CANCER FORUM



July 2012

Volume 36 Number 2

FORUM: Radiotherapy

Australian behavioural research in cancer

Medical Oncology Group of Australia Cancer Achievement Award

Cancer Council Australia

www.cancerforum.org.au

CANCER FORUM

Cancer Forum is produced by Cancer Council Australia for health professionals working in cancer control. It is the official journal of the Clinical Oncological Society of Australia.

Editorial Policy

The policy of Cancer Forum is to provide a forum for debate and the exchange of medical, scientific, political, social and educational comment related to cancer research, treatment, prevention and control. Cancer Forum invites submissions of original research articles, reports and letters relating to these themes.

Authors are advised to read the "Information for contributors" printed on the inside back cover.

The views contained in this journal are not necessarily those of Cancer Council Australia and the Cancer Council does not accept responsibility for the information contained herein.

Cancer Forum is published in March, July and November and is available online at www.cancerforum.org.au

Cancer Forum
GPO Box 4708
Sydney NSW 2001

Telephone: 02 8063 4100
Facsimile: 02 8063 4101
Email: info@cancerforum.org.au
Website: www.cancerforum.org.au

Design by Wolff Design

Printed by SOS Print & Media

July 2012
Volume 36 Number 2
ISSN 0311-306X



CANCER FORUM

Contents

Radiotherapy

RADIOTHERAPY – MAINTAINING FOCUS THROUGHOUT THE CANCER JOURNEY

Gerard Adams[1] and Sandro V Porceddu[1,2]
1. Department of Cancer Services, Princess Alexandra Hospital, Brisbane, Queensland.
2. University of Queensland, Faculty of Health Sciences, School of Medicine, Brisbane, Queensland.
Email: Gerard_Adams@health.qld.gov.au and Sandro_Porceddu@health.qld.gov.au

Unfortunately, one in two Australians is destined to suffer from cancer in their lifetime.[1] Fifty per cent of them should receive radiotherapy at some point during their treatment.[2] Any person without a personal experience of radiotherapy is, at some point in their life, likely to watch a family member or close friend undergo treatment, yet specific knowledge of radiotherapy and its application in modern practice is not well understood in either the lay or health professional communities.

In this edition of *Cancer Forum* we aim to give some insight into important issues, surrounding modern radiotherapy practice. While far from comprehensive, we will touch on many key issues including the development of technologies that allow better identification and delivery of radiation to the target with minimisation of dose to normal tissues, as well as novel applications of radiotherapy that can assist in tumour control while retaining organ function. We also discuss the challenges in dealing with the after effects of treatment in long-term survivors, along with the balancing act required to optimise treatment for those not destined to survive long term.

There have been major advances in our ability to deliver radiotherapy over the last few decades. Matthew Foote gives a summary of the technical developments that allow us to prescribe plans that are highly conformal to the target volume.[3] The sharp drop-off in dose at very short distances from the target has the dual potential of allowing more dose to the tumour while sparing surrounding normal tissues. While evidence showing that adoption of these techniques has resulted in improved survival figures is lacking, the clear evidence of reduced toxicity in itself merits their use in modern practice. However, such highly conformal radiotherapy planning can be counterproductive unless it is coupled with confident and precise identification of the target at both the planning and delivery stages.

Mike Fay describes how the emergence of new functional imaging modalities – typically with ^{18}F-deoxyglucose PET – has aided our ability to accurately define the target volume.[4] In the past, when radiotherapy targets were delineated with the aid of anatomical imaging, initially x-ray and later CT scans, there was more uncertainty in differentiating tumour and normal tissues. Less conformal plans probably helped reduce the chances of a geographical miss. Although PET has its own limits of resolution, under some circumstances it can be used to precisely identify the target more accurately, allowing the confident application of highly conformal plans with less chance of a geographical miss.

Throughout a course of treatment there may be changes to the tumour volume, organ shift and changes in body shape (eg. weight loss). This can create further uncertainty in the accuracy of radiotherapy delivery. Tomas Kron describes how a third aspect of radiotherapy – accurate and consistent delivery – has developed.[5] The concept of image guided radiotherapy (IGRT) relates to the ability to identify the target volume at the time of treatment delivery, with the option to adapt the beam depending on findings. As discussed in this article there are many important aspects to take into account when choosing the appropriate method of IGRT. These include the indication for radiotherapy, financial cost, time and additional radiation dose.

It is clear that the developments described so far are dependent on each other and that the delivery of modern highly conformal radiotherapy techniques would be neither possible nor desirable unless coupled with improvements in target identification and IGRT.

Bryan Burmeister explores the complex process of radiotherapy,[6] which relies on the work of a highly skilled team that includes radiation oncologists, radiation therapists and medical physicists. Safe and accurate delivery of treatment for patients relies on the skills of all individuals, with many potential sources for error. Coupled with this is the importance of consistency in delivery between departments. Good quality assurance methods are essential to ensure consistent high quality radiotherapy within a department, as well as between departments at a national and international level. Radiotherapy is perhaps unique in its complexity and this paper highlights how failure to provide high quality radiotherapy plans can result in significantly poorer outcomes for patients.

In an era where the availability of technology described in the first three papers appears to be expanding exponentially, some objective evaluation of the relative merits of the various options is necessary.[3-5] Improvements in the delivery of radiotherapy over the last few decades have resulted in the ability to use it as the backbone of non-surgical cancer treatments aimed at curing cancer

while maintaining organ function. Organ preserving radiotherapy treatments with reasonable chances of cure are now possible for head and neck,[7] oesophagus,[8] lung,[9] prostate,[10] bladder,[11] anal,[12] cervix,[13] and vulval cancers.[14] Not all developments however, rely on expensive high end technology. Arthur Sun Myint and colleagues describe the use of fairly simple (and inexpensive) technology that can be applied to a selected population of early low rectal cancers.[15] This technology relies on the direct application of very high doses – 110 Gy to the tumour using superficial x-rays. The properties of these x-rays mean that the dose falls off very rapidly over only a few millimetres, sparing surrounding tissues from significant dose. Clearly this technology is only suitable for use in a small, select group of patients. However, wider application of these techniques has the potential to not only save patients from the morbidity and mortality of aggressive surgery – but also to achieve significant cost savings for the health service as a whole.

Another aspect of this paper is discussion of a "wait and watch policy for complete responders." While we classify various tumour types as "radiosensitive" or "radioresistant", it is clear that within any tumour group there is a wide spectrum of responses in individual tumours. There is ongoing research trying to identify factors that predict response – but currently this is largely poorly understood. Nevertheless, modern treatment strategies are moving away from a one size fits all approach towards an individualised approach, whereby a predictable marker of good response (such as favourable response on post-treatment MRI scan) can be used to safely select patients who may avoid morbid surgery. Although currently only around 10% of patients undergoing chemoradiation for rectal cancer fulfil the wait and watch criteria,[16] improvements in imaging and or therapy – eg. more potent chemoradiation - may mean that in the future even more patients with rectal cancer will be able to be spared surgery.

Such tailored, individualised treatments are not new to the world of radiotherapy. Susan Wiltshire and Andrew Potter discuss provisions for palliative radiotherapy in modern practice.[17] A wide range of total dose and number of fractions are possible. The art of radiotherapy is selecting the "correct" schedule for individual patients. This takes into account symptoms, location of metastases, nature of primary lesion, time since diagnosis or progression, as well as other factors such as the workload of the department. It is encouraging to see that such a large body of high quality research has been undertaken in an area that some may consider is less important than potentially curative treatment. Also as shown in the article by Foote, the application of high intensity techniques involving stereotaxis has been readily incorporated into palliative treatment options.[3] However, it is important that clear and realistic treatment goals are made at the outset and that radiation oncologists use the resources available to them wisely.

The final two articles in our series address radiotherapy issues from a different perspective, namely treatment related side-effects. Speech pathologists Ellen Mills and Robyn Burnett discuss the important role allied health professionals play in helping us minimise the unwanted effects of radiotherapy.[18] Patients do suffer significant short-term side-effects from radiation that need to be managed during treatment. But potentially more disabling are the long-term side-effects, with detrimental effects on long-term quality of life. It is interesting to think about the difficulties in carrying out research in this field. It appears that many patients are unwilling to take part in studies – possibly due to them (and perhaps their doctors) rating avoidance of long-term side-effects as a low priority at the time of treatment. However, the final article by Wheeler illustrates what a heavy burden the toxicity from treatment places on survivors as well as society as a whole.[19]

It is not really surprising that the perspective of both patients and health professionals changes depending on what point of the cancer journey they are at. However, if we learn lessons from the past, it is important that we as health professionals encourage current patients to actively take part in studies that help us evaluate both the short-term and long-term effects of treatments for their cancers. It is only by gaining this information now that we will be able to address the significant issues affecting the increasing proportion of patients who survive long term after cancer treatment.

Common abbreviations used in this forum

ACTH	adrenocortocotropic hormone
ESCC	epidural spinal cord compression
CBCT	cone beam CT
IMRT	intensity modulated radiotherapy
IGRT	image guided radiotherapy
Linac	linear accelerator
SBRT	stereotactic body radiation therapy
SRS	stereotactic radiosurgery
SRT	stereotactic radiotherapy
TSH	thyroid stimulating hormone
WBRT	whole brain radiotherapy

References

1. Cancer Council Australia. Frequently Asked Questions (FAQ). [Internet] Sydney: Cancer Council Australia, September 2011. Available from www.cancer.org.au/aboutcancer/FAQ.htm#573. Accessed May 2012.
2. Cancer Council NSW. Improving Radiotherapy. Where to from Here? A report for the NSW Government. [Internet] Sydney: Cancer Council NSW, May 2009. Available from: http://www.cancercouncil.com.au/wp-content/uploads/2011/10/Improving-Radiotherapy_Roadmap_May-2009.pdf Accessed May 2012.
3. Foote M. The Development of Advanced Radiotherapy Treatment Techniques. Cancer Forum. 2012;36(2):73-76.
4. Fay M, Thomas P. Impact of Developments in Functional Imaging in Defining the Target for Radiotherapy. Cancer Forum. 2012;36(2):77-79.
5. Kron T. New Developments in Image Guidance for Radiotherapy. Cancer Forum. 2012;36(2):80-85.
6. Burmeister B. Quality assurance in radiation oncology. Cancer Forum. 2012;36(2):86-88.
7. Pignon JP, Le Maître A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92:4-14.
8. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA, Al-Sarraf M et al. Chemoradiotherapy of Locally Advanced Esophageal Cancer:

Long-term Follow-up of a Prospective Randomized Trial (RTOG 85-01). JAMA. 1999;281:1623-1627.
9. Aupérin A, Le Péchoux C, Pignon JP, Koning C, Jeremic B, Clamon G et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients. Ann Oncol. 2006;17:473-483.
10. Denham JW, Steigler A, Lamb DS, Joseph D, Turner S, Matthews J et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol. 2011;12:451-459.
11. James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C et al. Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer. N Engl J Med. 2012;366:1477-1488.
12. Anal Cancer Trial Working Group. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-flurorouracil and mitomycin. Lancet. 1996;348:1049-54.
13. Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet. 2001;358:781-786.
14. Wahlen SA, Slater JD, Wagner RJ, Wang WA, Keeney ED, Hocko JM et al. Concurrent radiation therapy and chemotherapy in the treatment of primary squamous cell carcinoma of the vulva. Cancer. 1995;75:2289-94.
15. 15. Sun Myint A, Ramani VS, Montazeri A, Perkins K, Myerson R, Gerard JP. Novel Radiation Techniques – A Personalised Approach for Patients with Rectal Cancer. Cancer Forum. 2012;36(2):89-92.
16. Maas M , Beets-Tan RGH, Lambregts DMJ, Lammering G, Nelemans PJ, Engelen SME et al. Wait-and-See Policy for Clinical Complete Responders After Chemoradiation for Rectal Cancer. J Clin Oncol. 2011:4633-4640.
17. Wiltshire S, Potter A. Palliative Radiotherapy in Modern Practice. Cancer Forum. 2012;36(2):93-97.
18. Mills E, Burnett R. Functional outcomes after radiotherapy for early glottic cancer. Cancer Forum. 2012;36(2):97-99.
19. Wheeler G. Surviving radiotherapy -what the future holds. Cancer Forum. 2012;36(2):100-105.

THE DEVELOPMENT OF ADVANCED RADIOTHERAPY TREATMENT TECHNIQUES

Matthew Foote
Radiation Oncology, Princess Alexandra Hospital, Brisbane, Queensland, University of Queensland, Brisbane, Queensland.
Email: matthew_foote@health.qld.gov.au

Abstract

Radiation therapy has come a long way in the last few decades from treatment planning based on orthogonal radiographs with large margins around tumours. Developments in imaging and radiation planning software have led to improved radiotherapy treatment techniques such as intensity modulated radiotherapy, rotational intensity modulated radiotherapy and stereotactic body radiotherapy. These radiotherapy treatment advances enable sculpted dose distributions, with the ability to monitor and adapt to changes in patient and tumour position during radiotherapy. The purpose of this paper is to review the recent advances in radiotherapy treatment delivery with reference to how this may improve outcomes for cancer patients treated with radiotherapy.

Radiotherapy is one of the most efficacious and cost-effective modalities for the treatment of cancer. Over the past decade there have been many attempts to increase its efficacy. Two basic strategies exist to achieve this. Firstly, reduce the treatment volume by sparing tissue not suspected of tumour involvement while irradiating the defined target volume at each treatment session. This strategy includes techniques of treatment planning and delivery of radiotherapy, but is also intimately linked to the ability to define the anatomical margins of the tumour and therefore is heavily dependent on advances in medical imaging. The second strategy is to increase the differential response between the tumour and normal tissue using chemotherapeutic drugs, biologic agents including radioprotectors, and genetic or proteomic techniques. This paper focuses on the advances in radiotherapy treatment techniques that may provide therapeutic gains in the treatment of cancer. The paper will also discuss some of the advances that have enabled the widespread use of highly conformal techniques, particularly stereotactic radiotherapy.

Three dimensional conformal radiotherapy

Historically, the ability to define tumour volume accurately and to tailor radiation dose to this volume has been a constant challenge for the radiation oncologist. The introduction of axial CT technology in treatment planning has allowed for increasingly more precise anatomic definition of tumour volumes and surrounding normal tissues.[1] Three dimensional radiation treatment planning systems have been available to most radiation oncology centres in Australia since the early 2000s.The importance of three dimensional CT-based treatment planning on tumour control and reduced treatment complications has been recognised in a number of subsites including lung cancer, prostate cancer and head and neck cancer.[2-4] It is now considered the standard to which new treatment techniques are compared.

Fixed gantry (static) intensity modulated radiotherapy

Since its introduction more than a decade ago, intensity modulated radiotherapy (IMRT) has spread to most radiotherapy departments worldwide for a wide range of indications,[5] and recently has become widely used throughout Australia. The basic principle behind IMRT is the use of intensity modulated beams, which are defined as beams that deliver more than two intensity levels for a single beam direction and a single source position in space. In simple terms, IMRT enables the dose of radiation

to conform better to the three dimensional shape of the tumour by controlling, or modulating the radiation beam's intensity. IMRT is frequently chosen over non-modulated external-beam three dimensional techniques (known as non-IMRT) on the basis of studies showing better planning target volume coverage and better sparing of organs at risk.

Many publications discuss the advantages of IMRT. There is now compelling evidence that this technique improves patient outcome in a number of sites. In head and neck cancer xerostomia is one of the most debilitating long term side-effects of treatment resulting from the effects of radiotherapy on salivary flow, particularly from the parotid glands. There is evidence from randomised control trials in head and neck cancer, comparing IMRT techniques to non-IMRT techniques, showing that IMRT with its ability to spare the parotid glands, significantly reduces the incidence of xerostomia with resulting improvements in associated quality of life.[6,7]

In prostate cancer, there is clear evidence from randomised control trials of a dose response to radiotherapy above 68 Gy for local and biochemical control, the latter being a robust surrogate for disease control.[8-10] The rationale for using IMRT in prostate cancer is clear, in that dose escalation to the primary tumour can be achieved while securing safe doses to organs at risk (eg. rectum and bladder). Consistency in the findings of clinical comparative studies and predictions from planning studies (external validity), allow the conclusion to be made that IMRT enables adequate dose escalation with unchanged or lower gastrointestinal and genitourinary toxic effects and unchanged or better sexual function.[5]

In gynaecological and breast cancer, non-comparative studies of IMRT suggest that this technique may reduce both the acute and late treatment related complications with radiotherapy. In breast cancer there are now a number of randomised trials showing that breast IMRT significantly reduces the development of severe moist desquamation and the probability of having late changes in breast appearance compared to non-IMRT techniques.[11,12]

There is also evidence in non-comparative studies that IMRT may reduce long-term sensorineural hearing loss in paediatric patients with brain tumours,[13] may allow safe dose escalation for patients with pancreatic cancer,[14] and allow less toxic treatment for patients with anal cancer.[15]

A recent meta-analysis collated data from 56 trials and showed that IMRT can reduce toxicities when compared to non-IMRT treatments.[16] Although data relating to overall survival and local control are inconclusive at this time, a reduction in toxicity is an appropriate outcome measure worthy of use as a benchmark for implementation of a particular technique. The evidence for its benefit in planning and non-comparative studies is so compelling that many clinicians consider it the standard of care in some tumour subsites.

Rotational (dynamic) intensity modulated radiotherapy

Rotational IMRT builds on the technology of fixed gantry (static) IMRT, but rather than the treatment being delivered by multiple static beams, it is delivered in one or multiple arcs of radiotherapy while the beam is being modulated throughout the arc.

Both Helical Tomotherapy and Volumetric Modulated Arc Therapy are rotational IMRT modalities. Helical Tomotherapy delivers intensity-modulated fan beams in a helical rotational pattern similar to a diagnostic CT scan. Volumetric Modulated Arc Therapy, by comparison, uses a conventional linear accelerator to deliver radiation in a cone-beam geometry with no couch movement during the treatment.

Both modalities achieve superior target dose quality in a range of tumour sites when compared to static IMRT and require lower radiation doses, with shorter treatment times than static IMRT. This results in a significant improvement in the efficiency of delivering complex IMRT treatments. These benefits have been established in head and neck cancer,[17] prostate cancer,[18] as well as complicated lung and spine treatments,[19] but it is likely that the greatest benefit of this technology is the shorter treatment time enabling greater patient throughput in already busy departments.

Proton radiotherapy

Although not currently available in Australia, proton radiotherapy is a technique that may enable better target volume coverage with significantly reduced normal tissue dose. This is due to the physical properties of protons in that they deposit very little energy as they pass through tissue, but deposit it at the 'Bragg peak,' which can be spread out to provide a uniform dose across the target volume and virtually zero dose deep to the target.[20] As such, most of the clinical advantages are when high doses are required to cure tumours but are adjacent to critical structures (eg. base of skull tumours and prostate cancer), but also where the effects of lower dose to a significant volume are important (eg. paediatric radiation oncology).

