was important. Our patients were not prioritized for treatment like patients with cancer types for whom literature existed. We felt a need to create the literature so that we could argue our patients also needed treatment in a timely manner. The candidate did a retrospective analysis of patients identified in our skin clinic with a poor outcome following a delay in starting PORT.

The candidate found that a delay in PORT for SCC, BCC and Merkel cell carcinoma (MCC) was associated with a worse outcome in ten of 330 patients who had to wait longer than our unit benchmarks. This publication was the second in the literature at that time to describe a similar poor outcome with delay in skin cancers, The previous, another Australian study, had described the impact of waiting on MCC (Tsang et al. 2004). This finding had never been reported before for the more common skin cancers.

This literature enabled us to insist in our institution that we start PORT in skin cancer within four weeks of surgery for squamous cell carcinoma and three weeks for Merkel cell carcinoma and melanoma. This study demonstrates the importance of correct scheduling of therapies. This study means that Radiation Oncologists and Surgeons need to communicate about patients so that PORT is not only given but given at the appropriate time. This will probably be the only level of evidence available as doing a

prospective trial with an intended delay will be difficult to get ethics committee approval and to accrue, now that there is some published date. The candidate was responsible for the concept, design, data collection, analysis and interpretation of data; drafting, revision and submission of the article.

This project is relevant to the thesis. This project is directly relevant to the timely care of post operative skin cancer patients. Prompt use of radiation may have prevented recurrence a positive for the therapeutic ratio. The project emphasises the need for interdisciplinary communication so that patients are not kept waiting for radiotherapy because of poor communication or inaccessibility to prompt radiotherapy review post operatively so that treatment is started in a timely manner.

4.2.3 RT in Recurrent BCC

This paper describes what can happen when PORT is not offered for a positive perineural deep margin following resection of a large BCC of the back. This gentleman had a neglected BCC of his back. He had a positive deep margin with perineural invasion following resection. He was not referred for PORT. Post-surgery he attended follow-ups assiduously with the surgical team. Unfortunately, he then suffered from spinal cord compression from progression of disease from the positive deep margin some years later. His neurological deficit was reversed with RT. He went on to die from unrelated causes some years later.

The candidatediscovered this interesting case during a routine skin clinic at PMCC. It deserved publication to document what can happen if a fundamental absolute indication for PORT, in this case extratumoral perineural margin positivity, is not recognized. This is a case of a lack of communication between the multi disciplinary team.

This report was the second report in the world literature of basal cell carcinoma causing spinal cord compression. It is the first report where salvage radiotherapy resulted in reversal of symptomatic spinal cord compression from BCC. This gentleman's mobility returned and he was able to look after himself independently. He went on to die many years later of unrelated causes. BCC is radiosensitive and aggressive radiotherapy can

reverse new onset spinal cord compression. The candidate was responsible for the concept, design, data collection and interpretation of data; drafting, revision and submission of the article.

This project is relevant to the thesis. It involves the use of radiotherapy in skin cancer. It shows that radiotherapy even in the event of complete cord compression can restore function if given appropriately. It highlights the need for appropriate referral and contrasts well with the prior case. The therapeutic ratio was increased with salvage RT.

4.2.4 Rituximab and Skin SCC

The candidate was working in a part of rural Australia with the highest incidence of lymphoma in the country per head of population. Lymphoma and its treatments are immunosuppressive. Many of the patients were of Celtic descent and had much sun exposure and so had a high incidence of skin cancer suitable for radiation treatment. The candidate noticed that older patients with sun-damaged skin were developing rapidly growing cutaneous SCC when started on maintenance lymphoma therapy with Rituximab, a chimerical anti-CD20 monoclonal antibody.

This drug was used in treatment and maintenance of non-Hodgkin's lymphomas that are B cell CD20 positive. At the time there were initial reports that this drug was also causing neutropeania and activation of hepatitis unexpectedly as per the references of the publication. It is well known that skin cancers progress more rapidly in the setting of immune suppression. We also hypothesised that Rituximab may have cross reactivity with the immune system which has since been verified as per the project references.

This project describes activation and rapid progression of cSCC in three Caucasians with long histories of sun damaged skin following administration of Rituximab. Following this observation patients on this drug were followed more closely and haematologists in our institution were consulted early about a possible dose reduction of Rituximabwhen new skin cancers arose. This paper added to the evidence of cross reactivity of this drug with the immune system. These findings were the result of good communication between the radiotherapy and medical oncology teams. The candidate

was responsible for the concept, data collection and interpretation of data; drafting, revision and submission of the article.

This project is relevant to the thesis. It shows how a new drug can be associated with activation of skin cancer possibly via increasing immunosuppression. Involvement of a radiation oncologist can help in treating new SCCs with tissue conserving definitive radiation rather than tissue sacrifice with surgery especially in cosmetically and functionally sensitive areas. The new advance is knowledge that Caucasians patients with a history of sun damaged skin who start prolonged therapy with Rituximabneed close monitoring with a view to rapid intervention and consideration of possible dose reduction in the event of activation and rapid progression of cSCC.The therapeutic ratio has been increased by this new knowledge.

4.2.5 Radiation Recall

Gemcitabine was a relatively new cytotoxic chemotherapy at the time. A patient presented to our clinic with a skin reaction similar to her previous radical radiation fields following palliative chemotherapy with Gemcitabine for recurrence of non small cell lung cancer. We had a high enough level of suspicion to realize that this was a radiation recall reaction. Radiation recall reactions were seen in skin and muscle. The patient recovered with cessation of drug, and administration of steroids, and then transfer to another cytotoxic to continue her therapy. Since then, gemcitabine has been used as a radiation sensitizer. This study may have been important in suggesting this use.

This was the third case report in the world literature of any radiation recall with Gemcitabine. Cutaneous recall had only been reported twice before with this drug, myositis as recall phenomena had never been described. This is the first report of myositis as a radiation recall event of gemcitabine. The case report details a hypothesis of the causation of radiation recall. The recognition of this condition was only possible due to astute clinical thinking and good communication between the treating teams. The candidate wrote up the case report as quickly as possible in order to report this promptly. He was responsible for the data collection and analysis and interpretation of data; drafting, revision and submission of the article.

The project is relevant to the thesis. The topic is about a radiation effect on skin. The advance was linking the initiation of a supposedly non-toxic chemotherapy to the beginning of the rash which needed a high level of clinical suspicion. The therapeutic ratio was maximized by immediate relief of symptoms through substitution of another cytotoxic and prompt reporting to alert the oncology community of this new finding.

Part 4.2 Conclusions of Chapter 4

These projects have been the most cited of all those presented in the thesis. *4.1.3* has been cited 57 times. This is understandable given the growing importance of imaging and the increasing amount of multidisciplinary care in RT.

The clinical advances described happened mainly because of astute observation in clinical practice. Unexpected occurrences in patient and disease behaviour were discovered by careful history taking and examination. These discoveries arise often by serendipity and are noticed by clinicians with an interest. They were further researched and analysed and new lessons were learnt. They shed more light on the biology of skin cancer. These clinical observations give an insight into tumour and normal tissue biology that can serve as hypothesis generating exercises for translational research.. They are of interest to the whole skin cancer community hence their acceptance for publication, especially in international journals. Many are described in the literature for the first time.

This chapter is divided into two parts. The first part (*4.1*) comprises three projects that have to do with the advent of new imaging modalities pertinent to the radiation treatment of skin cancer. These three projects all have to do with staging. Staging prior to treatment ensures the appropriate treatment is delivered, resulting in a better therapeutic ratio. From a study of 100 melanoma patients (*4.1.1*) it was found that staging MRI brain was only needed if patients already had Stage IV disease, had symptoms that may have come from a cerebral secondary, or were contemplating significant treatments for which the finding of an incidental brain metastasis would have made that treatment inappropriate. This aided prompt patient treatment and helped with resource allocation. The next project (*4.1.2*) showed that astute thinking resulted in

finding that a PET scan, which diagnosed a melanoma patient as having stage IV disease, actually had a warthin's tumour causing a false positive. This was the second report in the world. The patient was subsequently treated with curative intent. This report shows that imaging helps but does not replace clinical acumen. The last imaging study (*4.1.3*), investigating the utility of PET in finding the head and neck primary in 21 cases of patients who presented with cervical lymphadenopathy found that PET does not add significantly to the yield of finding occult primary tumours above that given by careful clinical, endoscopic, and radiological examinations. It was of some usefulness in finding further occult disease in patients with N2 disease. It also helped to achieve more accuracy in radiation planning by delineating regional disease, and in finding metastatic disease in patients with undifferentiated histology. All these projects show that imaging is helpful but not a replacement of the basic clinical skills of proper history taking and examination.

The second part of the chapter (*4.2*) comprises projects that examine the interaction of other anti-cancer treatments like surgery and chemotherapy with radiotherapy. These interactions are important to know about in these days of multidisciplinary care when one treatment may have an effect on another, and patients are required to start sequential treatments in a timely manner.

The initial three projects were about interactions of surgery and radiotherapy. The first project (*4.2.1*) describes a case of complete reversal of neurological symptoms following haemorrhage into a cerebral melanoma metastasis with palliative surgery rather than immediate Whole Brain Radiotherapy. This case highlights the need for multidisciplinary care and communication in the palliative as well as in the radical situation. The second project (*4.2.2*) found that a delay in PORT for cSCC, BCC and MCC was associated with a worse outcome in ten of 330 patients who had to wait longer than our unit benchmarks. These cases also highlight the need for communication and understanding of tumour biology between the teams giving multidisciplinary care to ensure timely treatment. The third project (*4.2.3*)describes what can happen when PORT is not offered for a positive perineural deep margin following resection of a large BCC of the back. The patient developed spinal cord compression from progression of disease from the positive deep margin some years

later. His neurological deficit was reversed with RT. This case once again emphasizes the need for appropriate referral and understanding of tumour biology between the multidisciplinary teams.

The last two projects deal with the interaction between radiotherapy and chemotherapy in skin cancer. The first project (*4.2.4*)describes activation and rapid progression of cSCC in three Caucasians with long histories of sun damaged skin following administration of Rituximab. This paper added to the evidence of cross reactivity of this drug with the immune system. These findings were the result of good communication between the radiotherapy and medical oncology teams. The second project (*4.2.5*)was the third case report in the world literature of any radiation recall with Gemcitabine and the first about radiation recall myositis. Again this was only possible due to astute clinical thinking and good multidisciplinary communication.

The key point of this chapter is that clinicians need to know the relevant place of each diagnostic and therapeutic modality and cannot be just an isolated expert in their own subspecialty if they want to maximize the therapeutic ratio for skin cancer patients. This chapter, devoted to the interaction of imaging and other oncological specialties with radiation oncology, emphasizes two important pillars of good medical practice. Firstly that imaging compliments but does not replace fundamental clinical skills such as history taking and physical examination. Secondly, that in these days of multidisciplinary care, knowledge of the indications for treatment of other modalities and excellent communication between the multidisciplinary teams in crucial to timely treatments and best outcomes. The need for knowing about other specialties and when to refer based on evidence leads logically to the need for quality assurance and guidelines, the subjects of the next chapter.

