



Recent Australian Advances in the Radiotherapy of Skin Cancer

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Abstract: This paper is an expository report on some recent and current research on clinical problems in the control of skin cancer in Australia, which has a high prevalence and an increasing incidence of this disease.

Keywords: Skin cancer, Therapeutic ratio, Melanoma, Basal cell carcinoma, Cutaneous squamous cell carcinoma, Positron emission tomography, Axillary fields, Lymphadenectomy, Nevoid basal cell carcinoma syndrome.

Introduction

The most common malignancy in the human person is skin cancer and the incidence is increasing [33]. 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). Australia has the highest incidence of skin cancer in the world, at nearly four times the rates in Canada, the USA and the UK. The incidence of skin cancer is five times that of any other cancer in the country [34]. On an annual basis, over 10 600 Australians will develop a melanoma [2].

Furthermore, the incidence of skin cancer in Australia is rising. From 1985 to 2002, age-standardized incidence rates of BCC and SCC had increased by 35% and 133% respectively [34]. 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 [1].

Skin cancer is also 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 [4]. Most skin cancers are treated at an early stage with therapies such as surgery, cytotoxic or immunogenic skin lotions. Radiation is also an effective treatment modality in many scenarios of the treatment of skin cancer [29].

The therapeutic ratio

A fundamental concept in cancer management is the therapeutic ratio [28]. The therapeutic ratio is that ratio of tumour cure to normal tissue toxicity. The aim of all cancer therapy is to maximize 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 new technologies 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 maximizing the therapeutic ratio is expressed more simply as improving patient outcomes. Hence the statement that a new technology is embraced as it delivers a better outcome.

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. The paradigm situation is breast conservation, now the most common reason for prescribing radiation on a world scale [27]. Tissue conservation plays a role in other tumor types such as head and neck (larynx preservation) [25], SCC anus (sphincter preservation) [30] and also skin cancer, with preservation of normal skin within the treatment volume [24]. 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 [32]. This allows for improved conformality of radiation dose to the volume at risk of disease yet sparing the unnecessary irradiation of normal tissue so reducing toxicity [7]. This is not always easy as external beam radiotherapy often needs to enter and exit the body through normal tissues in order to cover tissue at risk of tumour.

Methodologies

The various types of projects, on which the research in this paper is based, and the associated methodologies are listed in the Table 1. The row headings are the numbers in the reference list at the end of this paper. Other ways of reaching clinical decisions may be found in [6, 30, 32, 35].

New technologies

New technologies can play a significant role in decreasing skin cancer related mortality, morbidity and cost. New technologies can be considered by whether they involve molecular, clinical, imaging or therapeutic advances. Molecular advances are examined in a laboratory setting and include technologies that bring new understanding to how things work at a fundamental biochemical level.

The new technologies are new discoveries or new ways of integrating current technology that impact on the outcomes of skin cancer patients. 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 the development of these new technologies. The rate of discovery and utilization of new technologies in radiotherapy are accelerating [3, 26, 31].

Table 1.

Ref	Randomized trial	Laboratory study	Retrospective series	Audit	Case study	Planning
8					×	
9				×		
10			×			
11				×		
12		×				
13					×	
14						×
15			×			
16			×			
17			×			
18						×
19			×			
20						×
21			×			×
22		×				
23		×				
24	×					

Molecular analyses (see section (a) below) investigate the most foundational mechanisms in cancer research. 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 [5]. Advances in radiation techniques are essential to maximizing the therapeutic ratio (see section (b)). Clinical advances (see section (c)) are new technologies that impact on actual clinical practice; that is, what actually happens at the bed side. Clinical Imaging advances cover new ways of using investigations that evaluate tumour or normal tissues to guide therapy. Treatment advances describe how these new technologies specifically affect an outcome. Timing of clinical interventions especially in the multidisciplinary era is important for disease control. These divisions can seem artificial; all worthwhile new technologies should lead to a specific advance in the therapeutic ratio. However, it is a useful division to enable comparison of current versus new and better modalities.

Some related research results

(a) The molecular analyses were all translational projects. The first concentrated on cutaneous squamous cell carcinoma. The Peter MacCallum Cancer Centre (PMCC) in Melbourne, Victoria, Australia, is a tertiary referral centre for locally advanced cutaneous squamous cell carcinoma (cSCC) from that State. This study was 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. For the study [22] we used a quantitative western block technique called the LiCor system that was new to our laboratory. We compared these results to immunohistochemistry 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 paper led to recognition in our institution 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.

The second project [23] 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 project investigated the relationship of SNPs of MC1R and their relationship with unexpectedly severe radiation reactions. The MC1R genotype of a cohort of Australians with unexpectedly severe acute and/or late skin reactions from radiotherapy for cancer ($n = 30$) was analyzed. 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 “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 ($p = 0.003$). 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 ($p = 0.043$). 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 radiotherapy.

The third project [12] found that patient in question was for the NBCCS genetic test. We postulated that they may represent a new tumour suppressor gene mutation that impacts on immunity as well as malignancy and development.