Stereotactic radiotherapy and stereotactic radiosurgery

Stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS) is an application of precise delivery of a single (SRS) or several (SRT) high dose radiotherapy treatments for non-invasive ablation of an intracranial lesion (typically less than three to four centimetres in maximum diameter). Conventionally, SRS/SRT is performed with the use of a stereotactic head frame that is fixed to the calvarium in order to provide rigid patient immobilisation during planning and treatment delivery. The doses of radiation are much higher than daily fractionated radiotherapy in order to ablate the target lesion (typically 12-24 Gy in a one day treatment and even up to 140 Gy for radiosurgical thalamotomy). SRS/SRT is delivered to a target localised in three dimensions based on CT and/or MRI imaging. Although SRT/SRS are not new technologies, in recent years, there have been rapid developments in computing and instrumentation that have revolutionised these techniques.[21] SRS delivery systems can be broadly categorised by the method of radiation delivery as either from a series of Cobalt-60 (^{60}Co) sources (Gamma Knife®) or from a single-source linear accelerator (linac). For institutions initiating a

radiosurgery program, the choice of system will depend on a variety of factors including the relative caseload of malignant and benign disease.

Gamma Knife® SRS

The Gamma Knife®, invented by Swedish neurosurgeon Lars Leksell,[22] contains 192-201 cobalt-60 sources. Each source emits a beam of radiation, and all the beams converge to the point of intersection (isocentre) to deliver a "shot" of radiation. With scores of intersecting beams centred on the target, the radiation dose at the isocentre is very large and drops off rapidly within a few millimetres. Therefore, much of the brain receives a low dose.[21] The Gamma Knife® is a dedicated cranial SRS unit by virtue of its geometric design, and requires an invasive stereotactic head frame for localisation and immobilisation. The first Australian centre offering Gamma Knife® opened in 2011.

Linear accelerator (linac) based SRS

There are now a number of commercially available systems which enable SRS/SRT on standard linacs. Some of the difficulties with the early linac based SRS systems were the need for dedicated planning systems, retrofitted hardware, as well as the onerous quality assurance measures required during patient treatment. The initial limitations of linac based units were overcome by developments in treatment planning software and more recently linacs better designed for SRS have emerged.[23] The major advantage of linac based systems is the versatility in the machine, in that it is still able to be used for all of the other requirements of a busy radiation oncology department. As a result, is widely available throughout Australia.

CyberKnife® SRS

The CyberKnife® Robotic Radiosurgery System began as a frameless alternative to existing stereotactic radiosurgery systems such as the Gamma Knife® and conventional linacs equipped with head frames and stereotactic beam collimators. In the original CyberKnife® configuration, a linac mounted on a robotic manipulator delivered many independently targeted (non-isocentric) and non-coplanar treatment beams with high precision under continual x-ray image guidance.[24] Although this can be used for standard fractionated radiotherapy, it is ideal for both intra- and extra-cranial stereotactic treatments. It is not currently available in Australia but is used widely in North America, Asia and Europe.

Stereotactic body radiation therapy

Stereotactic body radiation therapy (SBRT) is an external beam radiation therapy method that has been developed based on the principles of intracranial SRS, but to an extracranial target within the body using a single dose or a small number of fractions.[25] This has been enabled by technical advances integrating various imaging modalities into the everyday practice of radiotherapy directly at the linear accelerator. It requires significantly improved delivery precision over that required for conventional radiotherapy and standard IMRT. Due to the high target dose and steep dose gradients beyond the target, limiting or compensating for target movement during treatment planning and delivery are often required.

Lung SBRT

SBRT has gained much attention as a novel and promising treatment option for early stage non-small cell lung cancer and patients with solitary or low volume lung metastasis. The rational for the practice of SBRT is the finding that very high radiation doses are required to locally control non-small cell lung cancer, higher than achievable with conventional radiation techniques.[26] Lung SBRT has largely been used for smaller, peripheral lesions. It allows treatment with escalated radiation doses to the site of the primary tumour by optimal lung sparing accounting for breathing motion compensation and image-guidance. This has resulted in increased local tumour control which, based on a number of prospective phase II trials, ranges consistently between 84-98%.[26-28] Lung SBRT is now being evaluated for patients with low volume metastatic lung disease.[29]

Spine SBRT

SBRT is an emerging technology in the multidisciplinary management of benign and malignant spinal/paraspinal tumours.[30] The spine is an ideal site for SBRT due to its relative immobility and potential clinical benefits of high dose delivery to optimise local control, given that disease progression can often result in spinal cord compression. Spinal SBRT is largely used for metastatic disease to the spine and aims to improve on existing rates of clinical response (eg. pain relief), tumour control, and to reduce re-treatment rates by delivering high biologically effective doses per fraction. Tumour doses typically range from 16 to 24 Gy in a single fraction or 6-9 Gy by three fractions, which are significantly greater than current palliative radiation oncology practice.[31]

The role of SBRT in metastatic spine tumours is being evaluated in a randomised trial by the Radiation Therapy Oncology Group (protocol 0631) for patients with significant pain and no history of radiation or surgery. The aim of the trial is to compare pain response after delivery of 16 Gy in a single fraction by using SBRT to delivery of 8 Gy in a single fraction with conventional radiation. However, it does not address the role of higher-dose SBRT in patients who have not received radiotherapy, in patients with previously irradiated spinal metastases or in postoperative patients.

Liver SBRT

With the emergence of SBRT techniques for both lung and spine disease there has been renewed interest in the use of radiotherapy for both primary and secondary disease of the liver.[32,33] The clinical experience in both primary and metastatic disease of the liver is emerging, with phase I and II trials demonstrating excellent local control and occasional long-term survivors. With appropriate patient selection and sparing of the uninvolved liver, serious toxicity can be avoided.[32]

Future directions

The advances in radiotherapy over the last few decades have been numerous and this article only addresses those relating to treatment techniques. The advances described would not have been possible without the availability of faster, more powerful computer systems that enable

the efficient running of the advanced softwares required for planning and delivery. These systems have enabled advanced treatment delivery techniques to be planned and delivered in a timely fashion. With the evidence of improved outcomes for patients treated with IMRT, investment in the ability to utilise this technology for a larger number of patients, as is possible with fixed gantry and rotational IMRT, is required.

These advanced techniques require precise methods of targeting delivery, emphasising the importance of image-guided radiotherapy, another topic in this edition of *Cancer Forum.* The cost of these advanced techniques include increased training requirements for physicians and therapists, the need for powerful and efficient computing to manage all of the data and the complex and increasing nature of physics quality assurance measurements. It is likely that the role of the physicist in radiation oncology departments will increase due to the complexities of these treatment techniques.

As previously discussed, another powerful way to improve the therapeutic ratio in treating cancer is by using chemotherapeutic drugs, biologic agents including radioprotectors, and genetic or proteomic techniques. There is little known about the interaction of targeted therapies and radiotherapy. Through collaboration with our medical oncology colleagues, there will be increased interest in investigating the role of these agents in concurrent or adjuvant use, combined with these advanced techniques, particularly SBRT.

Finally, although these rapid developments in radiotherapy delivery will continue to occur, it is paramount that we evaluate them adequately prior to considering their routine use. However, it may also need a rethink of the way in which we evaluate the benefit of a new treatment technique. As overall survival advantages are often difficult to detect, consideration of treatment toxicity, the number of treatment visits (treatment burden) and the ability to provide this technique to a larger population by improving efficiency, needs serious consideration as outcomes worth pursuing.

References

1. Heron DE, Godette KD, Wynn RA, Arterbery VE, Streeter OA, Roach M, et al. Radiation medicine innovations for the new millenium. J Natl Med Assoc. 2003;95:55-63.
2. Robertson JM, Ten Haken RK, Hazuka MB, Turrisi AT, Martel MK, Pu AT, et al. Dose escalation for non-small cell lung cancer using conformal radiation therapy. Int J Radiat Oncol Biol Phys. 1997;37:1079-1085.
3. Sandler HM, McLaughlin PW, Ten Haken RK, Addison H, Forman J, Lichter, A. Three dimensional conformal radiotherapy for the treatment of prostate cancer: low risk of chronic rectal morbidity observed in a large series of patients. Int J Radiat Oncol Biol Phys. 1995;33:797-801.
4. Eisbruch A, Ship JA, Martel MK, Ten Haken RK, Marsh LH, Wolf GT, et al. Parotid gland sparing in patients undergoing bilateral head and neck irradiation: techniques and early results. Int J Radiat Oncol Biol Phys. 1996;36:469-480.
5. Veldeman L, Madani I, Hulstaert F, De Meerleer G, Mareel M, De Neve W. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. Lancet Oncol. 2008;9:367-375.
6. Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS, Leung LH, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys. 2006;66:981-991.
7. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol. 2011;12:127-136.
8. Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol. 2006;24:1990-1996.
9. Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys. 2002;53:1097-1105.
10. Zietman AL, DeSilvio ML, Slater JD, Rossi CJ Jr, Miller DW, Adams JA, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA. 2005;294:1233-1239.
11. Pignol JP, Olivotto I, Rakovitch E, Gardner S, Sixel K, Beckham W, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol. 2008;26:2085-2092.
12. Donovan E, Bleakley N, Denholm E, Evans P, Gothard L, Hanson J, et al. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol. 2007;82:254-264.
13. Huang E, Teh BS, Strother DR, Davis QG, Chiu JK, Lu HH, et al. Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. Int J Radiat Oncol Biol Phys. 2002;52:599-605.
14. Bai YR, Wu GH, Guo WJ, Wu XD, Yao Y, Chen Y, et al. Intensity modulated radiation therapy and chemotherapy for locally advanced pancreatic cancer: results of feasibility study. World J Gastroenterol. 2003;9:2561-2564.
15. Milano MT, Jani AB, Farrey KJ, Rash C, Heimann R, Chmura SJ. Intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer: toxicity and clinical outcome. Int J Radiat Oncol Biol Phys. 2005;63:354-361.
16. Hummel S, Simpson EL, Hemingway P, Stevenson MD, Rees A. Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation. Health Technol Assess. 2010;14:1-108, iii-iv.
17. Verbakel WF, Cuijpers JP, Hoffmans D, Bieker M, Slotman BJ, Senan S.. Volumetric intensity-modulated arc therapy vs. conventional IMRT in head-and-neck cancer: a comparative planning and dosimetric study. Int J Radiat Oncol Biol Phys. 2009;74:252-259.
18. Yoo S, Wu QJ, Lee WR, Yin FF. Radiotherapy treatment plans with RapidArc for prostate cancer involving seminal vesicles and lymph nodes. Int J Radiat Oncol Biol Phys. 2010;76:935-942.
19. Matuszak MM, Yan D, Grills I, Martinez A. Clinical applications of volumetric modulated arc therapy. Int J Radiat Oncol Biol Phys. 2010;77:608-616.
20. Suit H, Kooy H, Trofimov A, Farr J, Munzenrider J, DeLaney T, et al. Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No. Radiother Oncol. 2008;86:148-153.
21. Sahgal A, Ma L, Chang E, Shiu, A, Larson DA, Laperriere N, et al. Advances in technology for intracranial stereotactic radiosurgery. Technol Cancer Res Treat. 2009;8:271-280.
22. Leksell L, Lindquist C, Adler JR, Leksell D, Jernberg B, Steiner L. A new fixation device for the Leksell stereotaxic system. Technical note. J Neurosurg. 1987;66:626-629.
23. Andrews DW, Bednarz G, Evans JJ, Downes B. A review of 3 current radiosurgery systems. Surg Neurol. 2006;66:559-564.
24. Kilby W, Dooley JR, Kuduvalli G, Sayeh S, Maurer CR Jr. The CyberKnife Robotic Radiosurgery System in 2010. Technol Cancer Res Treat. 2010;9:433-452.
25. Potters L, Kavanagh B, Galvin JM, Hevezi JM, Janjan NA, Larson DA, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys. 2010;76:326-332.
26. Partridge M, Ramos M, Sardaro A, Brada M. Dose escalation for non-small cell lung cancer: analysis and modelling of published literature. Radiother Oncol. 2011;99:6-11.
27. Fakiris AJ, McGarry RC, Yiannoutsos CT, Papiez L, Williams M, Henderson MA, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys. 2009;75:677-682.
28. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010;303:1070-1076.
29. Siva S, MacManus M, Ball D. Stereotactic radiotherapy for pulmonary oligometastases: a systematic review. J Thorac Oncol. 2010;5:1091-1099.
30. Foote M, Letourneau D, Hyde D, Massicotte E, Rampersaud R, Fehlings M, et al. Technique for stereotactic body radiotherapy for spinal metastases. J Clin Neurosci. 2011;18:276-279.
31. Sahgal A, Larson DA, Chang EL. Stereotactic body radiosurgery for spinal metastases: a critical review. Int J Radiat Oncol Biol Phys. 2008;71:652-665.
32. Swaminath A, Dawson LA. Emerging role of radiotherapy in the management of liver metastases. Cancer J. 2010;16:150-155.
33. Hoffe SE, Finkelstein SE, Russell MS, Shridhar R. Nonsurgical options for hepatocellular carcinoma: evolving role of external beam radiotherapy. Cancer Control. 2010;17:100-110.

FUNCTIONAL IMAGING USING PET AND RADIOTHERAPY PLANNING

Michael Fay[1] and Paul Thomas[2]
1. Department of Radiation Oncology, Division of Oncology, Royal Brisbane and Women's Hospital, Brisbane, Queensland.
2. Queensland PET Centre, Royal Brisbane and Women's Hospital, Brisbane, Queensland.
Email: Michael_Fay@health.qld.gov.au

Abstract

Functional imaging with PET allows new insights into the extent of a tumour. This information has been rapidly included into treatment protocols. There are some complications in the process, not least of which is how to define the edge of the tumour. This review outlines current uses of PET in radiotherapy treatment planning. Concepts of radiotherapy volumes are outlined and common applications explored. PET now has an established role in radiotherapy planning. It is hoped that in those areas where it has not shown benefit, the development of new PET tracers will allow further improvement. There is still much work to be done, especially in the area of standardisation of techniques.

Increasingly, radiotherapy planning is relying on functional imaging to assist with tumour delineation. This is re-writing the radiation oncology literature in a significant number of areas as we improve both our ability to choose patients for treatment and to adequately cover the target. Combined with image guided radiotherapy, we are likely to see continuous evolution in treatment protocols over the next few years.

The planning process involves defining the volume of tumour (gross tumour volume), volume which may contain microscopic tumour (clinical tumour volume), and a margin incorporating movement (planning treatment volume). Traditionally, a significant proportion of radiotherapy failures were felt to be due to missing the tumour, geographic miss, where the radiotherapy field fails to cover adequately the volume the tumour encompasses. The treating team is increasingly getting better at sculpting the irradiated volume to match the tumour volume plus a margin for movement. Decreasing the irradiated volume so much runs the risk of geographic miss increasing.

Functional imaging, utilising PET, has been developed from the late 1970s. However, the vast majority of the current PET workload is oncology. PET can be utilised to look at a number of functional characteristics of tumours. The most widely used PET tracer has been ^{18}F-deoxyglucose (FDG). Because most tumour types overexpress glucose transporters compared with normal tissues, FDG is preferentially taken up into the tumour rather than normal tissues. The ^{18}F isotope attached to the glucose subsequently undergoes radioactive decay releasing a positron, which quickly annihilates to give off two gamma rays at almost 180 degrees to each other. These two photons are detected by a PET scanner and the point of decay resolved. All modern PET scanners now incorporate a diagnostic CT scanner in the gantry. This allows generation of both PET and CT image sets which are fused together to give precise anatomical localisation, and PET image quality improvements by allowing attenuation correction of the PET image.

Although FDG is the workhorse tracer for PET imaging, there are a number of other PET tracers which can be used for clinical imaging or to shed insight into tumour biology.[1] Examples include imaging of cellular proliferation with ^{18}F-thymide (FLT) and tumour hypoxia using nitroimidazole based PET tracers (eg. ^{18}F-misonidazole, FMISO). It is also possible to use positron emitters other than ^{18}F, but many have other problems. Carbon based tracers have the complication of a short half-life, meaning that the PET camera has to be situated in close proximity to a cyclotron as the half-life is in the order of 20 minutes. ^{11}C-Choline has found application in prostate cancer. ^{68}Ga DOTATATE DOTA-(Tyr^3)-octreotate) or DOTANOC, (^{68}Ga-labelled [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-1-Nal3- which target somatostatin receptors, have become mainstream imaging for neuroendocrine tumours.

Relatively few PET scans are performed solely for the purpose of radiotherapy planning. Much more often they are performed in the process of staging or therapy response monitoring. The advent of PET/CT and improved fusion tools in radiotherapy planning systems have vastly simplified the process of importing PET data. This presents an opportunity for radiotherapy departments to request diagnostic PET scans be performed in a radiotherapy treatment position, or at least close to it, to minimise the necessity to transform the image.[2] A particular problem in using PET in radiation therapy planning is the problem of edge detection. The apparent edge of the tumour varies widely depending on the contrast/window settings used in displaying the PET images. A number of approaches have been used ranging from manual delineation of the tumour boundaries by experienced clinicians to fully automated edge detection algorithms, which frequently define the edge as the contour defined by a particular percentage, say 60%, of the maximal uptake in the tumour. Such automated methods must be adapted for tumour type, location, size and PET scanner resolution and may require manual correction where the contour is rendered

incorrectly. Whatever method is chosen, it is important to standardise the methodology so that consistent results are achieved. This is particularly important in clinical trials. In practice, when delineating treatment volumes, PET is just one part of the information used and the final contour is also informed by other imaging (such as MRI and CT), and sometimes other information such as biopsy results, which may clear an equivocal node seen on other imaging.

Tumour movement can be a problem. With FDG PET the PET image is acquired over about 20 minutes, but the CT is acquired over about a minute. This tends to blur the tumour volume on PET, thus incorporating some tumour movement. This can be useful in lung treatments as there is some in-built margin for respiratory motion. Increasingly, literature demonstrates that FDG PET has a significant impact on treatment volumes. The volume treated may be smaller using PET, but in practice it often increases in size. In some situations such as in lung cancer causing distal collapse, the volume is significantly decreased.[1] PET may also be useful in adaptive planning, whereby the radiotherapy treatment is altered in response to treatment induced changes in the tumour volume. This is particularly useful in decreasing normal tissue dose, such as in head and neck treatment, or to allow intensification of the dose to a smaller volume.

Response criteria are evolving. It has been appreciated that growth in the size of a mass may not of itself represent progression. Nor may a failure of the mass to shrink represent treatment failure. Metabolic imaging with FDG PET may provide more accurate response measurements than traditional anatomic criteria such as, RECIST (Response Evaluation Criteria In Solid Tumors). For example, persistently enlarged (>1cm) cervical lymph nodes in the neck post therapy for head and neck cancer which are FDG negative, are reliably found to be benign, whereas these would be abnormal on CT criteria. The traditional RECIST criteria are being modified to take into account functional imaging.[3]

Specific tumour sites

Head and neck cancer

Although CT and MRI are better for delineating the extent of local tumour due to the lower resolution of PET, FDG PET has higher accuracy in head and neck cancer for nodal staging and higher sensitivity for detecting the occasional patient with distant metastases at staging.[4,5] PET may therefore modify the radiotherapy plan or change the treatment from a curative intent to palliative. In the setting of suspected recurrence, FDG PET may facilitate radiotherapy planning as the CT and MRI may be of limited utility in the setting of post-operative anatomical change. FDG PET can assist in finding the unknown primary site in squamous carcinoma of unknown primary. Fusion with the radiotherapy planning CT may be problematic if head positioning is different during the two scans. This can be minimised by reproducing the radiotherapy planning position during PET scanning using a flat palette, standard head holders or even a mask.