These projects reinforce the recurring themes of the thesis:

1. The need for communication – there is evidence here of good communication (*4.2.1* and *4.2.2*)and poor communication (*4.2.3*).
2. Personalized treatment of skin cancer with radiotherapy – in *4.2.1*, palliative surgery prior to radiotherapy increased patient independence and quality of life.
3. Clinical vigilance – In *4.1.2*, picking up the false positive warthin's tumour

changed treatment intent from palliation to radical.

CHAPTER 5 Quality Assurance and Guidelines

Part 5.1 Introduction

Chapter five examines quality assurance (QA) issues and guidelines of radiation treatments with a focus on skin and its cancers. There is a synergy between guidelines and QA. Guidelines help the clinician to know what is accepted by peers in the field on the basis of evidence and experience, and suggests how to implement safe practice in prescribing. QA ensures that the treatment prescribed is delivered.

QA measures how effectively treatments are delivered. Better treatments are only effective if they can be properly delivered. Advances may be rendered ineffective if delivered incorrectly, and a worse therapeutic ratio for the advance may be unfairly inferred. QA practices that the candidate has been involved in generating are addressed in the first part (Section *5.1*) of the chapter.

Guidelines are produced, usually on the basis of published evidence by recognized experts in the field to assist others in prescribing safe and effective treatments. They are essential to the creation of industry standards and benchmarks. They can be seen as a summary of experience from providers of new advances to new providers of those advances. Guidelines ensure that new treatment techniques are applied with the concept of maximizing the therapeutic ratio in mind. Section *5.2*describes guidelines that the candidate has been involved in generating.

Section 5.1 Quality Assurance

QA can be applied to both treatment structure and process and can be related to outcomes. The QA of process is important, but has not been analysed as much. This is vital especially in the conduct of randomized trials, upon which current standard treatments are based (Peters et al, 2010).QA of process is essential in treatment delivery. These programs are in themselves advances and are growing in number and importance especially in areas such as medical credentialing, the setting of minimum requirements

for licensing, and the refining of the treatment process. The first part of this chapter examines some examples of effective QA of process.

Projects presented in this section:

- *5.1 QA Chart Round* Fogarty, G. B., Hornby, C., Ferguson, H. M., & Peters, L. J. (2001). Quality assurance in a Radiation Oncology Unit: the Chart Round experience. *Australas Radiol, 45*(2), 189-194.
- *5.2 Skin Chart Round* Fogarty, G. B., & Ainslie, J. (2005). RE: Chart round in a skin radiotherapy unit. [Comment Letter]. *Australas Radiol, 49*(6), 526-527. doi: 10.1111/j.1440-1673.2005.01521.x
- *5.3 Peer Review* Fogarty, G. (2010). Peer Review: Physician's View from Australia. In T. Pawlicki, Dunscombe, P., Mundt, A.J., & Scalliet, P. (Ed.), *Quality and Safety in Radiotherapy (Imaging in Medical Diagnosis and Therapy)* (pp. 171-173). London: Taylor and Francis.

5.1 QA Chart Round

A chart is a record of a patient medical history including radiation treatments. A chart round is a group audit of whether items necessary for treatment have been included in the treatment process. This project is about quality in radiation treatment. RT should not be delivered if the quality cannot be guaranteed. This paper originated in our need to audit our chart round review in the head and neck unit at PMCC. Our audit showed that completion rate of items that were regarded as necessary for effective treatment increased from 80 to 99% with the institution of the chart round. The chart round became a standard practice in our unit and many others in our institution, and became a benchmark for QA in Australasia.

The candidate was responsible for the design, data collection, analysis and interpretation of data; drafting, revision and submission of the article. He completed this project while

a registrar in the head and neck unit. The project won a prestigious national prize for the candidate – The Varian Award for the best oral presentation by a registrar at the Royal Australian and New Zealand College of Radiologists (RANZCR)Annual Scientific Meeting (ASM) in Auckland in 2000. This was the first time a registrar from PMCC had won this award for 25 years.

The project is relevant to the thesis. The head and neck unit in the institution of this study looks after locally advanced skin cancer of the head and neck. These patients are included in this QA activity. The advance was the finding that this QA activity lifted the completion rate of items needed for radiation treatment by 19% to almost 100%. The chart round therefore assured that the radiation treatment given was of the highest quality, maximizing the therapeutic ratio.

5.2 Skin Chart Round

The second paper details an audit of the institution of a chart round review in our skin radiotherapy unit at PMCC following the example of the first paper. This audit was done some months after the chart round began in our skin unit to assess the impact of this new practice. The chart round in our skin unit led to a similar rate ofitem completion (98%) as the preceding project. We decided that the chart round was worthwhile and continued this. This led to other units adopting the chart round. The candidate was responsible for the design, data collection, analysis and interpretation of data; drafting, revision and submission of the article.

This project is relevant to the thesis. The patients involved were all having radiotherapy for skin cancer. The new advance led to better treatment recording and completion and therefore a better therapeutic ratio.

5.3 Peer Review

The candidate was invited to write this book chapter in this first edition of an international textbook as he had been identified as an expert in the field because of the publication of the previous two papers. QA as a field was taking off at the time,

especially following the expansion of RT with further indications into other cancer sites following successful research, and the desire of the profession to prevent any disasters happening. The peers referred to were those of the radiotherapy multidisciplinary team– other radiation oncologists, radiation physicists, therapists and nurses. The project was based on the above articles and a thorough literature search. It found that peer review is essential to smooth delivery of RT. The chapter received favourable commentary, which hopefully meant it was translated into practice in other institutions. The candidate was responsible for the design, data collection; drafting, revision and submission of the article. This textbook was an international first edition. The candidate was the only Australian contributor to the overall textbook.

The project is relevant to the thesis. The advance is the recognition of better outcomes with more peer input for quality assurance during RT. The finding that peer review helps task completion as shown in the previous projects was disseminated to an international audience comprised of all radiation craft groups by this publication.

Section 5.2 Guidelines

Projects presented in this chapter:

- *5.4 National Skin Cancer Guidelines*

  Fogarty, G. B. (2008). Radiation Oncology and Metastases In T. Reeve (Ed.), *Basal cell carcinoma, squamous cell carcinoma (and related lesions) - a guide to clinical management in Australia*. Sydney: Cancer Council Australia and Australian Cancer Network.

- *5.5 Skin Cancer Guidelines*

  Fogarty, G. B. (2006). Guidelines for radical radiotherapy in skin cancer. [Comment Letter]. *Australas Radiol, 50*(3), 286-287. doi: 10.1111/j.1440-1673.2006.01583.x

5.4 National Skin Cancer Guidelines

The candidate was invited as one of two Australian radiation oncologists with a national profile in the use of radiation in skin cancer to collaborate with the updating of the National Guidelines. A group of 10-15 skin cancer specialists met regularly over the year of 2007 and prepared these guidelines. These two chapters were the ones that the candidate contributed the most to. The chapters were endorsed by the group as the current guidelines at the time for the use of radiotherapy in skin cancer. These chapters represent a distilling of the current literature at the time about the radiation treatment of skin cancer in the country in the world where it is most prevalent. They are the result of a national multidisciplinary dialogue. These chapters thenformed the basis of evidence based skin cancer radiation practice in Australia. The candidate was responsible for the literature review, drafting, revision and submission of the chapters – tasks shared with another radiation oncology colleague.

The project is relevant to the thesis. These are national guidelines for radiation treatment for skin cancer. The advance is having a unified evidenced based guideline for the care of these patients. Hopefully these recommendations were adopted in skin cancer treatment units across the country, maximizing the therapeutic ratio for a larger population.

5.5 Skin Cancer Guidelines

This project originated in the need we had in our institution and state wide referral base to inform the medical staff of other units, particularly those involved with skin cancer, about when it was appropriate that a patient with skin cancer should be referred to our service. There had been some inappropriate referrals (Fogarty et al. 2006). This project clarified when referral of a skin cancer patient to a skin multidisciplinary clinic which included radiotherapists was appropriate.

The project was produced with the collected wisdom and experience of our multidisciplinary skin cancer team. These guidelines clarified for other doctors when a referral to our unit was relevant. They were circulated to plastic surgeons, dermatologists and skin cancer clinics within the capital city and to the training programs of each of those specialties. This led to increased communication and led to

enhanced and effective referral patterns for all involved. The candidate collected and collated the data; and was responsible for the drafting, revision and submission of the article.

The project is relevant to the thesis. The guidelines were aimed at skin cancer patients. The advance was to ensure timely and effective referral to our service to prevent problems outlined in the reference above, which is detailed in *4.2.2 RT in recurrent BCC*. The therapeutic ratio was enhanced by dissemination of these guidelines which ensured that multidisciplinary expertise in skin cancer was appropriately consulted and applied.

Part 5.2 Conclusions of Chapter 5

Chapter five examines quality assurance (QA) issues and guidelines of radiation treatments with for skin cancer. Three projects are presented under QA. They are about the QA of treatment process. The first (*5.1*) is an audit of a chart round review. A chart round review is a group audit of whether items necessary for treatment have been included in the treatment process. Our audit showed that completion rate of items that were regarded as necessary for effective treatment increased from 80 to 99% with the institution of the chart round. The conference presentation of this project won a prestigious award and the exercise became a benchmark for QA in Australasia. The second project(*5.2*) details an audit of a chart round review in our skin radiotherapy unit. The chart round in our skin unit led to a similar rate ofitem completion (98%). The third project (*5.3*) is a review of the importance of peer review in QA. The project was based on the above articles and a literature search. It found that peer review is essential to the smooth delivery of RT. This was written in response to an invitation to contribute to the first edition of an international textbook, the candidate was the only Australian contributor. Two projects were presented under guidelines. Guidelines are produced by recognized experts to assist others. They are a summary of experience from providers of new advances to help new providers of those advances. In project *5.4*the candidate assisted with the updating of the National Guidelines especially the radiotherapy sections. Thetwo chapters included here formed the evidence-based consensus for skin cancer radiation practice in Australia. Project *5*.5 clarifiedto referrers when referral of a

skin cancer patient to a skin multidisciplinary clinic which included radiotherapists was appropriate.

There is a synergy between guidelines and QA. Guidelines help the clinician to know what is accepted practice and suggests how to implement procedures that are safe and effective. QA, especially of treatment process, ensures that the treatment prescribed is delivered properly. Both of these activities are about effective communication. For QA to happen, there must be effective communication between the members of the multidisciplinary radiation team, both between the different craft groups, and from one point in time to another. The latter speaks to the importance of documentation. What is actually at the heart of *5.1* and *5.2* is an effective form that is conscientiously filled in as treatment progresses. Guidelines are only as good as their evidence base, their dissemination and their implementation. This involved communication, especially consensus, between experts in the field, and from them to the providers of the new advances.

These projects reinforce the recurring themes of the thesis:

1. The need for communication – as detailed in the last paragraph
2. Personalized treatment of skin cancer with radiotherapy– the chart rounds assured that each patient was being treated according to department protocol.
3. Clinical vigilance –the skin cancer guidelines owes it origin to the realization that inappropriate referrals were being made or, as was more common, appropriate ones not being made to our unit.