(b) Advances in radiation techniques are essential to maximizing the therapeutic ratio. These techniques [14, 18, 21] were developed in an era of three dimensional conformal radiotherapy (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 intensity modulated radiotherapy technique (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 (D_{max}) and the attenuation in tissue after the maximum dose point are dependent on the generating energy. This beam gradually attenuates in tissue

after the D_{max} . 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 centimeters. 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.

This is a collection of 3 projects of techniques for skin cancer treatment [14, 18, 20]. 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 definite radiotherapy in our country. We realized that there was a need and a duty to inform other units about our home grown techniques. The third 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. Further enquires after the publication of the first article led to the publication of the rest. Our techniques were well accepted. In the papers clinical considerations were stressed. Other units did implement some of our techniques. We knew this because of the feedback which led to the second paper in this section. Most importantly, linear accelerator time was used more efficiently.

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 tumor control, this requires knowledge of tumour type patterns of spread, details of interaction with other modalities eg surgery and the avoidance of dose limiting normal tissues. It also requires knowledge of the possibilities and limitations of different radiation modalities. Experience is key. This collection of techniques is an attempt to pass on the experience gained. They 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 [10, 13, 19, 21].

This paper [20] grew out of the need for standardization 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. This was becoming a problem when the quality assurance was being done on the first few cases. Standardization of radiotherapy axillary field planning was becoming a problem in our trial. I noticed that there were some cases treated in our institution off trial with axillary fields not consistent with the PMCC skin unit policy that had not done well. I decided to do a retrospective review. The paper describes the technique used at PMCC, the lead centre of the trial and details the outcomes in a series of patients. The trial has since closed and has shown a significant benefit for the addition of adjuvant radiotherapy in this setting. With a follow up of over 2 years, the technique had more than a 90% (10/11) regional control in the group of patients treated radically. Both of the radical patients who were not treated according to the technique had regional failure.

(c) Clinical advances can be considered from the imaging and treatment perspectives. Imaging advances have underpinned many advances in radiotherapy. Improving the therapeutic ratio in the radiotherapy of skin includes accurate staging. These studies [10, 13, 19] concern accurate staging. Better staging has meant that patients receive the treatment that

they need; for example, patients with disseminated disease found on a PET scan may avoid a useless major local treatment. Treatment related projects 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. Three projects were about interactions of surgery and radiotherapy. The first project [17] found that a delay in postoperative radiotherapy for skin cancer was associated with a worse. The second [8] describes what can happen when radiotherapy is not offered for a positive perineural deep margin following resection of a large skin cancer 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 radiotherapy. The third project [16] 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 projects emphasize the need for appropriate referral and understanding of tumour biology between the multidisciplinary teams. The key point of these projects 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.

Concluding comments

Better treatments are only effective if they can be properly delivered. Quality assurance measures how effectively treatments are delivered. New technologies may be ineffective if delivered incorrectly, and a worse therapeutic ratio for the technology may be unfairly inferred. QA can be applied to both structure and process and related to treatment outcome [9, 11]. 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. Quality assurance of process is therefore essential in treatment delivery. These programs are in themselves a new technology 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.

This paper has focused on increasing the control of skin cancer. The new technologies can be characterized by being mainly about molecular advances, or about clinical applications. Others can be seen as advances in imaging or treatment. All of them are interdependent. A better molecular understanding of decreasing toxicity will be manifested as a better clinical outcome. Better imaging is judged by its better treatment result.

Analyzing the impact from molecular, clinical, imaging and treatment perspectives has reflected the structure of the responsible medical disciplines. Studying how new technologies are applied to through quality assurance completes the journey from idea to safe routine clinical practice. The development of guidelines [15] 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 collaborative ongoing multicentre research.

These studies have led to clarification of the role of new technologies, and were either practice changing or confirming, in their time. The author had significant involvement in the discovery, design and implementation. All the projects attempted to enhance the therapeutic ratio of treatment for the benefit of patients in the present and of the future. Clinical

Perspectives include understanding the importance of timing and interaction of therapies. Different treatment modalities will lead to better outcomes if instituted in the correct sequence and scheduling. The discovery of new interactions between therapies is only possible if clinicians have a high index of suspicion in the clinic. These discoveries call for better multidisciplinary interaction [12, 22].

Additionally, the projects have shown that radiation is an effective treatment modality in the treatment of skin cancer when delivered correctly. These papers show in particular that radiation treatment in skin cancer has a real place. Radiation is a modality that can help maximize the therapeutic ratio, lends itself to translational medicine and to a personalized approach to decrease mortality and cost.

The studies outlined here are already generating new research to aid skin cancer patients of the future. Whole brain radiotherapy (WBRT), after local treatment of brain metastases in melanoma, is controversial, and so the author has set up a trial to investigate this question [23]. The trial has received Australian Federal funding of one million dollars to date and has accrued 78 of a needed 200 patients in 3 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 at last provide level one evidence on how to treat in this situation. This project is pivotal to the future of whole brain radiation treatment in melanoma. The author initiated and has driven this project and will continue to do so for the benefit of skin patients in his role as one of two radiation oncologists at the Melanoma Institute of Australia.

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