Central nervous system

FDG PET has only limited application in the setting of central nervous system malignancy, for example, detecting high grade transformation in a low grade glioma) due to the high background FDG uptake in normal gray matter. PET scanning using other tracers such as ^{18}FDOPA (3,4-dihydroxy-6-18F-fluoro-L-phenylalanine) and ^{11}C-Methionine (MET), have the advantage that the signal to background ratio is much higher, allowing the tumour to be delineated from background cortex. Current work is exploring the use of this in radiotherapy planning. This has been explored in low grade glioma and may image the residual tumour better than MRI alone.[6] Other PET tracers are useful in specific situations such as ^{68}Ga DOTOTATE, which has high affinity for meningioma.[7]

Thoracic malignancies

PET has found extensive use in radiotherapy planning of non-small cell lung cancer and this has given rise to an extensive literature. MacManus et al showed that in 22/102 patients the target volume increased and in 16 patients the volume decreased. The prospective trial showed a significant impact on survival.[8] Other series have shown that PET decreases the inter-observer variability.[9] A number of papers have shown high benefit in terms of delineating the volume needing to be irradiated. There has also been significant work looking at radiation response assessment. Indeed, one paper has shown that the response to radiotherapy can be predicted by PET just two weeks into a six week course of radiotherapy.[10]

Gastrointestinal tumours

There has been some work investigating oesophageal PET in defining the radiotherapy treatment volume. However, the situation is complicated by significant intra-lymphatic spread.[11] Pre-op assessment of rectal cancer treatment with nodal assessment is helpful both with MRI and with PET. MRI has the additional benefit of demonstrating tumour extension through the wall of the rectum, which is a key discriminating factor in deciding whether radiotherapy is required. PET may be helpful in pelvic nodal assessment and radiotherapy field design, but the data is not conclusive.[1] In the treatment of anal carcinoma, PET can be helpful in defining inguinal nodal involvement, decreasing the volume that needs to be irradiated and possibly the dose.[12,13]

Other malignancies

PET has been shown to influence the radiotherapy field design in Hodgkin's disease.[14] This is particularly important in the paediatric population as these patients have a long survival. PET can also be very helpful in therapy response monitoring.

Melanoma takes up FDG very readily but there is debate as to whether this changes staging.[15,16] There is interest in defining the role of FDG in Merkel cell carcinoma, but similar to squamous cell carcinoma, there is little published evidence. Current Trans-Tasman Radiation Oncology Group studies are incorporating PET.

In the treatment of carcinoma of the cervix,[17] FDG PET is under investigation; PET has considerably greater accuracy for detecting para-aortic nodal involvement than MR and CT.[17] It has been shown to be useful in adaptive brachytherapy planning, however the value in external beam planning over MRI imaging remains under investigation.[18]

The future

Increasingly, the approaches being looked at are more sophisticated. PET has moved from being solely an imaging modality to being able to probe the pathways driving tumour growth. It is hoped that with a combination of molecular markers it may be possible to define the events which are involved in a particular patient and continue to drive the cancer to divide. Such approaches may be extremely useful in terms of defining the benefit of biologic therapy, as traditional approaches have largely failed to assist us in planning treatment.

References

1. Paulino A, Teh B. PET-CT in radiotherapy treatment planning. (Saunders Elsevier: 2008).
2. MacManus, M. et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006-2007. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2009; 91:85-94.
3. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med.2009;50 Suppl 1:122S-50S.
4. Scott AM, Gunawardana DH, Bartholomeusz D, Ramshaw JE, Lin P. PET changes management and improves prognostic stratification in patients with head and neck cancer: results of a multicenter prospective study. Journal of nuclear medicine : official publication, Society of Nuclear Medicine.2008;49:1593-600.
5. Rodrigues RS, et al. Comparison of whole-body PET/CT, dedicated high-resolution head and neck PET/CT, and contrast-enhanced CT in preoperative staging of clinically M0 squamous cell carcinoma of the head and neck. Journal of nuclear medicine : official publication, Society of Nuclear Medicine.2009;50:1205-13.
6. Nuutinen J, et al. Radiotherapy treatment planning and long-term follow-up with [(11)C]methionine PET in patients with low-grade astrocytoma. International Journal of Radiation Oncology, Biology, Physics.2000;48:43-52.
7. Khan MU, et al. Clinical indications for Gallium-68 positron emission tomography imaging. Eur J Surg Oncol. 2009;35:561-567.
8. Kalff V, et al. Clinical impact of (18)F fluorodeoxyglucose positron emission tomography in patients with non-small-cell lung cancer: a prospective study. J Clin Oncol. 2001;19:111-118.
9. De Ruysscher D, et al. Effects of radiotherapy planning with a dedicated combined PET-CT-simulator of patients with non-small cell lung cancer on dose limiting normal tissues and radiation dose-escalation: a planning study. Radiother Oncol. 2005;77:5-10.
10. Feng M, et al. Using fluorodeoxyglucose positron emission tomography to assess tumor volume during radiotherapy for non-small-cell lung cancer and its potential impact on adaptive dose escalation and normal tissue sparing. Int J Radiat Oncol Biol Phys. 2009;73:1228-1234.
11. Leong T, et al. A prospective study to evaluate the impact of FDG-PET on CT-based radiotherapy treatment planning for oesophageal cancer. Radiotherapy and Oncology. 2006; 78: 254-261.
12. Krengli M, et al. FDG-PET/CT imaging for staging and target volume delineation in conformal radiotherapy of anal carcinoma. Radiat Oncol. 2010;5:10.
13. Winton ED, et al. The impact of 18-fluorodeoxyglucose positron emission tomography on the staging, management and outcome of anal cancer. British Journal of Cancer. 2009;100:693-700.
14. Paulino A, Margolin J, Dreyer Z, Teh B, Chiang S. Impact of PET-CT on involved field radiotherapy for pediatric Hodgkins lymphoma. Pediatr Blood Cancer. 2012;58:860-4.
15. Friedman KP, Wahl RL. Clinical use of positron emission tomography in the management of cutaneous melanoma. Semin Nucl Med. 2004;34:242-253.
16. Krug B, et al. Fluor-18-fluorodeoxyglucose positron emission tomography (FDG-PET) in malignant melanoma. Diagnostic comparison with conventional imaging methods. Acta Radiologica. 2000;41: 446-452.
17. Leblanc E, et al. Accuracy of 18-fluoro-2-deoxy-D-glucose positron emission tomography in the pretherapeutic detection of occult para-aortic node involvement in patients with a locally advanced cervical carcinoma. Annals of surgical oncology. 2011;18: 2302-9.
18. Haie-Meder C, Mazeron R, Magne N. Clinical evidence on PET-CT for radiation therapy planning in cervix and endometrial cancers. Radiother Oncol. 2010;96:351-355.

NEW DEVELOPMENTS IN IMAGE GUIDANCE FOR RADIOTHERAPY

Tomas Kron
Peter MacCallum Cancer Centre, Melbourne, Victoria.
Email: Tomas.Kron@petermac.org

Abstract

Image Guided Radiation Therapy refers to the concept of visualising the target or an important critical structure during radiotherapy to ensure accurate and reproducible radiation delivery throughout the course of treatment. There are many different methods for Image Guided Radiation Therapy, ranging from ultrasound to electronic portal imaging and volumetric CT scanning. In many circumstances, Image Guided Radiation Therapy can be enhanced by the use of implanted fiducial markers that are clearly visible and can make decision-making quicker and more robust. The most common application for image guidance at present is the accurate positioning of the target prior to treatment delivery. However, the availability of high quality imaging at the time of treatment delivery also facilitates management of intrafraction motion and adaptive radiotherapy. The latter encompasses a variety of methods to modify the treatment plan for individual patients in response to the images acquired during treatment. While there is still discussion as to what imaging approach is best for which purpose, there is no doubt that modern highly conformal or intensity modulated radiotherapy would not be feasible without some form of image guidance. The present article provides an overview of available techniques with the aim of illustrating their use in relevant clinical scenarios.

Radiotherapy is in most cases a local or loco-regional treatment, directing radiation to the tumour target while minimising the dose to surrounding normal structures. This requires the identification of the target and a means of delivering a high dose of radiation reliably to this target. Identification and characterisation of the target have improved significantly over recent years with state-of-the-art imaging technologies such as PET and MRI providing improved anatomical and functional definition of the target. This is discussed in detail in the article by Fay and Thomas in this issue of *Cancer Forum.*[1]

Once the target is identified, successful radiotherapy is based on two key tasks – the generation of a highly conformal radiation dose distribution and the ability to place this dose distribution in the correct position within the patient over the whole course of treatment, which typically lasts for 30 or more daily fractions. This is illustrated in figure 1. There have been dramatic improvements in our ability to deliver a highly conformal dose distribution, particularly through the use of Intensity Modulated Radiation Therapy (IMRT). The article by Foote in this issue highlights these developments.[2]

The final task is to ensure that the dose is actually delivered to the target in an accurate and reproducible fashion for every day of the treatment. This is in general associated with the term Image Guided Radiation Therapy (IGRT).

This article aims to review tools that have become available for IGRT and explore how they support the overall aim of radiotherapy. In doing this, the article first provides a working definition for IGRT and introduces methods that are available for image guidance. This is followed by trying to classify clinical applications and a discussion of adaptive radiotherapy, the logical extension of IGRT.

Definition of IGRT

There is no uniformly accepted definition as to where conventional verification imaging ends and where IGRT starts. However, there is general agreement that the key features of IGRT are:[3]

- Availability of high quality imaging equipment in the treatment room.
- Ability to visualise the target (not just external markers or bony anatomy) with the patient in treatment position.
- A protocol to act on the findings. This could be done on-line, ie. prior to turning the radiation beam on, or off-line between fractions if more complicated decision making is required.

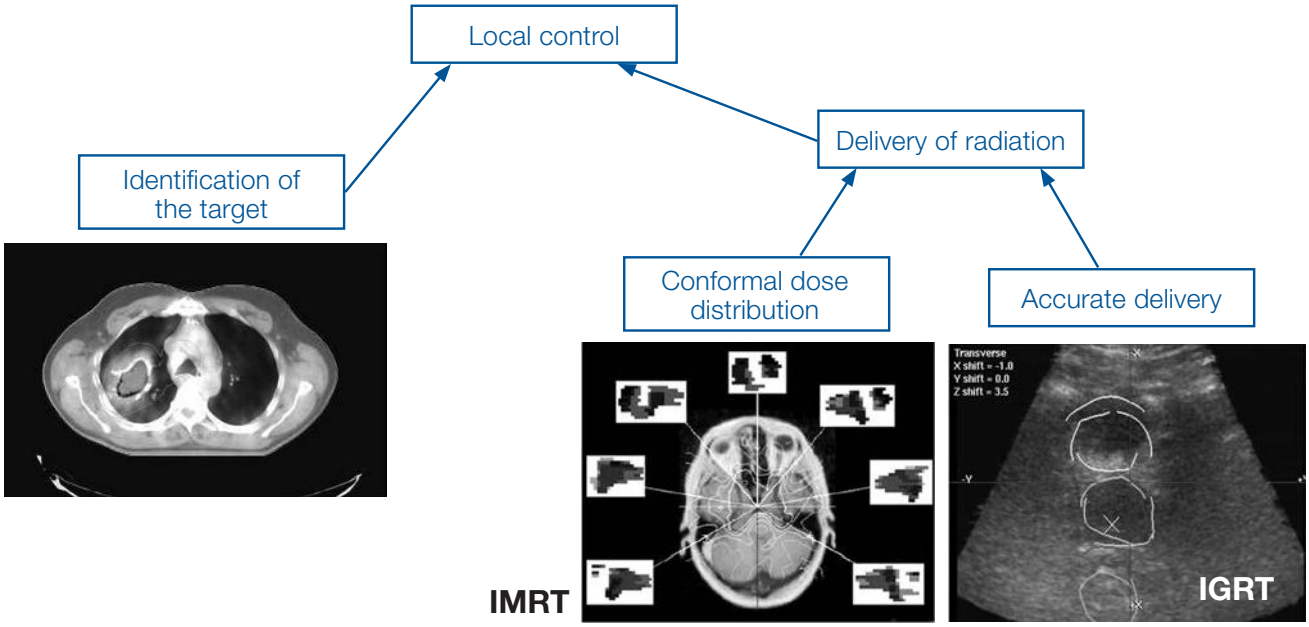
This article is based on the following working definition: IGRT is radiotherapy based on data pertaining to the relationship between beam and patient geometry acquired at the point of treatment delivery, with the intent to ensure geometric accuracy of radiation delivery appropriate to the clinical scenario. This definition is a result of discussions at a consensus workshop on IGRT in Melbourne in 2008.

This implies that IGRT does not necessarily require an image to be taken. A system which can locate the target in three dimensions in relation to the radiation beams would suffice. Electromagnetic beacons implanted in the prostate and detected with an external antenna system (Calypso company, Seattle US) are an example.[4-5]

Imaging methods

A large variety of imaging methods are now available.[6] They range from optical methods,[7] where one or more video cameras observe the patient, to ultrasound,[8] x-rays and even magnetic resonance imaging (MRI).[9-10] MRI in particular

Figure 1: *Achieving the aim of radiotherapy requires the identification of the target as well as the ability to deliver a highly conformal dose of radiation to the target. IMRT is the tool to produce the conformal dose distribution and IGRT guides it reliably and reproducibly in the correct position within the patient. The picture showing the target identifications shows a PET/CT image of a lung cancer while the one illustrating IMRT is the dose distribution for a meningioma treated with seven fields. The fluence distributions in each field are also shown. The picture for IGRT shows an ultrasound image for localisation of the prostate. Figure adapted from reference 39.*

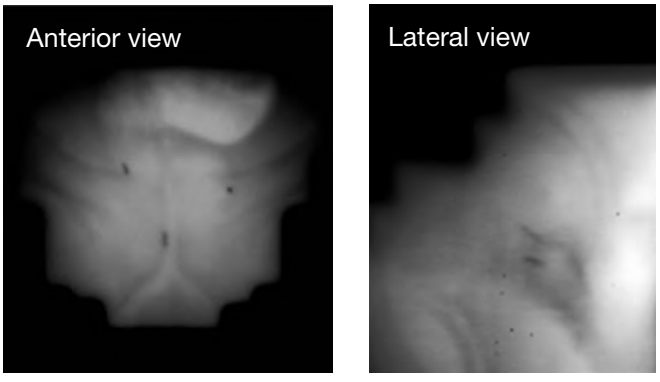


would be of considerable interest as it not only provides the best soft tissue contrast, but also promises functional information. As it uses a method completely independent of the treatment delivery, MRI can also, at least in principle, be used in real time to monitor motion and changes due to treatment. As such, it is not surprising that several groups are currently working on prototype units despite the formidable challenges of combining strong magnetic fields with the electromagnetic components of a linac.[11-13] For the time being, ultrasound is a soft tissue imaging method available in the clinic; the picture illustrating IGRT in figure 1 is an ultrasound image for localisation of the prostate. However, by far the most commonly used IGRT tools are x-ray based. These methods can utilise the megavoltage treatment beam, for example in electronic portal imaging,[14] or a dedicated diagnostic x-ray tube and detector.[15]

X-ray based IGRT approaches can be roughly divided into two main imaging approaches:[6,16]

I. **Acquisition of one, two or more planar x-ray images of the target volume** (typically two orthogonal images which allow localisation of an object in three dimensions). Examples for this are electronic portal imaging as shown in figure 2, or diagnostic x-rays mounted on the gantry. The advantage of electronic portal imaging is that the treatment beam is used for imaging, which also allows verification of the field shape of the treatment beam. However, the image quality of a dedicated diagnostic x-ray system is superior and most manufacturers have implemented a version of this technology. A linac with both imaging modalities, electronic portal imaging using the treatment beam and on-board imaging using a dedicated diagnostic x-ray tube, is shown in figure 3.

Figure 2: *Electronic portal image of a prostate cancer patient. Shown is the outline of the treatment field collimated by a multileaf collimator (MLC). The three fiducial gold markers implanted in the prostate gland can be clearly visualised in the treatment field.*



For IGRT with projection imaging, target visualisation is often enhanced through the implantation of fiducial markers into the target.[17,18] These markers can be small gold seeds (1mm diameter) that can be easily visualised using x-ray imaging. Figure 2 shows an electronic portal image of a patient treated with radiotherapy for prostate cancer. The implantation of markers overcomes the problem that the prostate (or other soft tissue targets) cannot be identified using projection x-ray imaging. Fiducial markers in the target volume can be easily visualised and allow for easy and fast decision making.

II. **Volumetric three dimensional imaging of the target area.**[3,19] This is most commonly performed using x-ray CT technology such as cone beam CT (CBCT),[20] or an in-room CT scanner where the linac and a CT scanner are housed in the same bunker.[21] Volumetric imaging provides significantly more information about the target region and the surrounding normal structures. This is illustrated in figure 4, which shows a planning CT and a CBCT of a patient treated with extracranial stereotactic radiotherapy for early stage lung cancer. On the axial and coronal images shown, the three dimensional location and shape of the target are clearly visible. As CBCT images are acquired over an extended period of time as the linac gantry rotates around the patient, the CBCT also allows some assessment of motion.[22] Also, information on critical structures such as the parotid in head and neck cancer,[23] or the rectum in prostate cancer,[24,25] can only be obtained using volumetric imaging. Volumetric imaging therefore allows for more complex decision-making, which is accompanied by an increased need for adequate operator training.