CHAPTER 6 Whole Brain Radiotherapy in Melanoma

Part 6.1 Introduction

Research on the role of radiotherapy in skin cancer has progressed duringthe candidature. The projectshere presented detail how this work is evolving to aid skin cancer patients of the future.

Project presented in this chapter:

- *6.1 WBRT Melanoma* Fogarty, G., Morton, R. L., Vardy, J., Nowak, A. K., Mandel, C., Forder, P. M.,Thompson, J. F. (2011). Whole brain radiotherapy after local treatment of brain metastases in melanoma patients--a randomised phase III trial. [Clinical Trial, Phase III Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. *BMC Cancer*, 11, 142.doi: 10.1186/1471-2407-11-142
- *6.2 VMAT* Fogarty G.B., Ng D., Liu G., Haydu L.E., Bhandari N., (2011). Volumetric modulated arc therapy is superior to conventional intensity modulated radiotherapy – a comparison among prostate cancer patients treated in an Australian centre. *BMC Radiation Oncology*, 6, 108. Accessed 5 September 2011 fromhttp://www.ro-journal.com/content/6/1/108

Section 6.1 WBRT Melanoma

6.1.1 Preamble

The role of WBRT after local treatment of brain metastases in melanoma is controversial. The candidate has set up and is running this international randomized controlled trial to investigate this question. The trial has received federal funding of one million dollars to date and has accrued 78 of a needed 200 patients in three years, the fastest accruing WBRT trial in history. The first interim analysis will take place one year after the randomization of the 100th patient. This trial will provide level one evidence on how to treat in this controversial situation.

6.1.2 Background

The incidence of central nervous system (CNS) metastases in patients with metastatic melanoma ranges from10% to 40% in clinical studies(Bafaloukos & Gogas, 2004) and is even higher in autopsy series, with as many as 72% of patients with metastatic melanoma having CNS involvement (Posner, 1992).Local control of brain metastases from melanoma is a significant problem. Sampson et al. reported an overall median survival time of 3.8 months in 702 patients with clinically significant melanoma brain metastases, treated with either palliative chemotherapy, radiotherapy or surgery(Sampson, Carter, Friedman, & Seigler, 1998). These metastases contributed to the death of94.5% of these patients.

As well as seeking to prolong survival, maintainingneurocognitive function in these patients is pivotal to their quality of life. The clinically apparent metastases can often be treated locally by neurosurgery and/or stereotactic radiosurgery (SRS), with the option of postoperativeWBRT. The objective of WBRT in this setting is to treat clinically undetectablemicrometastases elsewhere in the brain; these are considered likely to be present in many patients and, if not controlled, will later manifest as distant intracranial treatment failure. However the role of WBRT after local treatment is controversial. Proponents say thatWBRT to prevent or delay intra-cranial disease recurrence provides worthwhile palliation. Opponents argue against WBRT as a survival benefit has never been demonstrated in this situation and there is a risk of neurotoxicity. These opinions are based on studies in other malignancies, predominantly non small-cell lung cancer and lymphoma, and retrospective analyses(Aoyama et al., 2006; Broadbent, Hruby, Tin,

Jackson, & Firth, 2004; Fisher et al., 2005; Patchell et al., 1998). There have been no randomised clinical trials (RCTs) for this specific scenario in patients with metastatic melanoma. A complicating factor is that there exists a strong anecdotal impression among some clinicians that melanoma is a uniformly radioresistant tumour, although there is no level 1 clinical evidence for this. As a result, current clinical practice varies widely, with some units actively encouraging WBRT while others rarely or never offer it.

In a randomised controlled trial of 95 patients with a variety of solid tumour types who received WBRT following surgical excision of brain metastases, those receiving WBRT (50.4 Gy over 5 weeks) had a 52%reduction in intracranial recurrence and a 30% reduction in death from neurological causes compared to those randomised to observation (Patchell et al., 1998). Although the time to intracranial recurrence was substantially longer in theWBRT group (220 weeks versus 26 weeks, p = < 0.001),the median overall survival was not significantly different between the two groups (11 months versus 10months, p = 0.39), probably because a high proportion of patients in both groups had extra-cranial disease.

A second randomised controlled trial comparing SRSplus WBRT (30 Gy in 10 fractions) versus SRS alone in132 patients with 1-4 brain metastases reported a 30%reduction in local intracranial recurrence and a 22%reduction in distant intracranial recurrence at 12 months in the WBRT group (p = 0.001)(Aoyama et al., 2006). There was nodifference between the groups in overall survival(7.5 months versus 8 months) or neurological death. In a subset of patients neurological toxicity and neurological function were assessed radiologically and using theKarnofsky Performance Scale (KPS) and the MiniMental State Examination (MMSE). There were no significant differences in toxicity or function.

A more recent randomised trial undertaken by the European Organisation for Research and Treatment of Cancer (EORTC) comparing adjuvant WBRT (30 Gy in10 fractions) to observation after surgery or radiosurgeryof 1-3 brain metastases (predominantly from lung,breast and kidney cancer) assessed the time to functional decline (performance score > 2) (Kocher et al., 2011). Overall survival was similar in the WBRT and

observation arms(median 10.9 versus 10.7 months), however WBRTreduced the 2-year relapse rate both at both initial sites(surgery: 59% to 27%, p = 0.001; SRS: 31% to 19%, p =0.040) and at new sites (surgery: 42% to 23%, p = 0.008;SRS 48% to 33%, p = 0.023).

There has been some recent controversy aboutwhether WBRT affects neurocognitive function(Chang et al., 2009; Mahmood, Kwok, Regine, & Patchell, 2010).Assessment of neurocognitive function and healthrelatedquality of life (HRQOL) are essential for the interpretation of WBRT in the context of the patient's experience. It is clear that tools such as the MMSE, whilst appealing in their simplicity, were developed to screen for dementia and show poor sensitivity in detecting cognitive impairment in patients with brain tumours(Meyers & Wefel, 2003). The ideal tool should be brief, simple, sensitive, inexpensive and, if administered repeatedly, should have alternative versions to reduce the effects of learning(Meyers, Geara, Wong, & Morrison, 2000). A battery of tests which fit these criteria (including Hopkins Verbal Learning Test-Revised, Controlled Oral Word Association of the Multilingual Aphasia Examination, Trail Making Test, Stroop Color-Word Test and the Digit Span test) have been shown to be feasible in previous clinical trials in patients with brain metastases(Meyers et al., 2004).

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTCQLQ-C30) has been validated in numerous malignancies including neurological malignancies (Aaronson et al., 1993; Osoba et al., 1996) and measures five functional domains as well as global quality of life and symptoms of fatigue, nausea, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties. The EORTC BN-20 is a brain cancer-specific module that measures four multi-item domains (future uncertainty, visual disorder, communication deficit, and motor dysfunction)(Osoba et al., 1996). A change in scores of $\geq$ 10 on a scale of 0-100 persisting for 4 or more weeks has been shown to represent a clinically meaningful and subjectively significant change that is associated with change in disease status (Osoba et al., 1996). These tools are considered appropriate, validated and sensitive in this population.

Using MRI as the primary means of assessment, the current trial will investigate whether WBRT following complete local treatment of intracranial melanoma metastases improves distant intracranial control and hence demonstrate whether radiotherapy in this scenario can control microscopicintracerebral melanoma. If so, then it may contribute to more clinically meaningful outcomes such as increased time to functional decline from further intracranial disease or neurological death, without causing excessive neurotoxicity. Trial recruitment will be supported through referrals from multi-disciplinary melanoma teams. The trial will be offered to all eligible patients in whom intracranial disease control has been obtained by complete surgical resection and/or SRS.

6.1.3 Objectives

This study aims to assess the value of treating brain metastases in patients with AJCC stage IV melanoma using adjuvant post-operative WBRT in the hope of improving disease control, and quality of life, while maintaining satisfactory cognitive performance. The primary objective is to assess the effect of WBRT (after localised treatment for melanoma brain metastases) on distant intracranial control, as assessed by MRI scanning (Figure 2). Distant intracranial control is defined as control within the brain 1 cm or more from a previous metastasis. The primary hypothesis is that as a result of whole brain radiotherapy, there will be a 20% reduction in the rate (proportion) of distant intracranial metastases after at least 12 months of follow-up, compared to the control (observation only) arm.

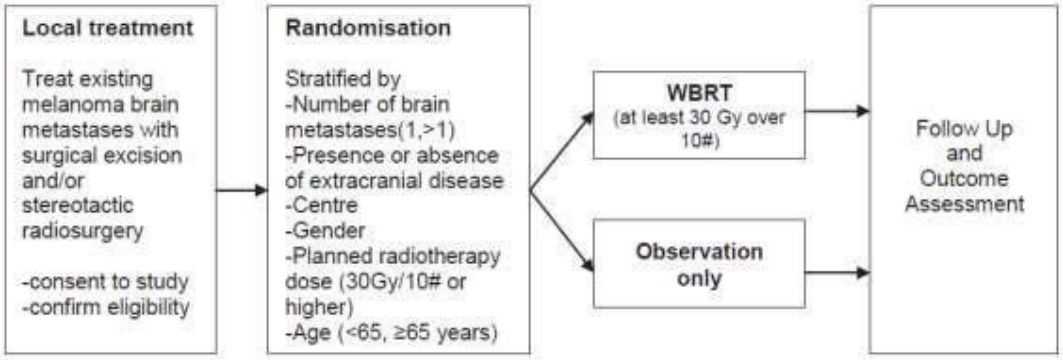

Figure 2. Trial schema

The secondary objectives are to assess the effect ofWBRT on:

1. Time to intracranial failure (local, distant and overall (local+ distant)) as assessed by MRI
2. Quality of life
3. Performance status
4. Neurocognitive function
5. Overall survival
6. Death from neurological causes

Deterioration in neurocognitive function and distant intracranial failure will be assessed for the following subgroups: one versus more than one treated cerebral metastasis; presence of extra cranial disease versus none;< 65 years of age versus ≥65 years of age.

6.1.4 Methods/Design

Trial Design

This trial is an international multi-centre, open-label, stratified, 2-arm randomised phase III trial. Patients will be randomised 1:1 to WBRT or observation. The trial has been approved by the Cancer Institute NSW Clinical Research Ethics Committee #2007C/11/032 and relevant hospital ethics committees in each participating centre.

Participants

Patients will be recruited mainly from participatingmulti-disciplinary melanoma treatment centres.Patients will be identified through routine scanning showing asymptomatic metastases or by investigation of intracranial symptoms. The eligibility criteria are listed in Table 6.