Figure 3: *Modern linear accelerator for radiotherapy. The treatment beam points down and an image can be generated using an electronic portal imaging device. A diagnostic x-ray tube and detector are mounted rotated by 90 degrees on the gantry.*

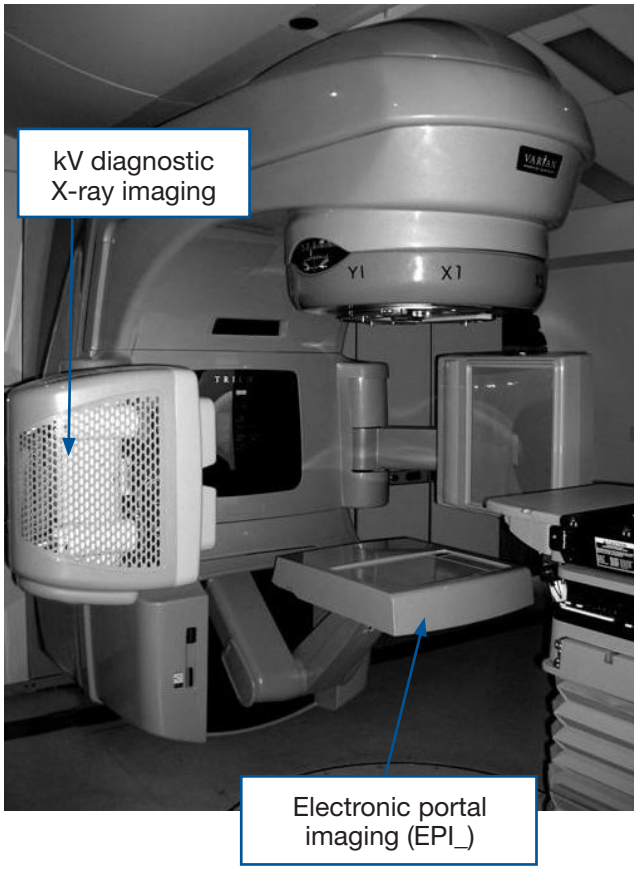


Figure 4: *Illustration of image guidance using volumetric imaging. Shown is an axial image of a planning CT (left side) and the corresponding CBCT images acquired at the time of treatment for a patient treated with extracranial stereotactic radiotherapy for early stage lung cancer. The contours for the Internal Target Volume (ITV) used for image matching are shown.*

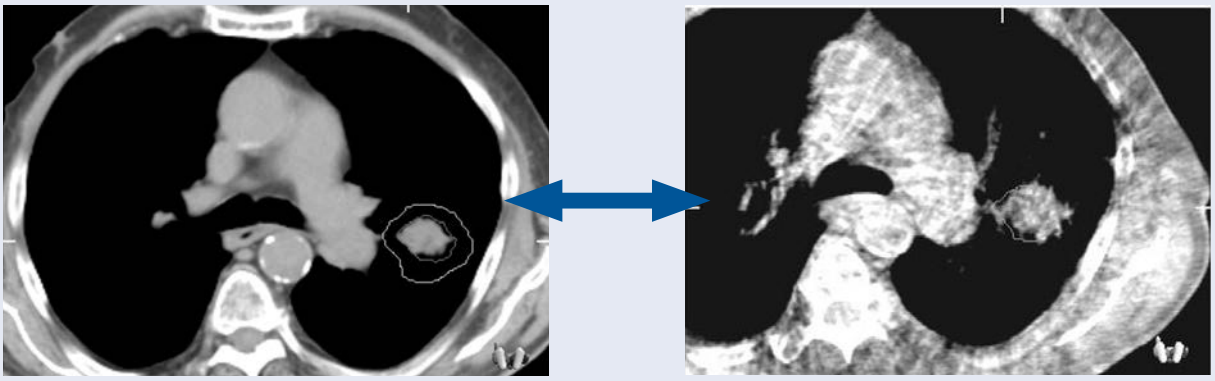


Table 1: *Advantages and disadvantages for selected methods for image guidance.*
Rating: - not good, 0 may be considered, + acceptable, ++ good, +++ excellent. Please note that this is for illustration purposes only: not all technologies are listed and the table does not constitute an endorsement of any of the techniques.

	Electronic portal imaging	kV imaging	CBCT	MVCT	Ultra sound	MRI
Dimensions	2	2	3	3	2.5	3
Allows assessment of beam portal	yes	no	no	no	no	no
Available while beam is on ('real time')	yes	possibly	unlikely	unlikely	possibly	yes
Image quality	-	+	++	+	+	+++
Spatial accuracy	+	+	+	+	0	0
Need for fiducials	yes	yes	no	no	no	no
Unwanted dose	no	small	yes	yes	no	no
Time per treatment session (min)	1	1	5	5	3	?
Key applications	breast	head and neck, fiducials	most	most	prostate, breast	pelvis, lung, abdomen
Cost	small	medium	high	high	small	very high

Table 1 gives a summary of features for a variety of imaging modalities.

IGRT applications

IGRT applications can be distinguished using several different features:

1. Volumetric versus projection based imaging – as discussed in the previous section.
2. Radiation dose – In the light of increasing use of image guidance, the American Association of Physicists in Medicine has devoted a task group report to this issue.[26] The use of imaging methods that use ionising radiation have to be restricted to minimise risk to the patient.
3. Imaging frequency – Imaging may be performed at specified time points during the course of treatment when particular decisions are required. Examples would be the use of decision-making models to reduce systematic errors,[27]or adaptive radiotherapy based on significant changes in the anatomy.[28,29] Daily imaging is the usual practice for targets that may move from day-to-day, such as the prostate. More frequent imaging is required for motion management where imaging is used to track the motion of a target in real time. Electromagnetic markers have been used for prostate cancer,[5,30] while a variety of techniques are available for following breathing motion.[31,32] Motion management affects targets that are likely to move during the delivery of radiation.[31,32] This is typically illustrated by breathing motion and needs to be considered for the treatment of lung, breast, liver and other abdominal cancers.
4. Decision-making – This pertains to both the person making a decision and the immediacy of the decision-making. While complex decision-making is currently restricted to off-line image guidance, a lot of research is directed to making it feasible to allow decision-making at the time of delivery. Autosegmentation,[33] registration and computer aided decision making tools are the subject of intense research.
5. Reliance of fiducial markers – This typically requires a few additional steps in the patient management process. For example, in IGRT of prostate cancer, implantation of fiducial markers would need to occur about one week before imaging for treatment planning to allow for reduction of swelling after the implant and reduce the chance of migration of the fiducial markers.[34]
6. Resource requirements – This includes not only the cost of the system, but also training requirements and the time added to the patient treatment appointment by IGRT.

Estimates for some of the features discussed above are given in table 1 for common IGRT tools. It is the responsibility of the user to select the most appropriate technology for a particular clinical scenario. A good example for a systematic review of IGRT for rectal cancer was given recently by Gwynne et al.[35]

Adaptive radiotherapy

Volumetric imaging in the treatment room is the prerequisite for a logical extension of IGRT – adaptive radiotherapy.[36] At present, IGRT is mostly used for repositioning of the patient to align the target with the radiation beams. In adaptive radiotherapy, the treatment plan is modified to take into account changes in patient shape, target volume or the spatial relationship between target and surrounding structures.[37] This requires either the preparation of multiple treatment plans from which to choose the 'plan of the day',[38] or the creation of a new treatment plan based on the image information from a small number of treatment fractions.[39]

Even one step further, biologically adaptive radiotherapy utilises functional imaging such as positron emission tomography to determine treatment response after part of the treatment and leads to modification of treatments in response to the biological changes observed.[40,41] This could result for example, in a boost to metabolically active or hypoxic regions.

IGRT processes and infrastructure

In the context of IGRT there is an increased number of decision-making points in the patient's treatment. The decision-making can be on-line while the patient is on the treatment couch, or off-line when the images are reviewed after a given treatment fraction. The resulting action will then affect future treatment fractions. It is intuitive that this will improve patient management. However, it also adds new costs and work processes to the treatment:

- cost of imaging equipment which is not always included in conventional linac purchases
- maintenance and quality assurance thereof
- training of staff
- development of protocols
- creation of new or modified reference images.

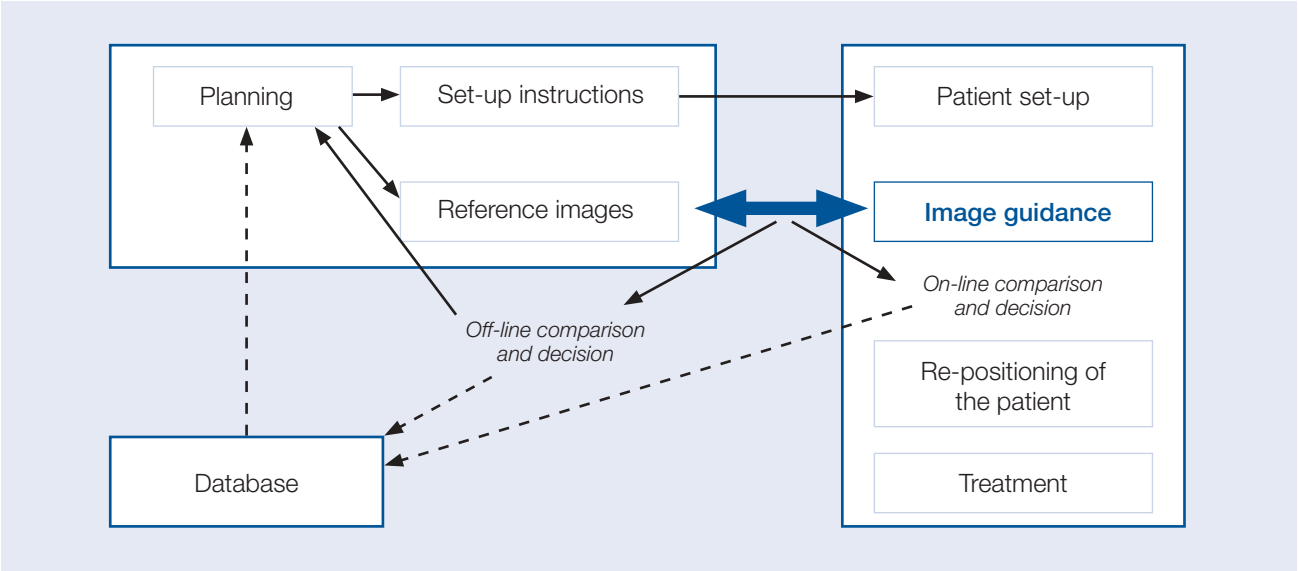
On the other hand, it also adds to the confidence that the correct treatment is delivered to the patient. In addition to this, the increasing responsibility for treatment staff and the need to acquire new skills in respect to image acquisition, interpretation and decision making, has the potential to improve job satisfaction.[42]

Figure 5 illustrates the workflow in IGRT. In practice, there are additional implications of image guidance for a radiotherapy department, which extend beyond the individual patient. The large amount of data generated in IGRT can be used to analyse departmental processes, determine the performance of equipment (eg. immobilisation devices), and decide on departmental procedures such as margins in a rationale way. Margins are placed around a target in treatment planning and allow for organ motion and daily variations in patient set-up.[43,44] Appropriate choice of margins has a significant effect on treatment quality and the increasing availability of IGRT has the potential to help optimise them for different treatment scenarios and the practice in individual radiotherapy centres. This process may require additional infrastructure such as a database.[45] However, the benefits from the additional information available for decision-making and departmental planning would likely be significant.

Outlook

Image guidance has had profound implications for radiotherapy. Without IGRT, modern delivery techniques such as IMRT would not be possible. IGRT also has the potential to link observations made during the course of treatment back to the planning images that have defined the target in the first place. More decision-making points

Figure 5: *Schematic diagram of the workflow in IGRT. Images acquired prior to treatment delivery are compared to reference images generated in the treatment planning process. Any differences between the target location in the two images is used to re-position the target for optimal radiation delivery (right side of the figure). At the same time information is generated that can be used to learn about the typical set-up variations in these patients. If this data is collected for a sufficient number of patients and evaluated, it can inform treatment approaches and planning practices, such as selection of margins, for future patients.*



in the patient's treatment course are the result. This not only has implications for staff and workflow, such as more training and quality assurance steps, but also increases confidence of all stakeholders that what was planned for management of the disease is actually happening for an individual patient. It is likely that IGRT in the future will provide more opportunities for adaptation of the treatment; why stick with the original treatment plan when one could adapt the plan to what has been seen during treatment? However, this will require communication and learning, and setting up an infrastructure that can facilitate this is essential for making optimal use of the new imaging tools available directly at the time of radiotherapy delivery. Image guidance has had profound implications for radiotherapy – and will continue to do so.

References

1. Fay M, Thomas P. Impact of Developments in Functional Imaging in Defining the Target for Radiotherapy. Cancer Forum. 2012;36:77-79.
2. Foote M. The Development of Advanced Radiotherapy Treatment Techniques. Cancer Forum. 2012;36:73-76.
3. Korreman S, Rasch C, McNair H, Verellen D, Oelfke U, Maingon P, et al. The European Society of Therapeutic Radiology and Oncology-European Institute of Radiotherapy (ESTRO-EIR) report on 3D CT-based in-room image guidance systems: A practical and technical review and guide. Radiother Oncol. 2010 Feb;94(2):129-44.
4. Kupelian P, Willoughby T, Mahadevan A, Djemil T, Weinstein G, Jani S, et al. Multi-institutional clinical experience with the Calypso System in localization and continuous, real-time monitoring of the prostate gland during external radiotherapy. Int J Radiat Oncol Biol Phys. 2007 Mar 15;67(4):1088-98.
5. Langen KM, Willoughby TR, Meeks SL, Santhanam A, Cunningham A, Levine L, et al. Observations on real-time prostate gland motion using electromagnetic tracking. Int J Radiat Oncol Biol Phys. 2008 Jul 15;71(4):1084-90.
6. van Herk M. Different styles of image-guided radiotherapy. Semin Radiat Oncol. 2007 Oct;17(4):258-67.
7. Tome WA, Meeks SL, Orton NP, Bouchet LG, Bova FJ. Commissioning and quality assurance of an optically guided three-dimensional ultrasound target localization system for radiotherapy. Med Phys. 2002 Aug;29(8):1781-8.
8. 8. Cury FL, Shenouda G, Souhami L, Duclos M, Faria SL, David M, et al. Ultrasound-based image guided radiotherapy for prostate cancer: comparison of cross-modality and intramodality methods for daily localization during external beam radiotherapy. Int J Radiat Oncol Biol Phys. 2006 Dec 1;66(5):1562-7.
9. Lagendijk JJ, Raaymakers BW, Raaijmakers AJ, Overweg J, Brown KJ, Kerkhof EM, et al. MRI/linac integration. Radiother Oncol. 2008 Jan;86(1):25-9.
10. Fallone BG, Murray B, Rathee S, Stanescu T, Steciw S, Vidakovic S, et al. First MR images obtained during megavoltage photon irradiation from a prototype integrated linac-MR system. Med Phys. 2009 Jun;36(6):2084-8.
11. Raaymakers BW, Lagendijk JJ, Overweg J, Kok JG, Raaijmakers AJ, Kerkhof EM, et al. Integrating a 1.5 T MRI scanner with a 6 MV accelerator: proof of concept. Phys Med Biol. 2009 Jun 21;54(12):N229-37.
12. Kerkhof EM, van der Put RW, Raaymakers BW, van der Heide UA, Jurgenliemk-Schulz IM, Lagendijk JJ. Intrafraction motion in patients with cervical cancer: The benefit of soft tissue registration using MRI. Radiother Oncol. 2009 Oct;93(1):115-21.
13. Constantin DE, Fahrig R, Keall PJ. A study of the effect of in-line and perpendicular magnetic fields on beam characteristics of electron guns in medical linear accelerators. Med Phys. 2011 Jul;38(7):4174-85.
14. Herman MG. Clinical use of electronic portal imaging. Semin Radiat Oncol. 2005 Jul;15(3):157-67.
15. Fox T, Huntzinger C, Johnstone P, Ogunleye T, Elder E. Performance evaluation of an automated image registration algorithm using an integrated kilovoltage imaging and guidance system. J Appl Clin Med Phys. 2006 Winter;7(1):97-104.
16. Dawson LA, Jaffray DA. Advances in image-guided radiation therapy. J Clin Oncol. 2007 Mar 10;25(8):938-46.
17. Kron T, Thomas J, Fox C, Thompson A, Owen R, Herschtal A, et al. Intra-fraction prostate displacement in radiotherapy estimated from pre- and post-treatment imaging of patients with implanted fiducial markers. Radiother Oncol. 2010 May;95(2):191-7.
18. Schiffner DC, Gottschalk AR, Lometti M, Aubin M, Pouliot J, Speight J, et al. Daily electronic portal imaging of implanted gold seed fiducials in patients undergoing radiotherapy after radical prostatectomy. Int J Radiat Oncol Biol Phys. 2007 Feb 1;67(2):610-9.
19. Jaffray DA, Siewerdsen JH. Cone-beam computed tomography with a flat-panel imager: initial performance characterization. Med Phys. 2000 Jun;27(6):1311-23.
20. Jaffray DA, Siewerdsen JH, Wong JW, Martinez AA. Flat-panel cone-beam computed tomography for image-guided radiation therapy. Int J Radiat Oncol Biol Phys. 2002 Aug 1;53(5):1337-49.
21. Owen R, Foroudi F, Kron T, Milner A, Cox J, Cramb J, et al. A comparison of in-room computerized tomography options for detection of fiducial markers in prostate cancer radiotherapy. Int J Radiat Oncol Biol Phys. 2010 Jul 15;77(4):1248-56.
22. Vergalasova I, Maurer J, Yin FF. Potential underestimation of the internal target volume (ITV) from free-breathing CBCT. Med Phys. 2011 Aug;38(8):4689-99.
23. Duma MN, Kampfer S, Wilkens JJ, Schuster T, Molls M, Geinitz H. Comparative analysis of an image-guided versus a non-image-guided setup approach in terms of delivered dose to the parotid glands in head-and-neck cancer IMRT. Int J Radiat Oncol Biol Phys. 2010 Jul 15;77(4):1266-73.
24. Haworth A, Paneghel A, Herschtal A, Duchesne G, Williams S, Tai KH, et al. Verification of target position in the post-prostatectomy cancer patient using cone beam CT. J Med Imaging Radiat Oncol. 2009 Apr;53(2):212-20.
25. Showalter TN, Nawaz AO, Xiao Y, Galvin JM, Valicenti RK. A cone beam CT-Based Study for Clinical Target Definition Using Pelvic Anatomy During Postprostatectomy Radiotherapy. Int J Radiat Oncol Biol Phys. 2008 Feb 1;70(2):431-6.
26. Murphy MJ, Balter J, Balter S, BenComo JA, Jr., Das IJ, Jiang SB, et al. The management of imaging dose during image-guided radiotherapy: report of the AAPM Task Group 75. Med Phys. 2007 Oct;34(10):4041-63.
27. See A, Kron T, Johansen J, Hamilton C, Bydder SA, Hawkins J, et al. Decision-making models in the analysis of portal films: a clinical pilot study. Australas Radiol. 2000 Feb;44(1):72-83.
28. Tanyi JA, Fuss MH. Volumetric image-guidance: does routine usage prompt adaptive re-planning? An institutional review. Acta Oncol. 2008;47(7):1444-53.
29. Mageras GS, Mechalakos J. Planning in the IGRT context: closing the loop. Semin Radiat Oncol. 2007 Oct;17(4):268-77.
30. Kupelian PA, Langen KM, Willoughby TR, Zeidan OA, Meeks SL. Image-guided radiotherapy for localized prostate cancer: treating a moving target. Semin Radiat Oncol. 2008 Jan;18(1):58-66.
31. Korreman SS, Juhler-Nottrup T, Fredberg Persson G, Navrsted Pedersen A, Enmark M, Nystrom H, et al. The role of image guidance in respiratory gated radiotherapy. Acta Oncol. 2008;47(7):1390-6.
32. Keall PJ, Mageras GS, Balter JM, Emery RS, Forster KM, Jiang SB, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. Med Phys. 2006 Oct;33(10):3874-900.
33. Anders LC, Stieler F, Siebenlist K, Schafer J, Lohr F, Wenz F. Performance of an atlas-based autosegmentation software for delineation of target volumes for radiotherapy of breast and anorectal cancer. Radiother Oncol. 2012 Jan;102(1):68-73.
34. Thompson A, Fox C, Foroudi F, Styles C, Tai KH, Owen R, et al. Planning and implementing an implanted fiducial programme for prostate cancer radiation therapy. J Med Imaging Radiat Oncol. 2008 Aug;52(4):419-24.
35. Gwynne S, Webster R, Adams R, Mukherjee S, Coles B, Staffurth J. Image-guided Radiotherapy for Rectal Cancer - A Systematic Review. Clin Oncol (R Coll Radiol). 2012 May;24(4):250-60.
36. Yang D, Chaudhari SR, Goddu SM, Pratt D, Khullar D, Deasy JO, et al. Deformable registration of abdominal kilovoltage treatment planning CT and tomotherapy daily megavoltage CT for treatment adaptation. Med Phys. 2009 Feb;36(2):329-38.
37. Thongphiew D, Wu QJ, Lee WR, Chankong V, Yoo S, McMahon R, et al. Comparison of online IGRT techniques for prostate IMRT treatment: adaptive vs repositioning correction. Med Phys. 2009 May;36(5):1651-62.
38. Foroudi F, Wong J, Kron T, Rolfo A, Haworth A, Roxby P, et al. Online Adaptive Radiotherapy for Muscle-Invasive Bladder Cancer: Results of a Pilot Study. Int J Radiat Oncol Biol Phys. 2011 Oct 5;81:765-71.
39. Ahunbay EE, Peng C, Chen GP, Narayanan S, Yu C, Lawton C, et al. An on-line replanning scheme for interfractional variations. Med Phys. 2008 Aug;35(8):3607-15.
40. Brahme A, Nilsson J, Belkic D. Biologically optimized radiation therapy. Acta Oncol. 2001;40(6):725-34.
41. Ling CC, Humm J, Larson S, Amols H, Fuks Z, Leibel S, et al. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. Int J Radiat Oncol Biol Phys. 2000 Jun 1;47(3):551-60.
42. Kron T. Image guidance in the radiotherapy treatment room: can 10 years of rapid development prepare us for the future? J Radiother Pract. 2011;10:71-5.
43. ICRU. ICRU report 62: Prescribing, recording, and reporting photon beam therapy (Supplement to ICRU report 50). Bethesda: International Commission on Radiological Units and Measurements; 2000.
44. van Herk M. Errors and margins in radiotherapy. Semin Radiat Oncol. 2004 Jan;14(1):52-64.
45. Fox C, Fisher R, Kron T, Tai KH, Thompson A, Owen R, et al. Extraction of data for margin calculations in prostate radiotherapy from a commercial record and verify system. J Med Imaging Radiat Oncol. 2010 Apr;54(2):161-70.

QUALITY ASSURANCE IN RADIATION ONCOLOGY

Bryan Burmeister
Radiation Oncology, Princess Alexandra Hospital, Brisbane, Queensland.
Email: Bryan_Burmeister@health.qld.gov.au

Abstract

Quality assurance is important for any medical procedure or intervention to ensure that patients receive management that is suited to their medical condition and that which has been described in textbooks, literature or by expert opinion. Currently many procedures are complex and require a multi-step process, each stage of which may be prone to mistakes, deviations or variation in interpretation. Radiation oncology involves a very complex process of consultation, preparation or planning and execution or treatment. Each of these processes requires stringent adherence to accepted standards both within a particular radiation oncology department or within a national health system. This is particularly important with rarer conditions, or where there is some debate regarding appropriate management. When conducting research it is vital that conformity across all researchers exists. While protocols go some way to ensure this, there have to be quality assurance mechanisms to ensure uniformity and compliance to the protocol. Some deviations may have minimal effects on outcome, while others may have a profound effect and compromise patient outcomes and results of clinical trials.

Radiotherapy is a local treatment for cancer. Hence the methodology used is highly operator dependant. In this case, the operator is not one person but a team of professionals including the radiation oncologist, planning radiation therapists, physicist and treating radiation therapist. Because of this sometimes complex, multi-step process, there is margin for error which may affect outcomes in tumour control and thus survival. It is important that the process of tumour assessment, treatment planning and treatment delivery be subject to acceptable standards in order to ensure optimal outcomes for the patient. Failure to do this can result in inadequate tumour control (due to inadequate doses to the tumour) or unacceptable complications (due to excessive doses to normal tissues). The process of ensuring that both these goals are met is the core of quality assurance in radiotherapy and should be present at a departmental, national and international level.

Departmental quality assurance

Radiotherapy departments either exist as stand-alone treatment facilities or as a department within a tertiary referral hospital. Most departments consist of more than one radiation oncologist with a team of radiation therapists and medical physicists. Radiation oncologists tend to have a major interest in one or more disease sites, but in smaller departments tend to be 'multi-skilled' with no particular tumour site interest. Radiation therapists tend to rotate through both planning and treatment areas and the frequency of this rotation may vary. Medical physicists may have special interests in specific areas, but may share the quality assurance role for various disease sites. Quality assurance within departments serves both as an educational tool for training staff, as well as a point of discussion whereby participants improve their knowledge about the management of rarer tumours, complex treatment situations and controversial settings.

Incident reports

Contemporary linacs are extremely reliable but complex machines with many potential areas of malfunction. The quality of therapy delivered by the linacs is however, dependent on the staff operating the machine and their compliance to the patient's plan. Much of a patient's treatment is now automated via record and verify systems, however minor faults can still occur due to human error in the treatment room. These 'incidents' usually occur only during a small segment of a patient's overall treatment and do not result in a major outcome issue. Typical examples are a misplaced field, an under or overdose for a few fractions, or the inappropriate use of associated features such as skin build-up and wedges. It is important the all incidents be reviewed regularly and reported to the treating clinician. If an incident is seen as a recurring problem associated with a staff member or machine, suspension of treatment involving those vectors should be considered until the problem is rectified.

Chart rounds

Typically, chart rounds may take the form a discussion of all or the more complex cases in a weekly forum. In such meetings the case is presented, any imaging displayed, the contoured volumes demonstrated and finally the proposed plan displayed on a large screen. Where controversy may exist, comments may be noted in order that the treating radiation oncologist may customise the patient's plan to obtain optimum results. The areas which frequently undergo debate are the coverage of the tumour volume by the appropriate target volume, the tolerance of dose-limiting tissue close to target volumes, the optimal dose and fractionation and sometimes the technique used, whether it be three dimensional conformal treatment or intensity modulated radiation therapy. Most national accreditation bodies mandate this activity for departments to remain viable as radiotherapy training centres.

Morbidity and mortality meetings

Most curative or radical radiotherapy treatments are associated with some degree of toxicity or morbidity. Over the past two decades much the toxicity has been offset by the employment of dedicated teams of allied health professionals aimed at minimising morbidity and keeping patients out of hospital. Most of the toxicity that requires admission revolves around the development of concurrent infections during therapy and difficulty in breathing or swallowing as a result of a compromised upper aero-digestive tract. While there is little that can be done to prevent infections, most require relatively short admissions and respond well to antibiotic therapy. Aero-digestive tract problems however, can be suitably prevented in any cases. Airway compromise from tumour of the larynx or bronchus can be prevented with steroids and nutritional compromise can be prevented with alternative forms of nutritional support such as percutaneous gastrostomy or nasogastric feeding. Nevertheless, some patients are admitted to hospital during and after therapy and a small proportion may die as a result of therapy. In the modern era the number of radiotherapy treatment related acute deaths is very low.

The other major reason for admissions is palliative care. Most departments still list up to 40% of treatment intents as being palliative or aimed at symptom relief rather than cure. The aim in such therapy is to make sure toxicity from therapy is minimal, however admissions occur due to patients being unable to cope at home as a result of poor pain control, fungating tumours, lack of social support and many other reasons.

With the increasing costs of health care, it is important that all radiotherapy departments review their admissions and severe morbid events on a regular basis to see if any unforeseen activity may reduce or prevent those events.

National quality assurance

In Australia, quality assurance between the radiotherapy departments is suboptimal. Most departments follow the International Convention of Radiation Units recommendations for dosimetry, which means that within the department, target volume coverage is specified to the 95% isodose line for photons and the 90% isodose line for electrons.[1] This essentially means that receiving 60 Gy to a tumour at institution should be equivalent to receiving 60 Gy at another institution. However, not all departments obey the International Convention of Radiation Units conventions, which means that subtle dose variations exist between departments and this can lead to problems in clinical trials and if patients move from one site to another.

There are also variations in the way clinicians interpret clinical findings and treatment protocols, which may mean a patient may receive different treatments according to the way the department operates. For instance, one department may treat localised prostate cancer with 74 Gy and weekly kilovoltage image guidance and another with 78 Gy and daily image guidance using cone beam CT scans. The second of these practices is more labour intensive and much more costly than the first, but any evidence to support the second approach is based on intuitive data and no formal comparison between the two approaches exists or is planned.

For the management of cancer patients, various attempts to try and standardise therapy have been made using guidelines for each tumour site. These guidelines are based on all available evidence, including the experience of known experts in the field. Even then controversy and disagreement exists and so most guidelines are just that, with many having a set of options for treatment available. Radiotherapy is clearly a cornerstone of cancer management and does form part of the guidelines for the management of common tumours, but the less common cancers tend to get managed in a variety of ways with a range of doses, fractions and techniques being used. Fortunately in most common cancers, this has a minimal or very marginal impact on outcomes.[2-4] There have however, been cases where an accepted radiation dose schedule was thought to be both safe and effective and yet resulted in several patients developing late toxicity and disabling morbidity.[5]

Clinical trials

In national clinical trials, quality assurance is vital to ensure consistency across all participating sites. Each trial has a rigid protocol which specifies doses (to both the target volume and dose limiting tissues), number of fractions, techniques and modalities. To ensure constancy, participating sites need to be accredited before talking part in the trial. This can involve several different approaches. The most costly involves a site visit by an independent team of radiation therapists, physicists and occasionally a radiation oncologist. This is to ensure that the participating site has the experience and expertise to comply with the protocol and provide accurate data for the trial. Sometimes it can involve the site doing a 'dummy run' on an imaginary patient, with the processes carefully evaluated for compliance before the first real patient is treated. The commonest method however, involves a review of a sample of patients treated by each site by an independent review committee. Once the trial management committee is satisfied that the site is fully compliant with the sample, accrual may continue without review. Some trials of a highly technical nature will insist that all the data from all the patients be reviewed throughout the trial to ensure a minimum of violations.

The Trans Tasman Radiation Oncology Group (TROG) is the peak body in Australia and New Zealand that co-ordinates clinical trials in radiotherapy. Since its inception in 1989, it has built up a formidable infrastructure in quality assurance to manage its portfolio of clinical trials. One of the first studies published by TROG members involved a survey looking at contouring localised lung cancer using the available imaging.[6] To everyone's surprise, there was great variation among the volumes generated and even considerable variation among so-called experts in the field. More recently the importance of quality assurance in clinical trials has been highlighted by the outcomes of the 'Headstart' trial, which compared two different radio-sensitisation regimens in the definitive management of locally advanced head and neck cancer.[7] While there

was no significant difference in outcomes related to the regimens, there was a highly statistical negative impact on local control when plans were found to comply poorly with the radiotherapy protocol. This clearly showed that when using definitive radiotherapy, strict compliance to the protocol is essential and that all definitive radiotherapy trials should have a strong quality assurance component.

The cornerstone of the current TROG infrastructure is the Central Quality Management Scheme, a computer based program which can compare plans of individual patients with an 'ideal' plan and thus immediately generate data relating to possible violations.[8-10] These can then be reviewed to see if they are significant and if so, whether they are major or minor. The quality assurance program run by TROG for its clinical trials has lead to other international trials groups adopting a similar approach.

New technologies

The field of radiation oncology is plagued by the desire to try new technologies and this interest exists at all staff levels. Whether it is driven by industry or just the desire to be one better than one's neighbour is unknown. It is however, clearly an attraction for new staff and the program of getting a new technology up and running represents a challenge which many staff actually enjoy. One of the problems alluded to earlier is that comparisons between old and new technologies seldom take place. Most departments adopt the new technology based on intuitive data and the charm of the vendor. TROG has over the past three years made an honest attempt to evaluate some of these technologies in a scientifically acceptable program known as the Assessment of New Radiation Oncology Technologies And Treatments (ANROTAT) study. The study aims to evaluate the efficacy, toxicity and cost-effectiveness of intensity modulated radiation therapy at three sites (nasopharynx, anal canal and post-prostatectomy). It also aims to evaluate the same criteria for image guided radiation therapy in the definitive management of localised prostate cancer. The evidence currently available to support the use of these therapies compared to three dimensional conformal radiotherapy is currently based on retrospective data. The ANROTAT study involves 20 institutions across Australia (public and private, rural and metropolitan) which means it will give clinicians and the rest of the world some idea as to the true value of intensity modulated radiation therapy and image guided radiation therapy.

Conclusion

This review has covered the major areas where quality assurance is important in radiation oncology. There are some areas not mentioned which are probably only of minor importance. In conclusion, it is quite clear that all definitive radiotherapy plans are dependent on operator, patient and tumour factors which are subject to variation. This in turn can compromise outcomes, so it is essential that some sort of quality assurance be performed where possible. It may be only a discussion with a colleague or be subject to expert review as part of a clinical trial. Adjuvant and palliative treatments clearly have much less impact on clinical outcomes and perhaps don't require the same resources as a definitive therapy.

References

1. ICRU Report 62: Prescribing, recording and reporting photon beam therapy (supplement to ICRU 50). Washington DC, International Commission on Radiation Units and Measurements. 1999.
2. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010; 362: 513-20.
3. Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. Lancet Oncol 2012; 13: 43-54.
4. Michalski J, Winter K, Roach M, Markoe A, Sandler HM, Ryu J et al. Clinical outcomes of patients treated with 3D conformal radiation therapy (3D –CRT) for prostate cancer on RTOG 9406. Int J Rad Oncol Biol Phys 2012; 83: 363-70.
5. Johansson S, Svensson H, Larsson LG, Denekamp J. Brachial plexopathy after postoperative radiotherapy of breast cancer patients – a longer term follow-up. Acta Oncol. 2000;39:373-82.
6. Hamilton CS, Denham JW, Joseph DJ, Lamb DS, Spry NA, Gray AJ et al. Treatment and planning decisions in non-small cell carcinoma of the lung : an Australasian patterns of practice study. Clin Oncol. 1992;10:1037-43.
7. Peters LJ, O'Sullivan B, Giralt J, Fitzgerald TJ, Trotti A, Bernier J et al. Critical impact radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. J Clin Oncol. 2010;28:2996-3001.
8. Ebert MA, Harrison K, Cornes D, Howlett SJ, Joseph D, Kron T et al. Comprehensive Australasian multi-centre dosimetric intercomparison for pelvic radiotherapy - issues and logistics. J Med Imag Radiat Oncol. 2009;53:119-23.
9. Ebert MA, Haworth A, Kearwell R, Hooton B, Hug B, Spry N et al. Comparison of DVH data from multiple radiotherapy treatment planning systems. Phys Med Biol. 2010;54:508-11.
10. Middleton M, Frantzis J, Healy B, Jones M, Murry R, Kron T et al. Successful implementation of image guided radiation therapy quality assurance in the Trans Tasman Radiation Oncology Group 08.01 PROFIT study. Int J Rad Oncol Biol Phys. 2011;81:1576-81.

NOVEL RADIATION TECHNIQUES – A PERSONALISED APPROACH FOR PATIENTS WITH RECTAL CANCER

Arthur Sun Myint,[1] Vidhya Sagar Ramani,[2] Amir Montazeri,[1] Kate Perkins,[1] Robert Myerson,[3] and Jean Pierre Gerard.[4] On behalf of the ICONE Group (International Contact Radiotherapy Society).
1. Clatterbridge Cancer Centre, Bebington, Wirral, United Kingdom.
2. Premion, Wesley Radiation Oncology, Brisbane, Australia.
3. University of Washington, St Louis, Missouri, United States of America.
4. Centre Antoine Lacassagne, Nice, France.
Email: sun.myint.@clatterbridgecc.nhs.uk

Abstract

Surgery remains the standard of care for most rectal cancer as it offers the best chance of cure. However, for patients with early stage low rectal cancers there are several treatment options available using novel radiotherapy techniques. Good responders to novel radiotherapy can avoid surgery. Poor responders need salvage surgery. Patient selection is important and careful assessment after preoperative chemoradiotherapy can identify good responders, even with advanced rectal cancers. Restaging magnetic resonance imaging scans can identify good radiological responses, which need to be confirmed by clinical examination and endoscopy. A watch and wait policy can be adopted for good responders, with surgery avoided or deferred. A boost with contact radiotherapy or brachytherapy can be offered to elderly patients to improve local control. This treatment strategy needs to be evaluated via clinical trials, for which the contact x-ray and transanal endoscopic microsurgery trials have been set up. In this way a personalised approach can be offered for patients with rectal cancer using novel radiotherapy techniques.

Colorectal cancer is the third most common cancer worldwide in men (663,000 cases, 10% of total) and the second in women (517,000 cases, 9.4% of the total). Almost 60% of the cases occur in high resource regions, with the highest rate being estimated in Australia and New Zealand, where more than 14,000 new cases are diagnosed and over 4000 deaths occur each from the disease. As the ageing population increases, colorectal cancer in high resource countries could pose a major burden on health care costs.

About a quarter present with early stage (Stage 1),[1] and 25% have metastatic disease at presentation.[2] Seventy five per cent of cases are operable, however curative resection can only be carried out in 60% of cases.[3] The standard of surgical care is total mesorectal excision. However, there is considerable morbidity and mortality associated with this for elderly patients. In addition, there are wide variations in the number of cases that require abdominoperineal resection (APR) across the surgical practice for small, early stage low rectal cancers, which is clearly unacceptable.[4] With an increasingly ageing population, not all patients diagnosed with rectal cancer will be fit for surgery. In addition, initiatives such as the National Bowel Screening Program for Australians who turn 50, if successful, are likely to identify even more early rectal cancers, but not all patients who are fit will agree to extirpative surgery that involves a stoma.