Table 6: Eligibility criteria – inclusions and exclusions

Inclusion criteria	Exclusion criteria
• One to three (1-3) intracranial metastases on MRI from melanoma, all locally treated with either surgical excision and/or stereotactic irradiation. (It will be assumed that the metastases are melanoma if the patient has documented histological or radiological	• Any untreated intracranial disease. • Any previous intracranial treatment (surgical excision and/or stereotactic irradiation treatment and/or WBRT) prior to this diagnosis of intracranial melanoma. • Evidence of leptomeningeal disease on

concurrent extra cranial disease that has already categorised the patient as stage IV). If the cerebral lesion(s) is/are the first presentation of stage IV disease, then one metastasis must be histologically proven to be melanoma for the patient to be included in the study. • Life expectancy of at least 6 months. • Aged 18 years or older. • WBRT must begin within 8 weeks of completion of local treatment and within 4 weeks of randomisation. • Able to have an MRI brain scan with contrast enhancement. Estimated glomerular filtration rate (eGFR) is adequate at the discretion of the radiologist and capable of having gadolinium-containing contrast medium for MRI (as per practice guidelines). • Localised treatment of all brain metastases no more than 6 weeks prior to randomisation. • An ECOG performance status of 0, 1 or 2 at randomisation. • CT scan of chest, abdomen and pelvis within 12 weeks of randomisation. • Serum lactate dehydrogenase (LDH) must be ≤ 2 times upper limit of the participating centre's reference range. • Able to provide written informed consent.	pre-local treatment MRI scan. • Patients with prior cancers, except: those diagnosed more than five years ago with no evidence of disease recurrence within this time; successfully treated basal cell and squamous cell skin carcinoma; or carcinoma in-situ of the cervix. • A medical or psychiatric condition that compromises ability to give informed consent or complete the protocol. • Positive urine pregnancy test for women of childbearing potential.

In order to be eligible, patients must meet all of the specified inclusion and exclusion criteria. In addition, patients will be excluded from the neurocognitive function(NCF) and quality of life aspects of the study if their fluency of oral and written English is less than Year 8 standard. Centres in countries where English is not a main language can still participate in the primary endpoint of the study but not the NCF component.

Setting

Melanoma treatment centres and tertiary cancer hospitals with facilities for WBRT.

Interventions

Neurosurgery for melanoma brain metastases

Neurosurgery will be conducted according to the usual practice at the treating centre. A lesion will be deemed tobe completely excised if the treating neurosurgeon reports

complete excision. A patient with a lesion not completely excised should be referred for SRS Incomplete excision is not an exclusion criterion; patients whose lesions are not completely excised may still be randomised into the trial to receive WBRT or observation. Histopathology reports using hematoxylin and eosin stains as well as immunostains(at least one of S100 or HMB45) are required.

Stereotactic radiosurgery (SRS) of melanoma brain metastases

SRS may be given to the target lesion(s) definitively or to the surgical cavity(ies) post resection. It should be given according to the usual practice at the treating centre. Full records of the procedure need to be included in the written SRS report. For quality assurance purposes, copies of the prescription page and computer dosimetryon axial, coronal and sagittal planning CT images through the target(s) are required.

Control intervention

Observation only (no WBRT) with regular assessment of outcomes at the same time points specified for the intervention arm.

Assessment of Outcome

The primary endpoint of the study will be the proportion of patients with distant intracranial failure (as determined through MRI assessment) at 12 months. Distant intracranial failure is defined as new lesions appearing 1 cm or more from a previous index metastasis. New onset leptomeningeal disease after the randomization MRI will be recorded as new distant intracranial disease. Patients who fail locally only will not be considered as having an event and their time will be measured from randomisation to their last known follow-up date. Patients progressing or dying from extracranialdisease or other causes will be considered as having a competing risk for distant intracranial failure.

The secondary endpoints include:

i. Time to distant intracranial failure as determined by MRI. This is defined as the time from the date of randomisation to recurrence of disease at a distance of 1 cm or more from previously treated metastases. In the absence of distant intracranial failure (i.e. for patients censored before intracranial failure could be

observed), time to failure will be measured from randomization to date of last known contact (i.e. censoring time).

ii. Time to local intracranial failure as determined by MRI. This is defined as the time from the date of randomization to recurrence of disease within 1 cm of previously treated metastases.

iii. Time to overall (distant + local) intracranial failure as determined by MRI.

iv. Deterioration in NCF. This is measured by a battery of assessments including Hopkins Verbal Learning Test, Controlled Oral Word Association Test, Trail Making Test Part Aand B, Stroop Color-Word Test (Adult Version),Digit Span (Forwards and Backwards). The proportion of patients completing neurocognitive function assessments at the baseline visit and at each 2-monthly follow up visit will be determined for each of the treatment groups (WBRT and Observation)together with a descriptive summary of Global Deficit Scores (GDS) scores. The main neurocognitivefunction endpoint will be defined as the proportion of patients who have deteriorated from the baseline visit at any time in the study period by at least 0.3units on the GDS scale.

v. Time to deterioration in health related quality of life. This is measured by EORTC QLQ-C30 with Brain module (EORTC BN-20) questionnaires. The completion rates for quality of life questionnaires at the baseline visit and at each 2-monthly follow-up visit will be determined for each treatment group together with descriptive summaries of scores. The primary QOL endpoint will be time to deterioration in role function from randomisation, with deterioration defined as a decrease of $\geq$ 10 points on a 0-100scale persisting for at least 4 weeks. Secondary endpoints will be time to deterioration in global QOL, drowsiness, communication difficulties, motor dysfunction and social function items/domains.

vi. Time to deterioration in performance status asmeasured by ECOG criteria. This is defined as the time that elapses between randomisation and the first recorded worsening (increase) in ECOG performance status.

vii. Overall survival. This will include time to death due to any cause; time to death due to a neurological cause; cause of death (cancer related or not); and cause of death if cancer related, due to neurological progression or not. Overall survival will be assessed from date of randomisation to date of death from any cause.

Patients remaining alive or lost to follow-up will be censored at the date of last known contact.

Sample size

It has been assumed on the basis of previous studies(Aoyama et al., 2006; Patchell et al., 1998)that the proportion of patients having distant intracranial metastases at 12 months post-randomisation will be 55% in the observation arm (surgery and/or SRSonly) and 33% in the WBRT arm. With 200 patientsandassuming 10% non-adherence, this study will have80% power to detect an absolute risk reduction of 22%at the 5% significance level (two-tailed). To achieve a total sample of 200 patients, it is assumed that patients will be accrued over five years. This assumes a uniform accrual rate of 40 patients each year, which will require participation from international centres as well as centres in Australia and New Zealand.

Interim analyses and stopping guidelines

An independent data safety monitoring committee(DSMC) will regularly monitor the occurrence of serious clinical events. One formal efficacy analysis will be performed after 45 events have been observed (the expected number of events after 100 randomised patients have completed 12 months of follow-up). The events used for this formal interim analysis will be distant intracranial failure after 12 months of follow-up. The stopping rule for the study on the basis of efficacy will be a nominal significance level of p = 0.003 (3 standard deviations) to maintain an overall probability of a Type I error = 5%.The DSMC will monitor the trial for safety outcomes including unacceptable acute radiotherapy toxicity (any Grade 4 toxicity); accrual less than 30% of the expected number of patients within the first 36 months; and the availability of a therapy that is clearly more effective.

Randomisation

Sequence generation and allocation concealment mechanism

Randomisation will be performed by a centralised trial coordinating centre using an interactive voice response system (IVRS). Authorised staff from the participating centres will submit eligible patients for randomisation. Randomisation will be stratified

by centre, gender, age, number of cerebral metastases, presence of extracranial disease and planned WBRT dose using minimisation.

Blinding

Study participants and treating clinicians will not be blinded to treatment allocation. The centralised personnel assessing MRI scans and neurocognitive function will be blinded to treatment allocation.

Statistical methods

Efficacy analyses will be conducted on the basis of 'intention to treat' and toxicity analyses will be by treatment received and unadjusted. All comparisons will be2-tailed with a 5% significance level. The primary endpoint, proportion of patients with distant intracranial failure, will be compared for the two groups using chi-squaredor exact tests (Pocock, 1983). Continuous outcomes will be analysed by using t-tests or suitable non-parametric methods if appropriate. The secondary endpoint, time to distant intracranial failure, will be compared for the two groups using the log rank test and Kaplan-Meier curves(Pocock, 1983). Exploratory analyses will be conducted adjusting for prognostic factors using proportional hazards or other suitable regression models. Other time-to-event endpoints will be analysed using similar methods.

Subgroup analyses

Deterioration in neurocognitive function and distant intracranial failure will be assessed for the following subgroups: one versus more than one cerebral metastasis; presence of extracranial disease versus none; patients< 65 years of age or ≥65 years of age. Other outcomes assessed for the main study will also be analysed for the subgroups with the acknowledgement that these analyses are exploratory and hypothesis-generating.

Quality Assurance

Radiotherapy treatment delivery

Technical review for all patients who undergo WBRTwill be conducted by the Trans-Tasman Radiation Oncology Group (TROG). Figure 3 provides an example of WBRT simulation, planning and treatment volume. Sites must submit copies of the case history,

treatment prescription, treatment administration sheet, dosimetry plans and portal verification films.

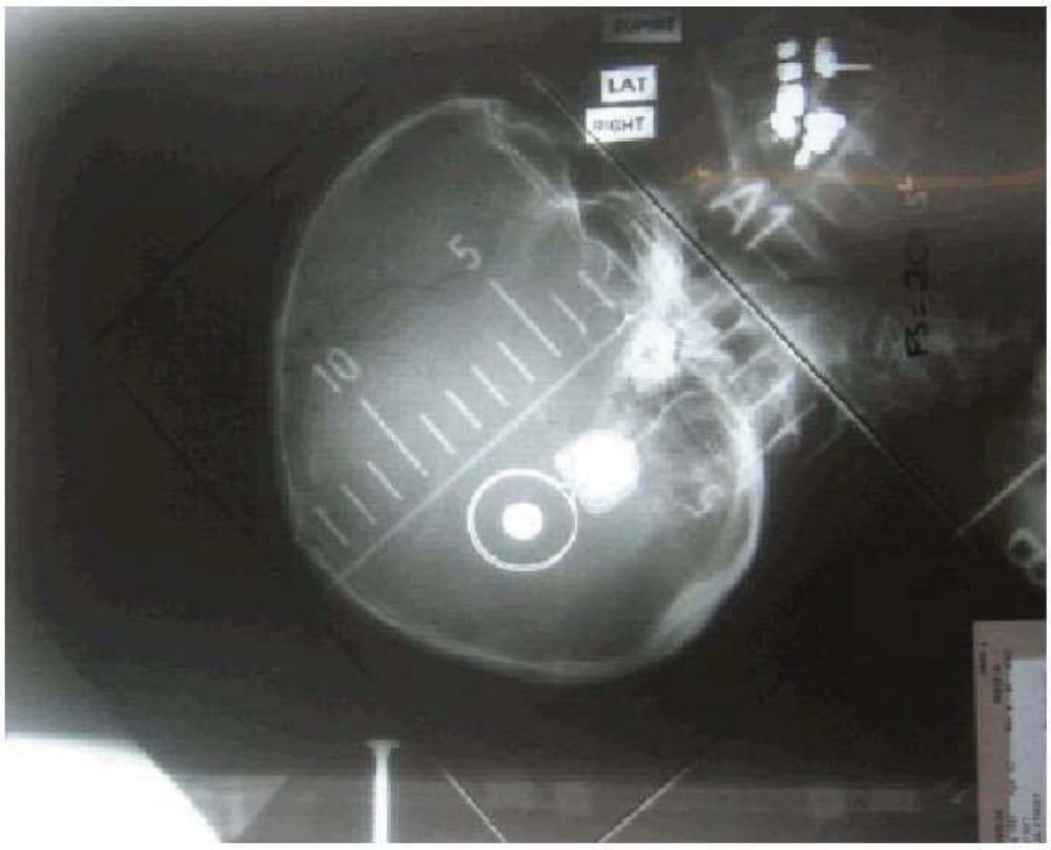

Figure 3. WBRT Quality Assurance. Plain simulation film showing isocentre on the caudal edge of the field to ensure that there is no divergence through the contralateral eye.

Simulation & Planning. The patient must be simulated supine, arms by the side, head resting on neck-shape as per department protocol. A personalised immobilisation mask can be used. Treatment Volume. The fields must cover the whole brain and include the cerebrum and cerebellum. The superior border of the field must be overshooting the skull by 2 cm to ensure adequate coverage. There must be adequate coverage of the intracranial contents by a margin of 1-2 cm. The caudal border needs to be angled to accomplish this and also avoid the eyes. The pituitary is usually included in the field by default. No effort should be made to cover it if it is not in field.

At least 25% of the patients will be audited, including the first 5 patients from each centre and a randomly selected patient from each subsequent 5 patients. Auditing will include an evaluation of MRI technique. The audit will be performed by a central radiologist with specialisation in MRI neuroradiology, with reference toa second central radiologist, similarly qualified, at the central radiologist's discretion. This second central radiologist will be blinded to the local and central radiologists' reports.

Operational considerations

Patients who are randomised to the observation arm of the study and have a recurrence of brain metastases will be able to crossover to WBRT at the treating physician's discretion. All participants will be monitored to death or to the closure of the trial.

6.1.5 Discussion

Feasibility

The possibility of conducting this trial was first discussed at a multi-disciplinary melanoma meeting in Sydney in 2004. A previous trial of WBRT for solitary brain metastases from mixed tumour types was abandoned by another Australian/New Zealand study group due to failure to accrue sufficient participants (TROG 98.05)(Roos et al., 2006). Given this background and the concern from some investigators about future WBRT trials, a feasibility study was undertaken to assess not only the number of potentially eligible patients but also the willingness of surgical and medical oncologists to have their patients with melanoma randomised to WBRT or not. The trial protocol was presented and critiqued at numerous scientific meetings both nationally and internationally, to multi-disciplinary melanoma treatment centres, and to neuro-oncology groups. There was broad agreement that the trial was needed to answer several fundamental questions and international participation was deemed essential for recruitment success. At present there are three participating countries: Australia, Norway and the United Kingdom. As of the 31st March 2012, 78 patients were randomised.

Registration

This trial is registered with the Australia and New Zealand Clinical Trials Registry (ANZCTR) #ACTRN12607000512426

6.1.6 Results

As at May, 2012, 79 patients have been randomised. As above the first interim analysis will take place one year after the randomization of 100 patients.

6.1.7 Conclusion

The candidate initiated and has driven this project and will continue to do so for the benefit of skin patients in his role as international principal investigator of the trial. The project is relevant to the thesis. It is aimed at a controversial question in melanoma, one of the worst skin cancers. The advance will be to answer this question and several interesting side questions. The therapeutic ratio will be maximized by selecting which patients need radiation treatment.

Section 6.2 Volumetric Modulated Arc Therapy (VMAT)

6.2.1 Preamble

To increase the therapeutic ratio in all cancers but also skin, more radiation needs to be delivered to the volume at risk of tumour and less to volumes not at risk that contain normal tissue. This conformality of dose can be done with IMRT but this takes up valuable linear accelerator time. There is a new technology called volumetric modulated arc therapy (VMAT) that has even better conformality of dose and takes the same time as normal treatment done with 3DCRT. At this stage the Australianauthority has declined to look at VMAT as a way of upgrading from 3DCRT. This publication was written by the candidate as the person in Australia most experienced with VMAT in order to show its superiority from a logistics point of view. We found that VMAT is significantly superior to IMRT. We produced this paper in record time in order to add to the debate. It is the only publication from Australia that includes patients actually being VMAT treated. This project provides local peer reviewed data to further the claims of VMAT as the preferred new radiation technology. The candidate was responsible for the design, data collection, analysis and interpretation of data; drafting, revision and submission of the article. The project is relevant to the thesis. We hope to be able to use VMAT to treat skin cancer especially brain metastases from melanoma. VMAT will enable simultaneous integrated boost (SIB) which delivers a stereotactic radiotherapy dose to the macroscopic lesions, a lesser dose to the rest of the brain that will be sufficient for microscopic disease and sparing the hippocampus, thought to be the organ responsible for short term memory and the most sensitive to radiation (Hsu et al., 2010).

6.2.2 Background

Radiotherapy technology is expanding rapidly. Newer technologies such as IMRT enable better radiation dose conformality to the target volume compared with 3DCRT. Better dose conformalitymeans that the dose of radiation to the volume requiring treatment can be escalated, thereby increasing cancer control. More volume can also be treated safely, while simultaneously decreasing the dose to surrounding radiation-sensitive normal tissues, thereby decreasing radiotherapy toxicities.

These technologies have been slow to be embraced in the Australian setting compared to other developed countries for various reasons. For example, IMRT has been

astandard therapy in the United States from mid-1995,whereas in Australia it is still not offered in every department and even then is reserved for special situations, for example, radical re-treatments and paediatric cases. However, there have been recent developments ata governmental level to investigate whether conventionalIMRT has benefits over 3DCRT. This project will ensure that increased government reimbursement for therapies is based on proper evidence. This process has been followed before with success (Foroudi, Lapsley, Manderson, & Yeghiaian-Alvandi, 2000).

In the meantime, IMRT technology has evolved even further. IMRT technology can now be delivered in a more efficient manner via VMAT. VMAT technologies may also be safer. External beam radiotherapy is delivered by a certain number of machine monitor units (MUs), a measure of machine radiation output. MUs are important as second cancer risk in patients treated with radiotherapy is proportional to how many MUs are needed per treatment course(Hall, 2006; Ruben et al., 2008).

The efficiency of VMAT has enabled the expansion ofIMRT-like techniques to routine treatments and not rationed to only rare situations. The Mater Hospital in Sydney was the first centre in the state of New South Wales (NSW) of Australia to treat with VMAT. This was possible following the installation of a new Varian® 21iX linear accelerator, which delivers VMAT under the tradename of Rapid Arc® (RA). The department went directly from treating with 3D to RA. Over 350 patients have now been treated with this new technology in this centre. This study is an audit of the RA experience to ensure that the newer therapy is recommended with proper evidence.

6.2.3 Methods

The audit is of the first thirty consecutive prostate cancer patients that have been radically treated for prostate cancer by one radiation oncologist with RA.Data gathered for these prostate cancer patients included the indication for radiation therapy. This was either definitive radiation (74 to 78 Gy); or post surgery radiation (64 to 66 Gy); or post high dose rate brachytherapy(50.4 Gy). Also collected were total beam time, total MUs per course and acute rectal toxicities as per the RTOG criteria (Cox et al., 1995) up to six weeks post radiotherapy.

Plans were accepted by the treating radiation oncologist if the IMRT dose constraints for external beam radiotherapy for prostate cancer were met as per the current local guidelines as detailed in Table 7. These constraints are essentially from Emami et al (Emami et al., 1991).

Table 7: Rectal dose constraints for 3D and IMRT as per local guidelines (Emami et al., 1991)

Dose (Gy)	% of total Rectum receiving dose
40Gy	≤ 60% (≤35% with IMRT)
65Gy	≤ 40% (≤17% with IMRT)
70Gy	≤ 30%
75Gy	≤ 10%

Comparison with replanning

The RA patients treated with definitive external beam radiotherapy were then completely re-planned with 3D; and a conventional sliding window IMRT technique; and anew RA plan. The IMRT technique was with a seven field plan, RA was planned using two arcs. Planning was done by a dosimetrist, qualified and experienced in this type of planning, but not familiar with these particular cases. The planning system used was Eclipse® version8.6 and was imported into the treatment system usingMosaiq® version 2.00W9. The time taken for the dosimetristto plan for each of the techniques for each case was recorded. Quality assurance on a phantom was then performed by a qualified physicist as per local protocol using our in-house phantom. It was assumed that there was no need for a quality assurance of 3D.

The phantom was then treated. The default dose rate used was 600MUs per minute. MUs per fraction we recorded. The beam time from start to finish of each fraction for all acceptable techniques was recorded. The total beam time for each technique was computed by multiplying this time by the number of fractions. The number of fractions prescribed was the same for the patient independent of technique. These data were then compared and analysed for any significant difference.

Comparison of treatment cost between IMRT and RA

Economic remuneration data for treatment radiation therapists was gleaned from the current NSW award (NSWGovernment, 2008) (Table 8). This information on payment per hour allowed an item for treatment staff costs to be estimated. Labour costs were computed for the total course. It was assumed that the treating radiation therapists were on the lowest paid level qualified to perform the relevant duties. In our NSW system, this meant that the two therapists involved in the treatment, were level 4, grade 1, year 1; and level 2, year 1 respectively. The difference in cost between the techniques was computed by multiplying the total treatment beam times by the staff remuneration per hour. In arriving at the different costs, it was assumed that the only difference between the treatments was the total duration of beam-on time from start to finish of each fraction. It was assumed that patient setup time and position verification, usually with an IGRT technique, was the same independent of technique. The treatment costs of each technique were compared andanalysed for any significant difference.

Table 8: Costs of radiotherapy staff in the planning and treatment of cancer patients as per the NSW award of 2011. (NSW Government, 2008)

Position	$AUD/hr
Treating Radiation therapist - level 4, grade 1, year 1	$53.43
Treating Radiation therapist - level 2, year 1	$29.37
Total labour cost of treating team	$82.80

It was assumed that the following were the same independent of the technique: time spent by the radiation oncologist to perform contouring, plan acceptance and to see the patients in follow up; the costs of the different linear accelerators (as all new modern linear accelerators are now capable of 3D, IMRT and VMAT); and costs of linear accelerator commissioning by physics for the different techniques. The latter are not considered important between the techniques as commissioning is a one-off cost for these machines which have a working life of around 10 years.

Statistical analyses were conducted using the IBMSPSS Statistic 19.0 software package. Independent andpaired t-tests were used to compare mean values where appropriate. Two-tailed p-values < 0.05 were considered statistically significant.

6.2.4 Results

Thirty consecutive prostate cancer patients treated radically via RA by one radiation oncologist in our institution were found and their characteristics are detailed inTable9.

Table 9: Indication for radiotherapy, total beam times, monitor units and acute rectal toxicity of the first 30 prostate patients treated with RA.

Indication for radiation	No of patients	Total beam time (minutes)	Total monitor units	Acute bowel toxicity(RTOG Grade)
Definitive	8	186	23050	4 x grade 1, 1 x grade 2
Post HDRBT	9	132	16496	2 x grade 1
Post surgery	13	138	21136	1 x grade 1

HDRBT – High Dose Rate Brachytherapy

Eight of these RA patients, those treated with definitive external beam radiotherapy were re-planned with3D, conventional IMRT and RA techniques. None of the3D plans that were attempted were acceptable by the local guidelines as per Table 7 for the 3D criteria. Allthe RA and IMRT plans were acceptable according to PTVcoverage and the dose constraints for IMRT as detailed inTable7. Planning times between IMRT and RA (Table 10)were not significantly different (p = 0.792). There wassignificantly greater machine output (MUs) per fractionfor IMRT (1813.9, SD = 159.1) compared with RA (590.2,SD = 67.1); p < 0.001.