Staging investigations using MRI are now mandatory for rectal cancer and those with threatened circumferential resection margins will be offered preoperative chemoradiotherapy.[5] A proportion of these cases will not have any residual disease at the time of surgery. So far, despite concerted efforts using sophisticated translational research, reliable and reproducible molecular biomarkers to predict patients who can achieve pathological complete response have not been discovered. Post treatment MRI staging may identify good responders following treatment and it may be possible to defer major surgery in those who wish to avoid it.[6] Novel radiotherapy techniques can improve local control in such cases without added toxicity and should be considered for the elderly and those medically not fit for extirpative surgery.[7]

Contact x-ray brachytherapy for small early rectal cancer (<3cm T1N0M0)

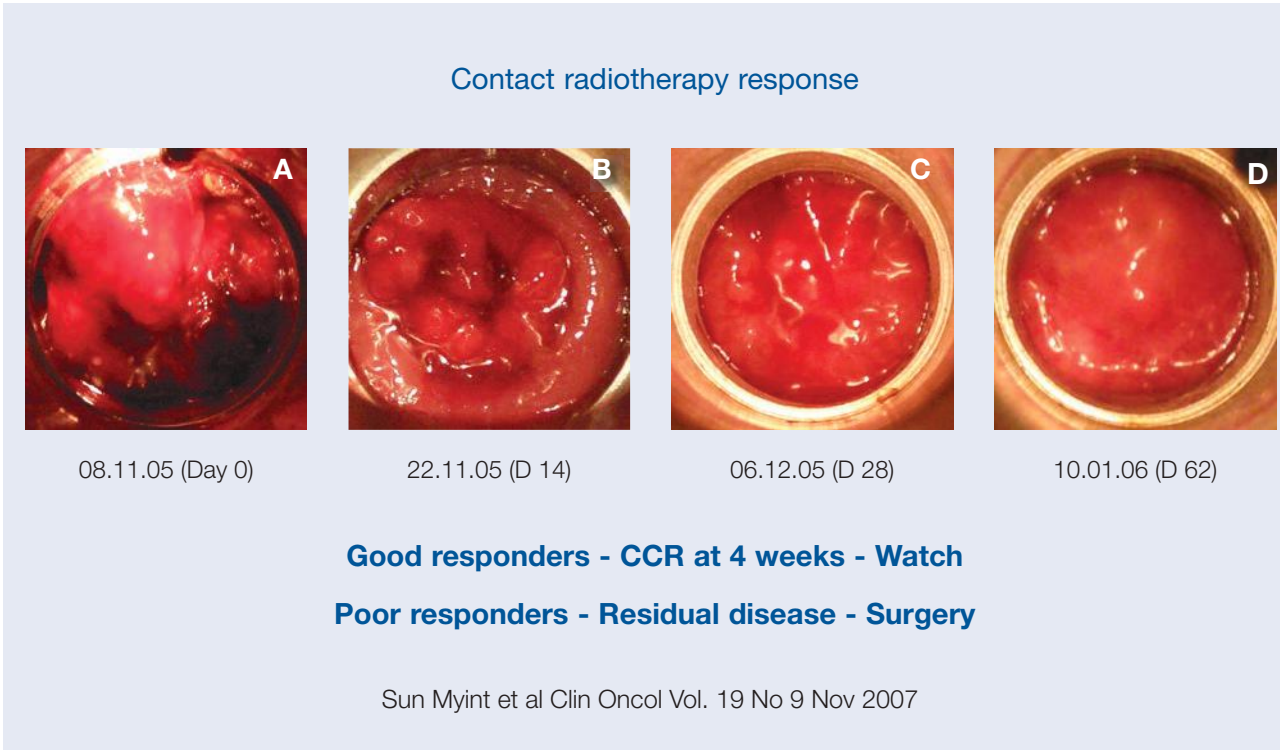
Contact x-ray brachytherapy, also called 'Papillon' technique after Professor J. Papillon who popularised this,[7] has been used to treat selected patients with small, early stage rectal cancer for the past 80 years. The main advantage of contact x-ray brachytherapy (topical radiotherapy) is its ability to target the tumour directly, with minimal damage to the normal surrounding tissue. It uses low energy x-rays (50 KV), which penetrate only a few millimetres (dose falls to 60% at 5mm depth). At each treatment tumour cells are destroyed layer by layer. Therefore, underlying normal tissues are not damaged. Contact x-ray brachytherapy uses a very high dose of radiation (30 Gy) so the tumour cell kill is proportionally higher[8]. Although the physical dose is 30 Gy, the biological equivalent dose is much higher (~45 Gy external beam equivalent). The treatment is given every two weeks -

allowing preferential recovery of normal tissue compared to tumour cells. The clinical response after two fractions can be used to differentiate between good responders and poor responders. Those who respond well after two fractions will continue with contact x-ray brachytherapy for a total of four treatments (total tumour dose 110 Gy). Figure 1 shows the typical evolution of changes seen during the treatment course of a responder to contact radiation. External beam radiotherapy (25 Gy/5#/5days) or chemoradiotherapy (45 Gy/25#/35days) can be offered to those with partial response, with the option to reassess response before extirpative surgery. If there is evidence of small residual tumour (<2cm) after radiotherapy, local excision such as transanal endoscopic microsurgery (TEMS) can be considered. If the response to radiotherapy is poor, it is important to proceed with extirpative surgery within eight to ten weeks after treatment.[9] The feasibility of this approach has been evaluated in the ongoing CONTEM -2 (CONtact and Transanal Endoscopic Microsurgery) trial, which is an observational study set up by the ICONE (International Contact Radiotherapy Society) group.

HDR brachytherapy for more advanced tumours (>3cm T1/T2/T3a N1 M0)

More advanced rectal tumours >3cm should be treated with external beam chemoradiotherapy initially to downstage and down size the tumour.[10] The response following treatment should be assessed. High dose rate (HDR) brachytherapy can be offered to those with residual tumours, which are still visible or palpable. This will treat deeper residual tumour with a higher radiation dose.[10] Contact x-ray brachytherapy delivers maximum radiation dose on the surface, whereas HDR brachytherapy also delivers radiation dose to deeper structures. Watch and wait policy can be offered to those who achieve complete clinical response. TEMS can be offered to those with minimal residual disease <2cm.[10] The value of HDR brachytherapy boost was evaluated in a phase 3 randomised Danish trial comparing HDR rectal boost following chemoradiotherapy with external beam chemoradiotherapy alone. This has shown benefit for brachytherapy boost in terms of increased pathological complete response rates and microscopically clear resection margin (R0) rates in T3 rectal tumours.[11]

Figure 1: *Typical response to contact x-ray brachytherapy in a responder. Image A shows findings at first treatment session for a patient with T1N0 low rectal tumour. Image B shows findings two weeks later at the second session with only a minimal change in appearance. Image C shows further response at the third treatment session. Almost complete resolution at the time of the fourth treatment session as illustrated by image D. Images reproduced from Sun Myint et al. (in press).*



The value of contact x-ray brachytherapy (Papillon) was evaluated in the Lyon 96-02 French trial and has demonstrated increased sphincter preservation (76% v 44%) in favour of Papillon boost.[12] The updated long-term results presented at the European Society for Radiotherapy and Oncology meeting in 2011 confirmed the initial conclusions.[13] The feasibility of this approach has been evaluated in the CONTEM-3 trial, which is an observational study set up by the International CONtact radiotherapy (ICONE) group for elderly and younger patients not keen on having a stoma.

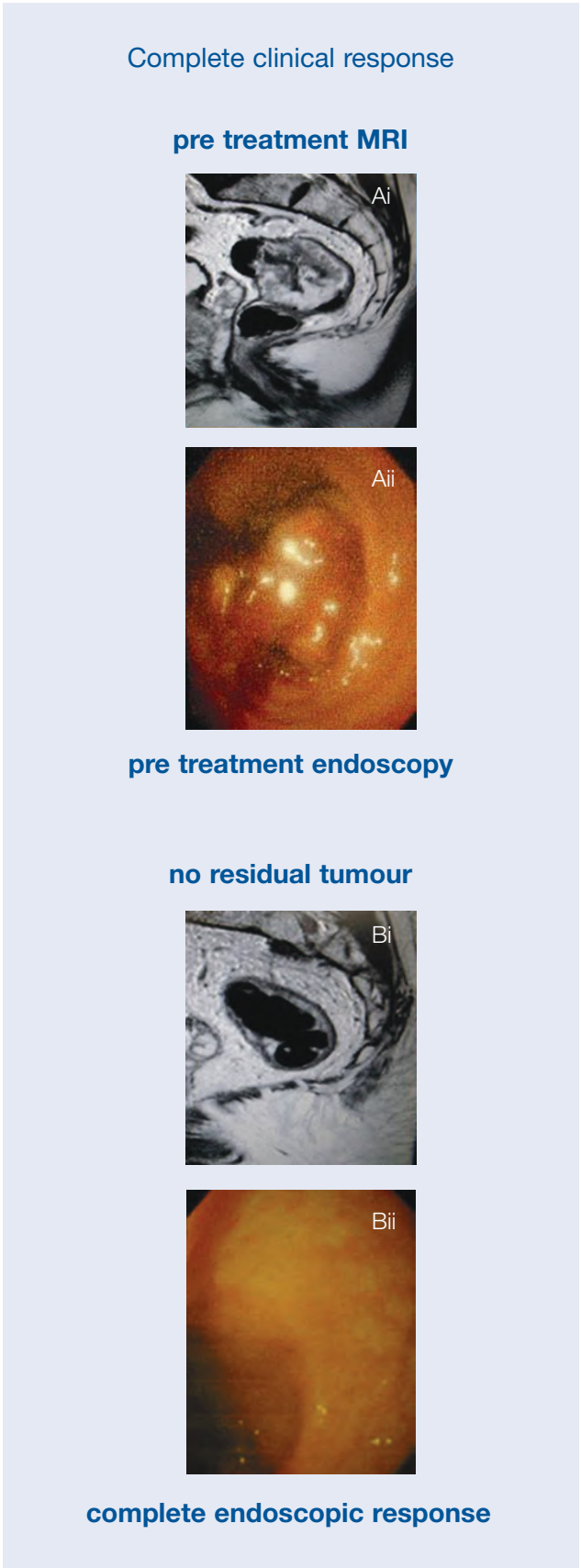
Watch and wait policy for clinical complete response? (T3/T4 - N1/N2 M0)

Approximately 15-20% of patients will achieve complete response following preoperative chemoradiotherapy for advanced rectal cancer. Regardless of the response, most of these patients, will be offered radical surgery, as planned prior to their pre-operative treatment. There are several publications on the long-term data on these patients who are regarded as good responders showing improved recurrence free survival and overall survival.[14,15] The question is how to identify these patients before planned surgery. Multidisciplinary teams recommend restaging MRI to assess the response. However, the majority of surgeons are reluctant to change the type of surgery that has been planned prior to treatment (eg. APR for low rectal cancer <6cm) regardless of the response.[16] A recent publication from the Magnetic Resonance Imaging in Rectal Cancer European Equivalence Study group on MRI response following chemoradiotherapy suggests that good responders can be identified prior to surgery (figure 2). Those who achieve complete pathological or near complete pathological response have better long-term outcomes than poor responders.[6] Therefore, a less aggressive management approach can be adopted for good responders, with deferral of extirpative surgery when the patient has achieved a complete clinical response. There are some concerns about microscopic sub-mucosal residual disease in these apparent complete clinical responders, where MRI may not be able to pick up small volumes of residual malignant cells.[17] These patients can be offered contact x-ray brachytherapy (Papillon) or (topical radiotherapy) to sterilise the residual cancer cells. A randomised trial, CONTEM-4, will address the role of contact boost in improving the outcomes for the good responders.

1.4 HDR brachytherapy or contact x-ray brachytherapy as a retreatment

Second malignancy in the pelvis is now increasingly recognised in patients who have had prior radiation treatment for carcinoma of the cervix, bladder or prostate cancer. These patients are usually offered extirpative surgery for their second malignancy. APR has to be offered even for small early stage low rectal cancers. Contact x-ray brachytherapy can be offered as an alternative for small low rectal cancer. If there is small residual tumour after contact x-ray brachytherapy, local excision or TEMS can be carried out. HDR brachytherapy can be used for more advanced tumours in the upper rectum that require preoperative radiotherapy for circumferential resection margin involvement. Due to the unique properties of

Figure 2: *Wait and watch policy for complete responders. Pre treatment MRI (Ai) and endoscopy (Aii) of a patient who subsequently showed complete clinical response to neoadjuvant chemoradiation as assessed by interval MRI (Bi) and endoscopy.*



brachytherapy, the radiation dose to the previously treated tissues will be lower, which helps reduce the damage caused by repeated or re-irradiation.[13]

Implications

The standard of surgical care in rectal cancer is total mesorectal excision. However, the mortality and morbidity from radical surgery is considerable, especially high in elderly and medically compromised patients. The mortality for a patient above the age of 80 years is 14% and 25% for those above 90 years.[18] Morbidity such as delayed wound healing (20%), para-stomal hernias (30%) and anastomotic leakages (10%) is much higher with radical surgery.[19] The proportion of cases presenting with early stage rectal cancer in Australia is expected to increase in the next decades due to the introduction of colorectal screening. Despite detection of early stage disease, the gold standard surgical treatment for low rectal cancer is APR with permanent colostomy. This is an over-treatment as some cases can be cured with less aggressive surgical treatment. There is a national trial known as Transanal Endoscopic Microsurgery and Radiotherapy in Early Rectal Cancer (TREC) trial addressing this issue in the UK. For most patients, general anaesthetic is necessary even for local excision such as TEMS. For those patients who are not fit for general anaesthetic, contact radiotherapy or brachytherapy can be offered as an alternative treatment. Although the cure rates are not as high as radical surgery, there is lower mortality and morbidity.[20] Patients should be fully aware of the treatment options that are available. All new cases should be discussed by the colorectal multidisciplinary teams. The outcome of the decision made at the multidisciplinary team should be conveyed to the patient by the clinician in charge and a plan of management mutually agreed. The patient's choice should be taken into consideration as they may accept a higher oncological risk treatment option to avoid a stoma. If there is doubt, complex cases should be referred to specialised centres with experience so their access to best possible treatment is not compromised.

Outlook

Radical surgery should be avoided in elderly patients with early stage small low rectal cancer (T1N0M0), as the mortality and morbidity is high.[18] Contact radiotherapy can be offered as an alternative treatment option. The response to treatment can be assessed immediately after treatment and major surgery can be avoided for good responders. Poor responders should be offered immediate salvage surgery. Partial responders can be offered local excision using TEMS. A small proportion of patients (approximately 20%) with more advanced low rectal cancers (T3 N1M0) could achieve complete clinical response after a course of chemoradiotherapy and the patients could be offered to adopt a watch and wait policy as part of a clinical trial. Those with more advanced tumours (T2/T3a N0M0) who are elderly can be treated with a similar approach as part of a clinical trial (CONTEM-3). Their long-term outcome is not compromised, however careful follow-up is necessary to detect recurrences.[20] As the treatment options are complex, they should be treated as part of the CONTEM trials in centres with experience and expertise.

We now have several novel radiation techniques available at our disposal in managing different stages of rectal cancer. This has allowed us to choose a modality that is suitable for a particular patient depending on the stage of disease, age and their choice of treatment, offering a personalised approach.[21]

References

1. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet. 2009;373:811-20.
2. Cancer Research UK. Bowel cancer: Survival statistics - England and Wales 2004. [Internet] London: Cancer Research UK, October 2009. Available from http://info.cancerresearchuk.org/cancerstats/types/bowel/survival Accessed May 2012.
3. NHS Information Centre. The National Bowel Cancer Audit Annual Report 2011. [Internet] Leeds: NHS Information Centre, 2011. Available from: http://www.ic.nhs.uk/bowelreports Accessed May 2012.
4. Morris E, Quirke P, Thomas JD, Fairley L, Cottier B, Forman D. Unacceptable variation in abdominoperineal excision rates for rectal cancer: Time to intervene? Gut. 2008;57:1690-1697.
5. Colorectal cancer: the diagnosis and management of colorectal cancer. NICE Colorectal guidelines. CG131,Published Nov 2011. [Internet] Available from: http://www.nice.org.uk/colorectalcancerguidance-CG131 Accessed May 2012.
6. Patel UB, Taylor F, Blomqvist L, George C, Evans H, Brown G, et al. Magnetic Resonance Imaging–Detected Tumour Response for Locally Advanced Rectal Cancer Predicts Survival Outcomes: MERCURY Experience. J Clin Oncol. 2011; 29:3753-3760.
7. Sun Myint A, Gerard JP, Lindegard J, Ramani VS, Montazeri A, Myerson R. On behalf of ICONE (International Contact Radiotherapy Society) group. Renaissance of contact radiotherapy with RT 50 Papillon machine – A new treatment option for elderly and other patients with early low rectal cancer? Colorectal Dis. 2011;13 (Suppl 5): Abst. 486.
8. Dale RJ. The Radiobiology of Papillon-type Treatments. Clin Oncol 2007: 19; 649-654.
9. Sun Myint A, Grieve RJ, McDonald AC, Levine E, Ramani S, Perkins K, et al. Combined modality treatment for early rectal cancer The UK experience. Clin Oncol. 2007;19:674-681.
10. Sun Myint A, Mukhopadhyay T, Ramani VS, Perkins K, Snee AJ, Jelly F, et.al. Can increasing the dose of radiation by HDR brachytherapy boost following pre-operative chemoradiotherapy for advanced rectal cancer improve surgical outcomes? Colorectal Dis. 2010; 12:(Suppl2) 30-36.
11. Jacobsen AKM, Appelt AL, Lindebjerg J, Ploeen J, Rafaelsen SR, Vuong T et al. The dose-effect relationship in preoperative chemoradiation of locally advanced rectal cancer: Preliminary results of a phase III trial. J Clin Oncol. 2011:29:(abstr 3512).
12. Gerard JP, Chapet O, Nemoz C, Hartweig J, Romestaing P, Coquard R et al. Improved Sphincter Preservation in Low Rectal Cancer with High-Dose Preoperative Radiotherapy: The Lyon R96-02 Randomized Trial. J Clin Oncol. 2004;22:2404-2409.
13. Sun Myint A, Lee CD, Hoskin P. Rectal Brachytherapy. 2nd ed. Peter Hoskin and Catherine Coyle editors. Radiotherapy in practice – Brachytherapy. London: Oxford University Press,2011,151-161.
14. Park IJY, You YN, Argarwal A, Skibber J, Crane C, Chang GJ et.al. Neoadjuvant treatment responseas an early response indicator for patients with rectal cancer. J Clin Oncol 2012; 30:17770-17776.
15. Gollins SW, Sun Myint A, Haylock BJ, Wise M, Saunders M, Neupane R et al. Preoperative Chemoradiotherapy using concurrent capecitabine and Irinotecan in magnetic resonance imaging-defined locally advanced rectal cancer: Impact on long–term clinical outcomes. J Clin Oncol 2011;29 :1042-1049.
16. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudelko M et. al Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short term radiotherapy vs. conventionally fractionated radiochemotherapy Radiotherapy and oncology 2004;72:15-24.
17. Bujko K, Sopylo R, Kepka L. Local excision after Radio (Chemo) therapy for rectal cancer: Is it safe? Clin Oncol. 2007;19:693-700.
18. Report of The National Bowel Cancer Audit Project "Knowing your results" (2005) The Association of Coloproctology of Great Britain & Ireland. [Internet] Available from: www.nbocap.org.uk Accessed May 2012.
19. Marijnen CAM, van de Velde CJH, Putter H, van den Brink M, Maas CP, Martijn H et.al. Impact of short term preoperative radiotherapy on health related quality of life and sexual functioning in primary rectal cancer: Report of a multicenter randomised trial. J Clin Oncol 2005;23:1847-1858.
20. Hershman MJ, Sun Myint A, Makin CA. Multi-modality approach in curative local treatment of early rectal carcinomas Colorectal Disease. 2003;5:1-6
21. Gerard JP, Myerson R, Sun Myint A. Contact radiotherapy Rectal Cancer-International perspectives on multimodality treatment. New York: Springer (Humana Press); 2010.