Table 10: IMRT and RA planning, and Motor units

Patient number	Planning Time (mins) p=0.792		MU's /fraction p<0.001	
	RA	***IMRT***	***RA***	***IMRT***
1	73	79	688	1589
2	75	82	589	1909
3	81	61	588	2025
4	85	74	506	1656
5	84	65	625	1898
6	48	72	544	1646
7	80	99	667	1889
8	87	67	515	1899

Total treatment times (hours) were significantly greater for IMRT (5.2, SD = 1.2) compared with RA (3.1,SD = 0.5); p = 0.001 as detailed in Table 12. This table also records the cost difference between the techniques using the data of Table 8. The average cost per patient for IMRT treatment ($ AUD 489.91, SD = $ AUD 107.53)was significantly higher than that of RA ($AUD315.66,SD = $ AUD 51.59), p = 0.001. The mean saving in cost for RA treatment was $ AUD 174.25 per patient (95%CI: $95.38-$253.11). This cost saving is only for the wages of the treating radiation therapy staff, based on the difference in the beam times between RA and IMRT. Theanalysed data of IMRT versus RA is summarized inTable11.

Table 11: Comparison of IMRT and RA for a matched cohort of eight patients.

Measure	IMRT	RA	P-value
Average Plan Time (minutes)	74.9	76.6	0.792
Average MUs (SD) (Units)	1813.9 (SD=159.1)	590.2 (SD=67.1)	<0.001
Average Treatment Time (SD)* (hours)	5.2 (SD=1.2)	3.1 (SD=0.5)	0.001
Average Treatment Staff Cost per Patient*	$ 489.91	$ 315.66	0.001

*Total time calculated for all fractions

Table 12: IMRT and RA treatment times and relative treatment staff costs

Pt No	Dose(Gy)/fraction	Total Treatment Beam Time (hours)		Difference in treatment (Time : hr/min; Cost : $)
		IMRT	*RA*	
1	78/39	4.72	2.57	2h 9m/$178.02
2	74/37	5.80	2.97	2h 50m/$234.50
3	78/39	4.98	3.00	2h/$165.60
4	74/37	5.92	3.18	2h 43m/$224.90
5	78/39	4.05	3.57	28m/$38.64
6	74/37	4.50	2.35	2h 9m/$178.02
7	78/39	7.48	4.05	3h 27m/$285.66
8	74/37	3.93	3.13	47m/$64.86

6.2.5 Discussion

In our audit, 30 prostate cancer patients treated radically with RA by one radiation oncologist were found to be treated with acceptable toxicity. In re-planning eight prostate cancer patients treated with definitive external beam, 3D was found to be incapable of covering a more modern radiotherapy volume even at the higher tolerances allowed with that technique. It is therefore definitely time for Australian radiotherapy to move on from 3D.

Modern radiotherapy volumes can be treated via conventional IMRT and RA, even at the more exacting dose constraints demanded by our local guidelines. There was no difference in planning times between these techniques. However, RA was significantly superior in terms of decreased monitor units and therefore safety as least as far as second malignancy risk is concerned (Hall, 2006; Ruben et al., 2008). RA also had a decreased treatment time, and so decreased treating staff time, and therefore costs. The average total beam time per radiotherapy course with IMRT was over two hours more than with RA. There was an average saving of treating staff costs for each patient of $AUD174 with RA overIMRT. RA cost only 64% of the treating staff cost of IMRT.The real saving is greater, as only the treating staff costs were computed, not the extra cost implicit inthe extra time needed for keeping the departmentopen with

administration and nursing staff etc, nor the extra capital costs for more buildings and machines that would be necessary to treat the same number of patients in a timely fashion. For interest we looked at a group of prostate cancer patients treated for the same indications by the same radiation oncologist and with the same machine with 3D before it was commissioned for RA. We found that the there was no difference in the average total beam time between the RA and the 3D groups ($p = 0.885$). RA then comparesfavorably with 3D from a logistical viewpoint with similar treatment times and therefore treatment costs. RA is preferred to 3D because of superior dosimetry. As previously mentioned, none of the 3D plans satisfied the dose constraints, whereas all the RA plans did. RA overall combines the superior dosimetry of IMRT, the logistics of 3D, and yet with a better safety profile.

RA efficiency means even more. Patients are on the hard accelerator bed for less time, so patient comfort is improved. There is less time for internal organ intrafractionmotion. Less treatment time per patient also leadsto better clinical flow. More indications for radiotherapycan be treated with this new technique. Even palliativeregimes can now access VMAT radiotherapy, e.g. whole brain radiotherapy with simultaneous integrated boost and hippocampal sparing (Lagerwaard et al., 2009). Our conclusion is that RAwas superior to the other modalities, even conventionalIMRT.

The finding of superiority of RA in this study is important in the Australian context. RA is just oneVMAT technology now available. Australian centres have been plagued by skilled staff shortages and waiting lists(Burmeister et al., 2010; Kenny & Lehman, 2004). VMAT can contribute to solving these problems as well as update our treatment complexity to the level expected of a developed country.

6.2.6 Conclusions

Thirty prostate cancer patients treated radically by one radiation oncologist with Rapid Arc® (RA), a type ofVMAT were treated with acceptable toxicity. When eight of these patients were re-planned, 3DCRTwas not capable of covering the volumes needed without exceeding local guidelines for toxicity.RA was significantly superior to conventional IMRT with more efficient total treatment times, less monitor units and with no increase in planning times. The average treatment staff cost per patient course

of radiotherapy was decreased from$489.91 to $315.66. RA combines the superior dosimetryof IMRT, the logistics of 3DCRT, and yet with a better safety profile.

Since submission of the thesis the applicability of this technique to skin cancer patients has been validated by further work by the candidate (Awad et al. 2013).

Part 6.2 Conclusions of Chapter 6

The two projects are about research now and for the future. Project *6.1* will provide evidence for WBRT in melanoma. At this stage, WBRT is given or withheld in melanoma on the basis of no specific randomized evidence. Project*6.2* will strengthen the case to provide cutting edge modern technology to the radiotherapy care of skin patients.

Once again the projects have reiterated the recurring themes of this work.

1. The need for communication – The international trial has only been built through effective communication especially in getting international sites, now in Norway and United Kingdom, on board.
2. The need for personalized treatment of skin cancer with radiotherapy – VMAT will be the personalized way of WBRT in the future.
3. The importance of clinical vigilance – Both studies owe their existence to a desire to establish robust evidence to back up our radiotherapy indications in skin cancer.

Other developing work connected with the themes of the thesis is being prepared for publication and includes:

- Fogarty, G. (2012). Increasing the Control of Skin Cancer in Australia. *International Journal Bioautomation*. Volume 16, number 1, pg 43-52

- Goh, R., Bova, R., & Fogarty, G.B. (2012). Cutaneous squamous cell carcinoma metastatic to parotid - analysis of prognostic factors and treatment outcome,*World Journal of Surgical Oncology*.2012, 10:117 DOI: 10.1186/1477-7819-10-117

CHAPTER 7 Conclusions of Thesis, Future Research and Summary

Part 7.1 Conclusionsof Thesis

The main purpose of the thesis has been to highlight the important role that radiotherapy has in the treatment of skin cancer. This has been achieved on the basis of 24 projects that have led to peer reviewed publications by the candidate. These have been linked by a reflection that has highlighted the contribution of each and discovered deeper important themes in skin cancer treatment. These themes really are the results or findings of the linking essay, and as such represent the conclusions of the overall thesis.

These conclusions are:

1. The need for communication within and without the multidisciplinary team treating skin cancers.
2. The need for personalized treatment of skin cancer with radiotherapy, given the great variety of patient, tumour and treatment factors.
3. The importance of clinical vigilance.

The contributions of the projects to these themes have been commented on in each chapter. There has been a growing momentum of the underlying importance of these themes in the radiotherapy care of patients with skin cancer as the thesis develops.

The thesis shows in particular that radiation treatment in skin cancer has a real place. The role of radiotherapy in skin cancer is undervalued in a global sense(Culleton et al., 2011). Australian radiation oncologists need to realize the enormous contribution they can make on a world scale to the care of patients with skin cancer given the amount of pathology in this country, and the acceptance our modality has amongst the skin cancer community.

Part 7.2 Further Research

This thesis brings additional value to the continuing research being done by the candidate. The projects described in chapter six have been influenced by the thesis conclusions.

For example, the *6.1 WBRT* project includes:

1. the need for communication within and without the multidisciplinary team. There has been to date an increasing number of conference presentations four in 2009, eight in 2010, 16 in 2011 in order to communicate this study to peers around the world. Eight of these were presentations at international conferences. An internet based video has also been made for patient education.
2. The need for personalized treatment of skin cancer with radiotherapy, given the great variety of patient, tumour and treatment factors. The WBRT trial has stringent inclusion and exclusion criteria that ensure that only patients in whom this treatment question will make a difference are incorporated.
3. The importance of clinical vigilance in the WBRT trial is seen in the quality assurance in the various trial specific tests – radiotherapy, pathology, radiology, neuro cognitive functioning. This will ensure that the trial has quality data and therefore ensures the reliability of the trial findings.

Also by way of example the *6.2 VMAT* study has been affected by the outcomes of this thesis. Research continues in this field by the candidate but with the following changes.

1.The need for communication within and without the multidisciplinary team. By virtue of this publication the candidate has been invited to assist in the application for recognition by Medicare of this treatment as a real cancer treatment in Australia.
2. The need for personalized treatment of skin cancer with radiotherapy. The technology will be also applied to the personalised treatment of skin cancer. The candidate presented at the last specialist College meeting (Cairns July 2012) an application of VMAT to cerebral metastases of melanoma so that patients will need just one course of radiotherapy with VMAT rather than two, the first with stereotactic radiosurgery followed by another for wholebrain radiotherapy.

3. The VMAT study is also imbued with the need to maintain clinical vigilance, another finding of the thesis. New technologies need to be run under the auspices of trials so that patient safety is safe guarded. The candidate, being the radiation oncologist with most local experience of VMAT is spear heading the first Australian trials of this technology with a collaboration with the radiation community in America. The first trials are always to assess clinic effect especially toxicity, for which clinical vigilance is paramount.

Further research is being contemplated. The candidate has been appointed the radiation oncology quality assurance person for a proposed trial in lentigo maligna, based in Sydney. He will ensure that the developing protocol embodies these thesis conclusions. He has submitted a publication on Merkel cell carcinoma that also embodies these principles.

Further research is vital. It is the best way of ensuring that skin cancer patients who can benefit from this tissue conserving treatment get it. It is vital that is done in Australia where there is a lot of pathology and a lot of experience that has yet to be converted into solid and reliable literature. It needs to happen sooner rather than later as skin cancer incidence, morbidity and mortality continue to rise.