PALLIATIVE RADIOTHERAPY IN MODERN PRACTICE

Susan Wiltshire and Andrew Potter
Royal Adelaide Hospital, Adelaide, South Australia.
Email: susan.wiltshire@health.sa.gov.au

Abstract

Radiotherapy provides effective symptom relief for patients with metastatic disease. The type and duration of radiotherapy depends on various factors including the patient's performance status and the symptom being palliated. Hypofractionated (shorter courses with larger doses per treatment) regimens are effective in relieving pain from metastatic bone disease and epidural spinal cord compression. Whole brain radiotherapy plays an important role in the management of brain metastases. More aggressive treatment with surgery, stereotactic radiosurgery, or high dose conventional radiotherapy may be appropriate for selected patients with a favourable prognosis.

Radiotherapy plays an important role in palliating the symptoms of metastatic disease. It is commonly employed to treat bone and cerebral metastases, as well as symptoms arising from the primary site of disease. Palliative treatments make up a significant proportion of a radiotherapy departments' workload, typically accounting for 30-50% of treatments delivered. Potential benefits from any palliative treatment must be carefully balanced against toxicities and optimal resource utilisation. Ideally, palliative treatments are effective, cause minimal side-effects, consume few resources and have little or no negative impact on quality of life. Many factors need to be considered when deciding on appropriate palliative treatment and on how aggressively to treat individuals. Here we discuss the palliative radiotherapy treatments commonly employed, as well as highlight selected emerging technologies.

Bone metastases

Bone is a common site of metastatic disease, with as many as 80% of patients with solid tumours developing painful bony metastases during the course of their illness.[1] Bone metastases are a particularly common manifestation of distant relapse from prostate, breast and lung cancers. They can cause severe and debilitating effects including pain, hypercalcaemia, pathological fracture and epidural spinal cord compression.

External beam radiotherapy can significantly reduce pain, with overall response rates of 60-70% and a complete response in one-third of patients.[2] The most commonly used schedules for treatment of bone metastases are a single 8 Gy fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions. Three meta-analyses,[3-5] and a recent update by Chow et al,[2] have demonstrated the efficacy of a single fraction compared to multiple fractions, with no difference in overall and complete response rates in patients with uncomplicated bone metastases. Dose fractionation choice does not significantly impact on pathological fracture or spinal cord compression rates at the irradiated site. Retreatment rates are higher after a single fraction (20% compared with 8%), however this may be due to radiation oncologists' increased willingness to retreat after a previous single treatment.[2] Single treatments have the advantage of being more convenient than fractionated courses, which is of particular importance in the palliative setting. Acute side-effects are generally similar between single and multiple treatment regimens; however several authors have reported more acute toxicities from multiple fractions.[6-8] These findings have led to a single 8 Gy fraction being the recommended treatment for uncomplicated painful bone metastases in the recent American Society for Radiation Oncology guidelines,[9] and by the UK Royal College of Radiologists.[10] Despite the evidence, there continues to be a reluctance to prescribe a single fraction. As studies of patterns of practice in Australia and New Zealand demonstrate, radiation oncologists continue to favour fractionated courses.[11] Surveys on an international scale also demonstrate this practice, with fractionated courses favoured over a single treatment, particularly in the US.[12]

Controversy remains regarding the optimal dose fractionation for certain subgroups of patients with bone metastases. Specific groups include patients deemed to have a relatively good prognosis, patients with bone metastases causing neuropathic pain and patients with 'complicated' lesions, ie. bone metastases causing a fracture, spinal cord compression, or with a soft tissue component. For patients deemed to have a better prognosis there is little evidence to support the use of multiple fractions. The RTOG (Radiation Therapy Oncology Group) 9714 trial,[8] which compared a single 8 Gy fraction with 30 Gy in 10 fractions, included only patients with breast or prostate cancer, with 75% of patients having a Karnofsky performance status of ≥70. The authors found no dose response and concluded that a single fraction should be the standard treatment for all patients, including those with a favourable prognosis.

For patients with neuropathic pain from bony metastases, the optimal dose and fractionation schedule remains unclear.[13] Only one randomised trial has addressed the issue comparing a single 8 Gy fraction with 20 Gy in 5 fractions, finding no significant difference in overall response rates.[14] Outcome measures other than pain response were generally poorer in the single-fraction arm, including time to treatment failure. Although interpreting

the results with caution, the authors concluded that it was reasonable to recommend multiple fractions (where resources allow), except in cases of poor performance status, where a single fraction is appropriate.

Stereotactic body radiotherapy (SBRT) is emerging as a promising technique for carefully selected patients. Vertebral metastases commonly cause pain and if left untreated may lead to fracture and/or epidural spinal cord compression (ESCC).[15] Conventional fractionated radiotherapy encompasses the tumour volume plus a margin to avoid geographical miss and treat subclinical disease extension. This approach limits the dose that can be delivered to the tumour, particularly in the setting of re-irradiation, due to dose constraints of adjacent normal tissue (most notably the spinal cord). Technological advances in radiotherapy planning and delivery, namely the advent of intensity modulated radiotherapy and image guided radiotherapy, have led to the emergence of SBRT as an alternative, more aggressive treatment option to conventional radiotherapy for selected patients with spinal metastases.[16]

Spine SBRT typically involves one to five fractions of high dose radiation to the target volume while sparing the surrounding normal tissues. Common doses include 24 Gy in 3 fractions or 16 Gy in a single fraction.[17] This allows delivery of four to six times the biologically effective dose of conventional external beam radiotherapy, with the aim of maximising local disease control and reducing re-treatment rates, while minimising the risk of radiation myelopathy. Vertebral metastases provide an ideal application for SBRT techniques given the anatomy of the spine and the potential morbidity associated with uncontrolled vertebral disease. SBRT is much more complex and resource intensive than conventional radiotherapy, with patient selection requiring a multidisciplinary approach. Hence this treatment is currently limited to patients with a good performance status, low volume of metastatic disease and 'radio-resistant' tumour histology.[16]

Published data confirms the efficacy of SBRT, with response rates comparable to conventional radiotherapy and local control rates of 80-95%. However, current evidence remains limited to non-randomised trials and retrospective series.[17] The clinical advantages of SBRT over conventional treatment remain controversial; a randomised RTOG trial (RTOG 0631) is currently underway to compare SBRT and conventional radiotherapy prospectively. Favourable dose distributions achievable with SBRT also show promise in the setting of re-irradiation of vertebral metastases.[17]

Epidural spinal cord compression

ESCC is an important complication of metastatic disease involving the spine or epidural space. If left untreated, ESCC can lead to relentless pain and major neurological deficits.[15] The goals of treatment are pain relief, neurological maintenance or recovery, and improving or maintaining quality of life. This should be achieved utilising treatments that are appropriate for the patient's life expectancy and burden of disease. In general, patient survival with ESCC is three to six months. However, factors indicating a better prognosis include a solitary skeletal metastasis, absence of brain and visceral metastases, and a long interval between diagnosis of cancer and presentation with ESCC.[18] The primary disease site is of prognostic value, with one report demonstrating poor survival with non-small cell lung cancer, (median survival 1.5 months), while myeloma had the best median survival at 6.7 months.[19]

The ability to ambulate at presentation is not only an important quality of life factor but is of prognostic value, with several authors documenting significantly improved survival in patients able to mobilise after treatment.[20,21] Rades et al also demonstrated that patients with a slower onset of motor deficits had favourable functional outcomes.[22] The single most important prognostic factor for regaining or maintaining ambulation after treatment of an ESCC is pre-treatment neurologic status,[20,22-24] highlighting the importance of prompt diagnosis and treatment.

Individualised treatment of ESCC requires consideration of prognosis, spinal stability, histology, presence of bony compression and previous spinal irradiation. Bony compression is a negative predictive factor for achieving ambulation after radiotherapy.[25] Although there is limited evidence, it is generally accepted that bony compression and/or spinal instability represent relative indications for surgery.[25]

In carefully selected patients, aggressive surgical debulking plus spinal stabilisation followed by radiotherapy, leads to higher ambulatory rates compared with radiotherapy alone. Patchell et al evaluated patients with a known diagnosis of cancer (other than lymphoma and primary spine tumours), a single level of cord compression, and paraplegia for no more than 48 hours.[26] Patients received either radiotherapy alone (30 Gy in 10 fractions), or direct circumferential surgical decompression followed by the same radiotherapy. The study was terminated early after a planned interim analysis demonstrated that patients treated with surgery followed by radiotherapy had a significantly higher ambulatory rate (84% versus 57%) and retained the ability to walk significantly longer than those treated with radiotherapy alone (median 122 v 13 days). However, surgery is associated with considerable morbidity which must be considered when deciding on optimal treatment.[25]

Neurologic progression during or directly after radiotherapy is another indication for surgical intervention. Patchell et al reported that 30% of patients who underwent surgical salvage following progression during or directly after radiotherapy, regained the ability to ambulate.[27] However, surgery following radiotherapy was associated with a near doubling of toxicity compared with those who underwent surgery first.

Radiotherapy alone remains an important primary modality in the treatment of ESCC, as many patients are unsuitable for surgery due to medical co-morbidities, poor performance status, short life expectancy, or extensive spinal involvement. Pain from ESCC is expected to respond to radiotherapy in 60-80% of cases,[23] but functional benefits are more variable. In a report by Maranzano et al, 90% of patients who were ambulant pre-treatment retained this ability and 30% of non-walking patients regained ability. However, none of the 17 paraplegic

patients improved with respect to ambulation.[28] Patients with radiosensitive tumours, such as myeloma, seminoma, lymphoma and breast cancer, have a higher likelihood of functional recovery, even if paraplegic at presentation.[29]

Optimal radiotherapy dose for treatment of ESCC remains uncertain. Various dose fractionation schedules have been reported, ranging from a single 8 Gy fraction to more protracted courses such as 30 Gy in 10 fractions. In patients with a good prognosis who are ineligible for surgery a more protracted course may be beneficial. A prospective, international non-randomised study of 231 patients treated with either short course (a single 8 Gy fraction or 20 Gy in 5 fractions) or long course (30 Gy in 10 fractions, 37.5 Gy in 15 fractions, or 40 Gy in 20 fractions) radiotherapy, concluded that longer fractionation schemes improved progression-free survival (72% v 55%) and local control (77% v 61%) at 12 months.[30] The radiotherapy schedule did not impact on overall survival or motor function post treatment. In addition, in a prospective study by Rades et al, 40 Gy in 20 fractions did not improve functional outcomes or ambulatory status compared to 30 Gy in 10 fractions.[31] As such, the debate as to whether protracted courses are truly beneficial remains open and is currently being evaluated in a randomised trial (SCORAD III) comparing 20 Gy in 5 fractions to a single 8 Gy fraction.

Radiotherapy schedules for patients with a poor prognosis have been evaluated in two randomised control trials by Maranzano et al.[28 32] The first compared 18 Gy in two fractions a week apart, with split course radiotherapy (15 Gy in three fractions, four day rest, followed by 15 Gy in five fractions) to a total dose of 30 Gy in two weeks. There was no significant difference in ability to ambulate, duration of ambulation, bladder function, overall survival, toxicity or pain relief. In the second study, patients were randomised to 16 Gy in two fractions over one week or a single 8 Gy fraction. The same outcomes were assessed with no difference shown between arms. Thus a single 8 Gy fraction is effective and safe in poor prognosis patients.

Brain metastases

Brain metastases are a common source of morbidity and mortality in cancer patients, affecting 20-40% of adults with systemic malignancy.[33] The mainstay of treatment for brain metastases has been corticosteroids and whole brain radiotherapy (WBRT). In patients with multiple unresectable brain metastases, the use of WBRT increases the average survival from one month with corticosteroids alone, to three to six months.[34] Similar to ESCC, prognosis is one of the key elements in deciding on the most appropriate treatment. Key parameters that determine survival after the diagnosis of brain metastases are performance status, the extent of extracranial disease and age – parameters included in recursive partitioning analysis prognostic classes.[35] More recently, the prognostic importance of primary site and number of metastases have been recognised by inclusion in the Diagnosis-Specific Graded Prognostic Assessment.[36]

The benefit of WBRT in poor prognosis patients has not been clearly established. A prospective observational study by Bezjak et al of patients treated with corticosteroids and WBRT found that only 19% of patients had improvement in their neurological symptoms or quality of life one month after radiotherapy.[37] Nearly a third of patients had worse neurological symptoms and 27% were deceased at one month or soon after treatment. The authors proposed that the apparent lack of benefit from WBRT seen in their study may be related to the poor performance status of subjects and also questioned whether even short fractionation schedules of radiotherapy were appropriate for some patients. This question is currently being evaluated in a phase III randomised control trial assessing the impact of radiotherapy versus supportive care on quality of life and survival in patients with inoperable brain metastases from non-small cell lung carcinoma.[38]

Patients with oligometastatic cerebral disease (ie.1-4 brain metastases), in the setting of otherwise favourable prognostic factors, may benefit from a more aggressive approach. Three randomised trials have addressed the utility of surgery in addition to WBRT for a solitary cerebral metastasis. Two of these trials demonstrated a survival advantage with the addition of surgery.[39-41] The third trial showed no difference in median survival with the addition of surgery.[42] This incongruent result may be due to inclusion criteria allowing patients with a Karnofsky performance status as low as 50. It is important to note that in the two positive trials, the survival was universally poor for patients with disseminated disease or advanced age. Thus, it appears that for some good prognosis patients with a resectable solitary cerebral metastasis, surgery can prolong survival relative to WBRT alone, however there is no evidence to support surgery for patients with a poor prognosis.[43]

Similarly, stereotactic radiosurgery has been shown to prolong survival in selected patients. Stereotactic radiosurgery utilises multiple convergent beams to deliver a single high dose of radiation precisely to a target volume, with rapid dose fall to minimise the risk of damage to surrounding normal tissue. An RTOG trial of WBRT +/- radiosurgery in patients with 1-3 brain metastases showed an improvement in survival for patients with a solitary lesion.[44] A randomised trial by Kondziolka et al of WBRT plus radiosurgery, versus WBRT alone, was terminated after accrual of just 27 patients when an interim analysis showed one-year local brain failure rates of 8% versus 100%, respectively.[45] There was no difference in survival between the two arms; however this may be due to the small sample size or the inclusion of patients with 2-4 metastases.

The positive results of aggressive local therapy have raised the question of the additional benefit of WBRT. This issue has been examined in multiple randomised trials which have demonstrated that in oligometastatic patients (≤ 4 cerebral metastases),[46-51] the addition of WBRT to local therapy leads to lower rates of intracranial failure (both at the original site of the metastasis and elsewhere in the brain), but does not improve survival.[52]

Multiple studies have compared different radiation schedules of WBRT.[53-61] Schedules examined include conventional fractionated regimens of 12 Gy in 2 fractions, 20 Gy in 5 fractions, 30 Gy in 10 fractions, 40 Gy in 20 fractions and an

accelerated schedule of 40 Gy in 20 fractions delivered twice daily. Despite extreme heterogeneity in these schedules, there is no compelling evidence to demonstrate differences in survival, palliation, or toxicity.[52] In the largest of these trials, performed by the RTOG,[53] patients were assigned to 40 Gy in 20 fractions, 40 Gy in 15 fractions, 30 Gy in 15 fractions, 30 Gy in 10 fractions, or 20 Gy in 5 fractions. The overall response rate and median survival were equivalent in all arms. Patients treated with larger fractions over a shorter time responded more quickly, but the duration of clinical response and time to progression were similar in all treatment arms. This has led to 30 Gy in 10 fractions or 20 Gy in 5 fractions being accepted as standard fractionation for palliation of brain metastases.

Conclusion

Radiotherapy is an effective modality in palliating symptoms of metastatic disease and in certain circumstances may prolong survival. Treatments should be individualised based on the patient's overall disease state and performance status, among other factors. In general, shorter fractionation schedules, or in the case of bony metastases a single fraction, provide effective treatment while minimising inconvenience for patients, and should be strongly considered as the treatment regimen for all palliative patients.