Part 7.3 Summary

The main purpose of the thesis is to highlight the important role that radiotherapy has in the treatment of skin cancer. This is critically important in Australia which has the highest burden of skin cancer in the world.

There are two main components for assessment in this thesis. The first and major component is made up of projects that have led to peer-reviewed publications. Significant work was done during the candidature (Chapter 6). The second component is a reflection on these advances. This reflection is in the form of a linking essay that introduces and integrates the projects. The purpose of the reflection is to highlight the unique and important contribution of each project in the role of radiotherapy in skin cancer. As well as the work done during the candidature, the reflection is what is new in this thesis submitted for the award of Doctor of Philosophy.

Chapter one introduces the thesis. Twenty four projects were selected from the total published works of the candidate. The majority are first in world literature reports hence their successful passage through peer review. These projects were either practice changing or confirming, in their time.

These projects were selected according to the following criteria:

- They are relevant to the radiation treatment of patients with skin cancer.
- They represent an advance in skin cancer treatment – they are either a new discovery or new way of integrating current technology in the skin cancer setting.
- They have been deemed worthy of publication by peers so that this information may be made available to other physicians involved in the care of skin cancer patients

All the projects attempted to enhance the therapeutic ratio of treatment for the benefit of patients in the present and of the future. Additionally, the projects have shown that radiation is an effective treatment modality in the treatment of skin cancer when delivered correctly. Most projects owe their origin to astute observation of unexpected findings in the clinic. The projects were usually initiated by the candidate.

The quality of the projects is high as they have been published in a peer reviewed journals. These journals have respectable Impact Factors and are listed in the ERA Journal list of 2012. A number have been significantly cited in subsequent articles and open access publications have received significant hits. Chapter one also includes a focussed literature review. The basis of radiation therapy is explained especially the ability to conserve infield normal tissue. The therapeutic ratio has been shown to be a useful tool to evaluate advances.

Chapters two to five describe the contribution to the thesis of projects according to whether their advances are in the molecular area, are radiation techniques, are in the clinical area or the quality assurance/guidelines area. This classification is arbitrary but does reflect where the projects fit in clinical practice. Chapter six examines ongoing projects, with publications that were generated from these projects during the candidature.

Chapter seven concludes the thesis with a focus on the main messages of the thesis. They are:

1. the need for communicationwithin and without the multidisciplinary team treating skin cancers.
2. the need for personalized treatment of skin cancer with radiotherapy
3. the importance of clinical vigilance.

Future research continues with projects started during the candidature. These have already resulted in significant publications. These projects have now taken into account the conclusions from the thesis.

APPENDICES

Appendix A: Publications of Projects in This Thesis

Code	Short title	Long title	Page number
2.1	EGFR	EGFR in Skin SCC	31
2.2	MC1R	MC1R Skin Effects	32
2.3	Skin Gene	Skin Tumour Gene	34
3.1	Axilla	Skin Cancer and Axilla	40
3.2	Supra	RT of Supraorbital Nerve	41
3.3	Eye Tox	Eye Toxicity	42
3.4	Tech S	Skin RT Techniques Spring	42
3.5	Tech F	Skin RT Techinques Fall	42
3.6	Electrons	Skin Electrons	42
4.1.1	MRI	MRI Brain in Melanoma	49
4.1.2	PET	PET in Melanoma	50
4.1.3	PET Occult	PET Occult Primary	50
4.2.1	MelBrain	Melanoma in Brain	53
4.2.2	Delay	RT Delay in Skin Cancer	53
4.2.3	RT BCC	RT in Recurrent BCC	55
4.2.4	Ritux	Rituximab and Skin SCC	56
4.2.5	Recall	Radiation Recall	57
5.1	Chart Round	QA Chart Round	62
5.2	Skin Chart	Skin Chart Round	63
5.3	Peer	Peer Review	64
5.4	National	National Skin Guidelines	65
5.5	Skin Guidelines	Skin Cancer Guidelines	66
6.1	WBRT Mel	WBRT Melanoma	74
6.2	VMAT	VMAT	74

Note: Fulltext not include due to copyright restrictions.

Project Code	Full Citation of Corresponding Publication
2.1	Fogarty, G. B., Conus, N. M., Chu, J., & McArthur, G. (2007). Characterization of the expression and activation of the epidermal growth factor receptor in squamous cell carcinoma of the skin. *Br J Dermatol, 156*(1), 92-98. doi: 10.1111/j.1365-2133.2006.07603.x
2.2	Fogarty, G. B., Muddle, R., Sprung, C. N., Chen, W., Duffy, D., Sturm, R. A., & McKay, M. J. (2010). Unexpectedly severe acute radiotherapy side effects are associated with single nucleotide polymorphisms of the melanocortin-1 receptor. *Int J Radiat Oncol Biol Phys, 77*(5), 1486-1492. doi: 10.1016/j.ijrobp.2009.07.1690
2.3	Fogarty, G. B., & McKay, M. J. (2005). Multiple malignancies and immunological diseases after radiotherapy: a new tumour suppressor gene disorder? [Case Reports Letter]. *Clin Oncol (R Coll Radiol)*, 17(8), 668.
3.1	Fogarty, G. B., Cassumbhoy, R., Martin, J. M., Fay, M., & Ainslie, J. (2007). Technique for axillary radiotherapy using computer-assisted planning for high-risk skin cancer. [Evaluation Studies]. *Australas Radiol, 51*(3), 267-275. doi: 10.1111/j.1440-1673.2007.01729.x
3.2	Fogarty, G. B., & Cassumbhoy, R. (2005). RE: Another technique for radiation treatment of the supraorbital nerve. [Comment Letter]. *Australas Radiol, 49*(6), 522-525. doi: 10.1111/j.1440-1673.2005.01511.x
3.3	O'Dea, N., & Fogarty, G. (*in press for* 2012). A technique to minimize eye toxicity using megavoltage photon radiotherapy for skin cancers involving the orbit in cooperative patients. *Radiation Therapist (in press)*.
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3.6	Fogarty, G. B. (2007). Electron Technique for Treating Skin Cancer *Rad Therap, 16*(1), 1-4.

Note: Fulltext not include due to copyright restrictions.

4.1.1 Fogarty, G. B., & Tartaguia, C. (2006). The utility of magnetic resonance imaging in the detection of brain metastases in the staging of cutaneous melanoma. *Clin Oncol (R Coll Radiol), 18*(4), 360-362.

4.1.2 Fogarty, G. B., Mok, M., Taranto, A., & Murray, W. (2005). Positron Emmission Tomography in Cutaneous Melanoma Staging – a False Positive with Warthins Tumour. *Acta Oncol, 44*(1), 87-89.

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4.2.2 Fogarty, G. B., Burt, J., & Ainslie, J. (2006). Delay of post operative radiotherapy in high risk skin cancer can be associated with recurrence. [Letter].*J Plats Reconstr Aesthet Surg, 59*(2), 203-205.

4.2.3 Fogarty, G. B., & Ainslie, J. (2001). Recurrent basal cell carcinoma causing spinal cord compression. [Case Reports]. *ANZ J Surg,* 71(2), 129-131.

4.2.4 Fogarty, G. B., Bayne, M., Bedford, P., Bond, R., & Kannourakis, G. (2006). Three cases of activation of cutaneous squamous-cell carcinoma during treatment with prolonged administration of rituximab. [Case ReportsLetter]. *Clin Oncol (R Coll Radiol), 18*(2), 155-156.

4.2.5 Fogarty, G.B., Ball, D., & Rischin, D. (2000).Radiation recall reaction following gemcitabine. *Lung Cancer*, 33:299-302.

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5.2	Fogarty, G. B., & Ainslie, J. (2005). RE: Chart round in a skin radiotherapy unit. [Comment Letter]. *Australas Radiol, 49*(6), 526-527. doi: 10.1111/j.1440-1673.2005.01521.x
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5.4	Fogarty, G. B. (2008). Radiation Oncology and Metastases In T. Reeve (Ed.), *Basal cell carcinoma, squamous cell carcinoma (and related lesions) - a guide to clinical management in Australia*. Sydney: Cancer Council Australia and Australian Cancer Network.
5.5	Fogarty, G. B. (2006). Guidelines for radical radiotherapy in skin cancer. [Comment Letter]. *Australas Radiol, 50*(3), 286-287. doi: 10.1111/j.1440-1673.2006.01583.x
6.1	Fogarty, G., Morton, R. L., Vardy, J., Nowak, A. K., Mandel, C., Forder, P. M.,Thompson, J. F. (2011). Whole brain radiotherapy after local treatment of brain metastases in melanoma patients--a randomised phase III trial. [Clinical Trial, Phase III Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. *BMC Cancer*, 11, 142.doi: 10.1186/1471-2407-11-142
6.2	Fogarty G.B., Ng D., Liu G., Haydu L.E., Bhandari N., (2011). Volumetric modulated arc therapy is superior to conventional intensity modulated radiotherapy – a comparison among prostate cancer patients treated in an Australian centre. *BMC Radiation Oncology*, 6, 108. Accessed 5 September 2011 fromhttp://www.ro-journal.com/content/6/1/108

Appendix B: Letters of Support

Professor Lester Peters, Director Radiation Oncology, PMCC. Co-authored 3 projects.

To whom it may concern

I collaborated with Dr Gerald Fogarty in the following projects and the resultant publications:

Fogarty GB, Hornby C, Ferguson HM, Peters LJ. Quality assurance in a radiation oncology unit – the Chart Round Experience. Austral Radiol 2001; 45:189-194

Fogarty GB, Peters LJ, Stewart J, Scott C, Rischin D, Hicks RJ. The usefulness of fluorine 18-labelled deoxyglucose positron emission tomography in the investigation of patients with cervical lymphadenopathy from an unknown primary tumor. Head Neck 2003; 25(2):138-45.

Fogarty GB, Tartaglia CJ, Peters LJ. Primary melanoma of the oesophagus well palliated by radiotherapy. Brit J Radiol 2004; 77(924):1050-52.

Dr Fogarty deserved to be the first author on these papers as he made a substantial contribution to conception, design, analysis, interpretation of data, drafting, revising and final approval of the publications.

Yours sincerely

Production Note:
Signature removed prior to publication.

Lester J Peters AM MD FRANZCR FRCR
Professor of Radiation Oncology
Peter MacCallum Cancer Centre
Melbourne

Date: 5/10/2011

Professor Grant Macarthur, Director DNA Repair Laboratory, PMCC Co-authored 1 project.

Professor Grant McArthur
SMORGON FAMILY BUILDING
St Andrews Place
East Melbourne Victoria
Locked Bag 1 A'Beckett Street
Victoria 8006 Australia
Phone +61 3 9656 1954
Fax +61 3 9656 1408

WWW.PETERMAC.ORG
East Melbourne
Moorabbin
Box Hill
Bendigo

Production Note:
Signature removed prior to publication.

To whom it may concern
I supervised Dr Gerald Fogarty in the following project and the resultant publication.
Characterization of the expression and activation of the epidermal growth factor receptor in squamous cell carcinoma of the skin. GB Fogarty, N Conus, J Chu, G McArthur Br J Dermatol. 2007 Jan;156(1):92-8.
Dr Fogarty met all possible criteria as first author as he made a substantial contribution to conception, design, analysis, interpretation of data; drafting, revising and final approval of the publication.

Yours sincerely

Grant McArthur

Digitally signed by Grant McArthur
DN: cn=Grant McArthur, o, ou, email=grant.mcarthur@petermac.org, c=AU
Date: 2011.10.24 08:31:42 +11'00'

Professor Grant McArthur
Peter MacCallum Cancer Centre
Melbourne
Date: 24 October 2011

ABN 100 504 883

Professor Michael McKay, Director Radiation Biology Laboratory, PMCC Co-authored 2 projects.

To whom it may concern

I collaborated with Dr Gerald Fogarty in the following projects and the resultant publications.

Multiple malignancies and immunological diseases after radiotherapy: a new tumour suppressor gene disorder? GB Fogarty, MJ McKay. Clin Oncol (R Coll Radiol). 2005 Dec;17(8):668

Dr Fogarty deserved to be the first author as he made a substantial contribution to conception, design, analysis , interpretation of data; drafting, revising and final approval of the publication.

Unexpectedly severe acute radiotherapy side effects are associated with single nucleotide polymorphisms of the melanocortin-1 receptor. G.Fogarty, R.Muddle, C. Sprung, W. Chen, D.Duffy, R.Sturm, M.McKay. International Journal of Radiation Oncology, Biology, Physics. Epub Nov 23 2009. 77 (5): 1486-92

Dr Fogarty deserved to be the first author as he made a substantial contribution to interpretation of data, drafting, revising and final approval of the publication.

Yours sincerely,

Production Note:
Signature removed prior to publication.

Professor Michael McKay

Director

Lismore Centre

North Coast Cancer Institute

Date: 17/10/11

Dr Fogarty is an energetic & highly useful collaborator; he has an impressive rate for contributing to publications.

Dr Jill Ainslie, Skin Cancer Unit, PMCC. Co-authored 4 projects

To whom it may concern

I collaborated with Dr Gerald Fogarty in the following projects and the resultant publications.

A technique for axillary radiotherapy for regional control of high risk skin cancer GB Fogarty, R Cassumbhoy, JM Martin, M Fay, J Ainslie Australas Radiol. 2007 51 (3), 267–275

Delay of post operative radiotherapy in high risk skin cancer can be associated with recurrence. GB Fogarty, J Burt, J Ainslie J Plast Reconstr Aesthet Surg. 2006;59(2):203-5.

Chart round in a skin radiotherapy unit. GB Fogarty, J Ainslie Australas Radiol. 2005 Dec; 49(6):526-7.

Recurrent basal cell carcinoma causing spinal cord compression. GB Fogarty, J. Ainslie: ANZ J Surg Feb 2001 Vol 71; 2: pgs 129-131.

Dr Fogarty deserved to be the first author as he made a substantial contribution to conception, design, analysis , interpretation of data; drafting, revising and final approval of the publications.

Yours sincerely

Production Note:
Signature removed prior to publication.

Dr Jill Ainslie

Staff Specialist

Peter MacCallum Cancer Centre

Melbourne

Date:

Appendix C: Other Publications by the Candidate

Section C.1 – Publications accepted during time of candidature (2011-12)

There are eleven in this section

Fogarty, G. Increasing the Control of Skin Cancer in Australia. *International Journal Bioautomation*. (2012). Volume 16, number 1, p43-52.

Fogarty, G., Morton, R.L., Vardy, J., Nowak, A.K., Mandel, C., Forder, P.M.,&Thompson, J. F. (2011). Whole brain radiotherapy after local treatment of brain metastases in melanoma patients--a randomised phase III trial. [Clinical Trial, Phase III Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. *BMC Cancer*, 11:142. doi: 10.1186/1471-2407-11-142

Fogarty, G.B., Ng, D., Liu, G., Haydu, L.E., &Bhandari, N. (2011). Volumetric modulated arc therapy is superior to conventional intensity modulated radiotherapy – a comparison among prostate cancer patients treated in an Australian centre. *BMC Radiation Oncology*, 6:108. Accessed 5 September 2011 fromhttp://www.ro-journal.com/content/6/1/108

Goh R, Bova R, Fogarty GB. Cutaneous squamous cell carcinoma metastatic to parotid - analysis of prognostic factors and treatment outcome.World Journal of Surgical Oncology. (2012).10:117 World Journal of Surgical DOI: 10.1186/1477-7819-10-117

Australia and New Zealand Melanoma Trials Group (ANZMTG). (October 25, 2011). *ANZTMG Whole Brain Radiotherapy in Melanoma Trial* [Video file]. Retrieved from http://www.youtube.com/watch?v=7gxrA7vNWPE

Carlino, M.S., Fogarty, G.B., &Long, G.V. (2012). Treatment of melanoma brain metastases: a new paradigm. *Cancer J*, 18(2):208-12.

Hong, A., & Fogarty, G. (2012). Role of radiation therapy in cutaneous melanoma. *Cancer J,* 18(2):203-207. doi: 10.1097/PPO.0b013e31824b241a

Hong, A., Fogarty, G., &Izard, M. (2012). The Role of Radiation Therapy in the Management of Metastatic Melanoma in the Brain.*Int. J. Surg Onc,*6. doi: 10.1155/2012/294735

Hong, A., Martin, A., Armstrong, B.K., Lee, C.S., Jones, D., Chatfield, M.D., Zhang, M., Harnett, G., Clark, J., Elliott, M., Milross, C., Smee, R., Corry, J., Liu, C., PorcedduS., VaskaK., VenessM., MorganG., FogartyG., VeiversD., Rees, G., & Rose, B. (2012). Human papillomavirus modifies the prognostic significance of T stage and possibly N stage in tonsillar cancer, *Annals of Oncology*,2013 Jan;24(1):215-9.

Seymour, E.L., Downes, S.J., Fogarty, G.B., Izard, M.A., & Metcalfe, P. (2011). In vivo real-time dosimetric verification in high dose rate prostate brachytherapy. [Evaluation Studies]. *Med Phys,* 38(8):4785-4794.

Thompson, J.F., Hong, A., & Fogarty, G. (2012). Publication and Interpretation of Clinical Trial Results: The Need for Caution. [Journal article]. *Ann Surg Oncol,* 5:5.

Section C.2 – Other publications

There are nine in this section

Chan, J., Fogarty, G., Ball, D., Wright, G., & Slavin, J. (2005). Tracheo-innominate artery fistula following stenting, surgery and radiotherapy for large glomus tumor of the chest. [Case ReportsLetter]. *ANZ J Surg*, 75(4):252-253. doi: 10.1111/j.1445-2197.2005.03341.x

Discover Radiation Oncology [Video file].(December 20, 2010). Retrieved from http://www.youtube.com/watch?v=xJUrbVgHgtE.

Fogarty, G.B., Cassumbhoy, R., & Ball, D. (2006). Magnetic resonance imaging changes in synchronous bilateral progressive facial nerve weakness. [Case Reports]. *J Thorac Oncol*, 1(5):487-488.

Fogarty, G.B., & Fay, M. (2004).*Syllabus for MMedRad 3389, Module 4 - "The Principles of Radiation Oncology Relevant to the Role of the Radiation Therapist"*.(Available from the Department of Medical Imaging and Radiation Sciences, Monash University, VICTORIA)

Fogarty, G.B., Tartaglia, C.J., & Peters, L.J. (2004). Primary melanoma of the oesophagus well palliated by radiotherapy. [Case Reports]. *Br J Radiol,* 77(924): 1050-1052.

Fogarty, G., Turner, H., & Corry, J. (2001). Plasma cell infiltration of the upper aerodigestive tract treated with radiation therapy. [Case Reports]. *J Laryngol Otol,* 115(11):928-930.

Izard, M.A., Haddad, R.L., Fogarty, G.B., Rinks, A., Dobbins, T., & Katelaris, P. (2006). Six year experience of external beam radiotherapy, brachytherapy boost with a 1Ci (192)Ir source, and neoadjuvant hormonal manipulation for prostate cancer. [Evaluation Studies]. *Int J Radiat Oncol Biol Phys,* 66(1):38-47. doi: 10.1016/j.ijrobp.2006.04.002

Middleton, M., Medwell, S., Bennie, N., & Fogarty, G.B. (2005). Unilateral lens sparing retro orbital irradiation in benign disease using multileaf collimators. *The Radiographer,* 52(1):14-6.

O'Lone, E.L., Park, E.K., Sandrini, A., Fogarty, G.B., & Yates, D.H. (2009). Early detection of malignant pleural mesothelioma through measurement of soluble mesothelin-related protein and positron emission tomography. [Case Reports]. *Med J Aust,* 190(3):158-159.

Appendix D: Clinical Trials Activity of the Candidate

No.	Year	Title
9	2005-current	Principal International Investigator, Phase 3 International Randomized Trial "WBRT: Whole Brain Radiotherapy following local treatment of intracranial metastases of melanoma – a randomised phase III trial" a collaboration between ANZMTG, TROG, SNOG and NHMRC CTC. Australia and New Zealand Clinical Trials Registry (ANZCTR) # - 12607000512426. Retrieved from http://www.anzmtg.org/documents/Background%20and%20rationale%20-%20WBRT.pdf
7	2008-current	Member of Trial Management Committee and Principal Investigator at St Vincent's for TROG 05-01 - Post-Operative Concurrent Chemo-Radiotherapy versus Post-Operative Radiotherapy in High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck - The 'POST' Study. ACTRN12607000146493
6	2005-current	Principal Investigator at Mater for ANZMTG 1-02 / TROG 02-01. A randomised trial of surgery vs surgery plus radiotherapy for regional control in patients with completely resected macroscopic nodal melanoma.
5	2007-current	Principal Investigator at St Vincent's Hospital. Impact of HPV infection on radiosensitivity in Head and Neck SCC.
4	2006-current	Co-investigator for NCIC CTG SC.20 / TROG 03.08: A phase III international randomised trial of single versus multiple fractions for re-irradiation of painful bone metastases. St Vincent's Hospital, Victoria St, Darlinghurst Sydney
3	2006-	Co-Investigator ZEST trial: A double blind placebo controlled trial of Zoloft's effects on symptoms and survival time in

	current	advanced cancer, Mater, Crow's Nest Sydney
2	2006-current	Co-Investigator Cancer Pain Education for Patients, Mater, Crow's Nest. Sydney
1	2005-current	Co-Investigator IBIS -II DCIS: A comparison of anastrazole and tamoxifen in post menopausal women who have treated for hormone sensitive ductal carcinoma in situ. Mater, Crow's Nest, Sydney

Appendix E: Bibliography

Asser, O.S., Fischbein, N.J., Caputo, G.R., et al. (1999) Metastatic head and neck cancer: role and usefulness of FDG PET in PET in Cervical Adenopathy from an Unknown Primary locating occult primary tumours. *Radiology*,210:177-181.

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fistula following stenting, surgery and radiotherapy for large glomus tumor of the chest. [Case Reports Letter]. *ANZ J Surg*, 75(4), 252-253. doi: 10.1111/j.1445-2197.2005.03341.x

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