References

1. Nielsen OS. Palliative radiotherapy of bone metastases: there is now evidence for the use of single fractions. Radiother Oncol. 1999;52(2):95-6.
2. Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clinical Oncol. 2012;24(2):112-24.
3. Wu JS, Wong R, Johnston M, Bezjak A, Whelan T, Cancer Care Ontario Practice Guidelines Initiative Supportive Care G. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. Int J Radiat Oncol Biol Phys. 2003;55(3):594-605.
4. Sze WM, Shelley MD, Held I, Wilt TJ, Mason MD. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy--a systematic review of randomised trials. Clin Oncol. 2003;15(6):345-52.
5. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. Am J Clin Oncol. 2007;25(11):1423-36.
6. Foro Arnalot P, Fontanals AV, Galceran JC, Lynd F, Latiesas XS, de Dios NR, et al. Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. Radiother Oncol. 2008;89(2):150-5.
7. Kaasa S, Brenne E, Lund JA, Fayers P, Falkmer U, Holmberg M, et al. Prospective randomised multicenter trial on single fraction radiotherapy (8 Gy x 1) versus multiple fractions (3 Gy x 10) in the treatment of painful bone metastases. Radiother Oncol. 2006;79(3):278-84.
8. Hartsell WF, Scott CB, Bruner DW, Scarantino CW, Ivker RA, Roach M, 3rd, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst. 2005;97(11):798-804.
9. Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys. 2011;79(4):965-76.
10. Radiotherapy Dose-fractionation. London: The Royal College of Radiologists; 2006. 64p.
11. Roos DE. Continuing reluctance to use single fractions of radiotherapy for metastatic bone pain: an Australian and New Zealand practice survey and literature review. Radiother Oncol. 2000;56(3):315-22.
12. Chow E, Hahn CA, Lutz ST. Global Reluctance to Practice Evidence-based Medicine Continues in the Treatment of Uncomplicated Painful Bone Metastases Despite Level 1 Evidence and Practice Guidelines. Int J Radiat Oncol Biol Phys. 2012;83(1):1-2.
13. Dennis K, Chow E, Roos D, DeAngelis C, Hartsell W, van der Linden Y, et al. Should bone metastases causing neuropathic pain be treated with single-dose radiotherapy? Clinical Oncol. 2011;23(7):482-4.
14. Roos DE, Turner SL, O'Brien PC, Smith JG, Spry NA, Burmeister BH, et al. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). Radiother Oncol. 2005;75(1):54-63.
15. Loblaw DA, Laperriere NJ. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. Clinical Oncol. 1998;16(4):1613-24.
16. Dahele M, Fehlings MG, Sahgal A. Stereotactic radiotherapy: an emerging treatment for spinal metastases. Can J Neurol Sci. 2011;38(2):247-50.
17. Sahgal A, Larson DA, Chang EL. Stereotactic body radiosurgery for spinal metastases: a critical review. Int J Radiat Oncol Biol Phys. 2008;71(3):652-65.
18. Rades D, Fehlauer F, Schulte R, Veninga T, Stalpers LJ, Basic H, et al. Prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression. Clinical Oncol. 2006;24(21):3388-93.
19. Loblaw DA, Laperriere NJ, Mackillop WJ. A population-based study of malignant spinal cord compression in Ontario. Clinical Oncol. 2003;15(4):211-7.
20. Maranzano E, Latini P, Checcaglini F, Ricci S, Panizza BM, Aristei C, et al. Radiation therapy in metastatic spinal cord compression. A prospective analysis of 105 consecutive patients. Cancer. 1991;67(5):1311-7.
21. Rades D, Rudat V, Veninga T, Stalpers LJ, Basic H, Karstens JH, et al. A score predicting posttreatment ambulatory status in patients irradiated for metastatic spinal cord compression. Int J Radiat Oncol Biol Phys. 2008;72(3):905-8.
22. Rades D, Karstens JH. A comparison of two different radiation schedules for metastatic spinal cord compression considering a new prognostic factor. Radiotherapy and oncology: journal of the German Rontgengesellschaft. 2002;178(10):556-61.
23. Maranzano E, Latini P. Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: final results from a prospective trial. Int J Radiat Oncol Biol Phys. 1995;32(4):959-67.
24. Kim RY, Spencer SA, Meredith RF, Weppelmann B, Lee JY, Smith JW, et al. Extradural spinal cord compression: analysis of factors determining functional prognosis--prospective study. Radiology. 1990;176(1):279-82.
25. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. Clinical Oncol. 2005;23(9):2028-37.
26. Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005;366(9486):643-8.
27. Patchell R TP, Regine F. A randomized trial of direct decompressive surgical resection in the treatment of spinal cord compression caused by metastasis. Proc Am Soc Clin Oncol. 2003;21(1 (abstr 2).
28. Maranzano E, Trippa F, Casale M, Costantini S, Lupattelli M, Bellavita R, et al. 8Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. Radiother Oncol. 2009;93(2):174-9.
29. Gerszten PC, Mendel E, Yamada Y. Radiotherapy and radiosurgery for metastatic spine disease: what are the options, indications, and outcomes? Spine. 2009;34(22 Suppl):S78-92.
30. Rades D, Lange M, Veninga T, Rudat V, Bajrovic A, Stalpers LJ, et al. Preliminary results of spinal cord compression recurrence evaluation (score-1) study comparing short-course versus long-course radiotherapy for local control of malignant epidural spinal cord compression. Int J Radiat Oncol Biol Phys. 2009;73(1):228-34.
31. Rades D, Fehlauer F, Stalpers LJ, Wildfang I, Zschenker O, Schild SE, et al. A prospective evaluation of two radiotherapy schedules with 10 versus 20 fractions for the treatment of metastatic spinal cord compression: final results of a multicenter study. Cancer. 2004;101(11):2687-92.
32. Maranzano E, Bellavita R, Rossi R, De Angelis V, Frattegiani A, Bagnoli R, et al. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. Clinical Oncol. 2005;23(15):3358-65.
33. Mehta MP, Tsao MN, Whelan TJ, Morris DE, Hayman JA, Flickinger JC, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys. 2005;63(1):37-46.
34. Posner JB. Management of brain metastases. Revue neurologique. 1992;148(6-7):477-87.
35. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys. 1997;37(4):745-51.
36. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys. 2010;77(3):655-61.
37. Bezjak A, Adam J, Barton R, Panzarella T, Laperriere N, Wong CS, et al. Symptom response after palliative radiotherapy for patients with brain metastases. Eur J Cancer Clin Oncol. 2002;38(4):487-96.
38. Mulvenna PM. The management of brain metastases in patients with non-small cell lung cancer-is it time to go back to the drawing board? Clinical Oncol 2010;22(5):365-73.
39. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med. 1990;322(8):494-500.

40. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann Neurol. 1993;33(6):583-90.
41. Noordijk EM, Vecht CJ, Haaxma-Reiche H, Padberg GW, Voormolen JH, Hoekstra FH, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. Int J Radiat Oncol Biol Phys. 1994;29(4):711-7.
42. Mintz AH, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, Fisher B, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. Cancer. 1996;78(7):1470-6.
43. Roos D. What is the randomised evidence for surgery and stereotactic radiosurgery for patients with solitary (or few) brain metastases? Int J Evid Based Healthc. 2011;9(1):61-6.
44. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet. 2004;363(9422):1665-72.
45. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. Int J Radiat Oncol Biol Phys. 1999;45(2):427-34.
46. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998;280(17):1485-9.
47. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA. 2006;295(21):2483-91.
48. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009;10(11):1037-44.
49. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. Clinical Oncol. 2011;29(2):134-41.
50. Roos DE, Wirth A, Burmeister BH, Spry NA, Drummond KJ, Beresford JA, et al. Whole brain irradiation following surgery or radiosurgery for solitary brain metastases: mature results of a prematurely closed randomized Trans-Tasman Radiation Oncology Group trial (TROG 98.05). Radiother Oncol. 2006;80(3):318-22.
51. Muacevic A, Wowra B, Siefert A, Tonn JC, Steiger HJ, Kreth FW. Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. J Neurooncol. 2008;87(3):299-307.
52. Scoccianti S, Ricardi U. Treatment of brain metastases: review of phase III randomized controlled trials. Radiother Oncol. 2012;102(2):168-79.
53. Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 1980;6(1):1-9.
54. Borgelt B, Gelber R, Larson M, Hendrickson F, Griffin T, Roth R. Ultra-rapid high dose irradiation schedules for the palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 1981;7(12):1633-8.
55. Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. The palliation of brain metastases in a favorable patient population: a randomized clinical trial by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 1981;7(7):891-5.
56. Komarnicky LT, Phillips TL, Martz K, Asbell S, Isaacson S, Urtasun R. A randomized phase III protocol for the evaluation of misonidazole combined with radiation in the treatment of patients with brain metastases (RTOG-7916). Int J Radiat Oncol Biol Phys. 1991;20(1):53-8.
57. Haie-Meder C, Pellae-Cosset B, Laplanche A, Lagrange JL, Tuchais C, Nogues C, et al. Results of a randomized clinical trial comparing two radiation schedules in the palliative treatment of brain metastases. Radiother Oncol. 1993;26(2):111-6.
58. Priestman TJ, Dunn J, Brada M, Rampling R, Baker PG. Final results of the Royal College of Radiologists' trial comparing two different radiotherapy schedules in the treatment of cerebral metastases. Clin Oncol. 1996;8(5):308-15.
59. Murray KJ, Scott C, Greenberg HM, Emami B, Seider M, Vora NL, et al. A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: a report of the Radiation Therapy Oncology Group (RTOG) 9104. Int J Radiat Oncol Biol Phys. 1997;39(3):571-4.
60. Davey P, Hoegler D, Ennis M, Smith J. A phase III study of accelerated versus conventional hypofractionated whole brain irradiation in patients of good performance status with brain metastases not suitable for surgical excision. Radiother Oncol. 2008;88(2):173-6.
61. Graham PH, Bucci J, Browne L. Randomized comparison of whole brain radiotherapy, 20 Gy in four daily fractions versus 40 Gy in 20 twice-daily fractions, for brain metastases. Int J Radiat Oncol Biol Phys 2010;77(3):648-54.

FUNCTIONAL OUTCOMES AFTER RADIOTHERAPY FOR EARLY GLOTTIC CANCER

Ellen Mills and Robyn Burnett
Royal Adelaide Hospital, Adelaide, South Australia.
Email: Ellen.Mills@health.sa.gov.au

Abstract

This paper discusses the current evidence for functional outcomes following radiotherapy treatment for early glottic cancer and the role of speech pathology intervention. Limited data exists for either voice or swallowing outcomes for these patients and even less evidence was found detailing speech therapy treatment outcomes after radiotherapy. The limited research reports improvement in voice quality over time to at least two years. It has been shown that it is possible to collect both subjective and objective voice quality data along with quality of life information, and this can be applied pre treatment and at post treatment intervals. We also report on our local clinical experience with this patient group, including unpublished swallowing outcome data. Ongoing standardised collection of voice and swallowing data will continue to add to the body of knowledge in this area and may define the role, if any, of active voice therapy for this population.

Variable incidence rates are reported for head and neck cancers across the world. In Australia, most recent statistics show two per cent of new cancer diagnoses are of head and neck origin each year. Mortality rates are reducing across developed countries. The major head and neck cancer sites are oral cavity, nasopharynx, oropharynx, larynx and hypopharynx.[1,2]

Treatment options may include surgical management, radiotherapy, chemotherapy or a combination. With better survival and control rates, organ function is now of prime importance when evaluating therapeutic interventions. Improved surgical and reconstruction techniques and more effective chemoradiotherapy protocols are helping to preserve function, however ongoing research regarding

functional outcomes is required to determine extent and impact of loss, long-term nature of losses and benefits of prevention and rehabilitation strategies.[3] Functional outcomes are commonly reported to depend upon multiple factors, including the site of origin and stage of the cancer, treatment modality, extent of resection and type of reconstruction, as well as the age and well being of the patient. The quality of support provided by the managing team is also highly valued by the patient.[3]

Radiotherapy for head and neck cancer commonly affects speech, swallowing and/or voice function and can result in overall changes to patients' quality of life. Radiotherapy treatment may result in xerostomia (dryness of the mouth), pain, inflammation, fatigue, fibrosis, muscle atrophy and joint fixation.[3]

Rehabilitation that prevents and/or alleviates the loss of function and increases the patients' quality of life would seem necessary. Further studies are required to determine whether rehabilitation conclusively improves function, whether there are preventative effects or whether gains, if any, are maintained long-term. Speech pathologists offer pre and post-assessment and management of changes to speech, voice and swallowing brought about by the presence of and treatment for head and neck cancer. This paper discusses the current functional outcome data and speech pathology involvement with patients following primary radiotherapy treatment for early laryngeal cancer.

Current evidence

Literature supports that early laryngeal cancer can be managed by radiotherapy or transoral laser microsurgery with similar control and survival.[4-8] It is therefore the functional outcomes (voice quality and swallowing) and quality of life outcomes that guide patient decision-making between the two treatment options for this disease. Current functional outcome data is limited, however demonstrates comparable outcomes for voice and quality of life for both treatment options.[4]

Waghmare and colleagues state that early glottic cancers treated with radiotherapy result in voice changes associated with geometric asymmetry, fibrosis, inelasticity and oedema of the vocal folds.[6] This presents as vocal fold vibratory slowness (lower than normal fundamental frequency), dysrhythmic vibratory pattern (increased noise component) and poor glottic closure (increased breathiness and weak vocal intensity). This is confirmed by acoustic analysis, which demonstrates changes to fundamental frequency, jitter and shimmer measures and harmonic to noise ratio. Perceptually, voice quality is characterised by breathiness, strain, roughness and glottal fry. Glottal fry is the term used to describe a particular vocal quality brought about by a thick flaccid vibrating vocal fold edge. There are also aerodynamic changes of reduced mean phonation time.[9,10]

Current literature regarding the functional outcomes after radiotherapy for early glottic cancers, indicates both subjective and objective improvement in voice quality over time, without specific functional therapy intervention (ie. speech therapy).[6,10] Waghmare and colleagues state that voice quality after radiotherapy improves but does not reach the standard of normal controls.[6] Similar studies have also shown an improvement in quality of life scores after treatment.[9,10] Positive changes in voice quality and quality of life measurers have been shown to last for at least two years post radiotherapy treatment.[3]

As a consequence of limitations in the published data, the value of voice therapy in preventing or reducing dysphonia following radiotherapy has not been established. Van Gogh and colleagues reported 44% of patients had evidence of voice impairment after radiotherapy treatment.[5] They concluded that voice therapy was effective in patients after treatment for early glottic cancer. The study grouped patients treated with either radiotherapy or laser surgery and did not provide voice outcome data specific to each treatment. Although voice improvement was measured by both patient subjective feedback – Voice Handicap Index scores - and some objective analysis of acoustic measures and perceptions of glottal fry,[11] no conclusions could be made with specific reference to outcomes after radiotherapy treatment alone. The authors noted that nearly 67% of eligible patients with voice complaints were not willing to participate in the study or withdrew. The high level of non-participation was thought to be due to therapy time requirements and acceptance that voice change was a logical consequence of treatment for a potentially life-threatening disease. Investigators concluded that regular assessment of voice after treatment was helpful for selecting patients that might benefit from voice therapy. Several other authors comment that appropriate voice therapy may be of benefit to this patient group, without supporting data.[6-8] Voice rehabilitation exercises post radiotherapy are reported to include vocal hygiene, reduction of abuses, deconstriction and breathing exercises.[6]

Royal Adelaide Hospital experience

Change in voice is frequently the initial symptom for patients with early glottic cancer, with subsequent general practitioner referral to an otorhinolaryngologist for further investigation. At the Royal Adelaide Hospital, a combined speech pathology and otorhinolaryngology consultant clinic captures data for patients pre-microlaryngoscopy and biopsy of laryngeal pathology. Voice and swallowing function are recorded via flexible nasendoscopic examination. A quality of life measure – the Voice Handicap Index score – is also collected. These assessments provide objective pre-treatment information for baseline comparison. Patient education regarding voice changes associated with laryngeal pathology is provided at this time. Once diagnosed with an early glottic cancer, patients are seen by both the otorhinolaryngology surgeons and radiation oncologists in order to discuss treatment options and possible outcomes. Patients then make an informed decision regarding their treatment of choice.

For those patients undertaking radiotherapy, it has been our clinical experience that during active treatment, patients are not concerned with voice quality, but rather the day-to-day experience of radiotherapy. It is also our experience that functional swallowing difficulties

are minimal in this population both before and during therapy. Therefore speech pathology input for this population has predominantly focused on vocal hygiene and general education around voice changes associated with radiotherapy.

In a recent publication, we have shown that it is possible to utilise a standardised battery of assessment to measure voice and quality of life pre-treatment and at intervals post-treatment to monitor functional outcomes and change over time.[10] Our small cohort of patients demonstrated statistically significant improvements in both self rated and objective assessments of voice quality over a two year period. Pre-treatment assessments also allow for speech pathology input and education as required for voice and swallowing disorders at this time, and to provide education regarding expectations throughout and after treatment. Swallowing dysfunction in early glottic cancers is minimal and the need for ongoing speech pathology swallowing intervention during or after treatment is rare. Unpublished swallowing and endoscopic data collected on the same patient cohort and at the same time as the voice data described by Adams and colleagues,[9] confirms minimal swallowing difficulties for patients with T1 or T2, N0 laryngeal cancer treated with radiotherapy. All patients continued their nutrition orally during and after treatment.

The endoscopic data also provided information about laryngeal function for voice production. Although unpublished, the data revealed improvement over time in laryngeal oedema, vocal fold edge irregularity, glottic closure and mucosal wave. Supraglottic constriction was demonstrated by half of all patients pre-treatment. Two thirds of these patients demonstrated persistent supraglottic constriction during the post-treatment assessment phase.

Overall, this data demonstrated that supraglottic constriction was the only feature apparent pre-treatment that was consistently present post-treatment. This feature was identified simply as present or not present. The improvements observed in other glottic features were made without specific therapy tasks beyond basic vocal hygiene information.

In our setting, patients who present with poor perceptual voice ratings and/or are assessed to have persistent supraglottic constriction on endoscopic assessment are offered individually tailored voice therapy tasks. These aim to achieve voluntary retraction of the ventricular folds to optimise true vocal fold function. In our experience the majority of patients with early glottic cancers choose not to engage in voice therapy as voice quality is not of prime concern.

There is a paucity of data in relation to functional outcomes for patients treated for early glottic cancer. In our experience, these patients present with poor voice quality due to their disease, but swallowing difficulties are rare. Despite experiencing poor voice quality during treatment, there is gradual improvement over time such that patients are happy with their voices without active voice therapy. Our patients report acceptance of a degree of disorder subsequent to treatment for cancer. These patients are relieved to have a good response to cancer treatment with any residual voice issues accepted as a natural consequence.

Pre-treatment assessment in a formal clinic using a standardised format, provides the opportunity for baseline voice and swallowing data collection and provision of pre-treatment vocal hygiene education both verbal and written. It also establishes a clinical relationship with the patient so that if patients are concerned about functional outcomes, they are able to contact the speech pathology department for input. Ongoing standardised collection of voice and swallowing data will continue to add to the body of knowledge in this area and may define the role if any, of active voice therapy for this population.

Conclusion

There are documented subjective and objective improvements in voice quality following radiotherapy treatment for early glottic cancer. Swallowing function appears minimally affected by this treatment, but this is not well documented in the literature. Speech pathology input consists of pre-treatment assessment for baseline data collection and education for vocal hygiene. Discussions around general radiotherapy side-effects and the impact on speech, voice and swallowing are also presented. The benefit of additional speech pathology involvement requires further investigation. Ongoing standardised collection of voice and swallowing data will continue to add to the body of knowledge in this area and may define the role, if any, of active voice therapy for this population.

References

1. Cancer Australia. Head and Neck Cancers Factsheet [Internet] Sydney: Cancer Australia, October, 2010 Available from: http://www.canceraustralia.gov.au/sites/default/files/images/Factsheets/Head_and_Neck_Cancers_Factsheet.pdf Accessed May 2012.
2. Cancer Council Australia. Head and Neck Cancers. [Internet] Sydney: Cancer Council Australia, September 2011. Available from: http://www.cancer.org.au/aboutcancer/cancertypes/headandneckcancers.htm Accessed May 2012.
3. Van der Molen L, van Rossum MA, Burkhead LM, Smeele LE, Hilgers FJM. Functional outcomes and rehabiliatation strategies in patients treated with chemoradiotherapy for advanced head and neck cancer: a systematic review. Eur Arch Otorhinolaryngol. 2009;266:889-900.
4. Spielmann PM, Majumdar S, Morton RP. Quality of life and functional outcomes in the management of early glottic carcinoma: a systematic review of studies comparing radiotherapy and transoral laser microsurgery. Clin Otolaryngol. 2010;35:373-382.
5. Van Gogh CDL, Verdonck-de Leeuw IM, Boon-Kamma BA, Rinkel RNPM, de Bruin MD, Langendijk JA, Kuik DJ, Mahieu HF. The efficacy of voice therapy in patients after treatment for early glottic carcinoma. Cancer. 2006;106:95-105.
6. Waghmare CM, Agarwal J, Bachher GK. Quality of voice after radiotherapy in early vocal cord cancer. Expert Rev Anticancer Ther. 2010;10:1381-1388.
7. Hocevar-Boltezar I, Zargi M, Strojan P. Risk factors for voice quality after radiotherapy for early glottic cancer. Radiother Oncol. 2009;93:524-529.
8. Honocodeevar-Boltezar I, Zargi M. Voice quality after radiation therapy for early glottic cancer. Arch Otolaryngol Head and Neck Surg. 2000;126:1097-1100.
9. Adams G, Burnett R, Mills E. Objective and subjective changes in voice quality after radiotherapy for early (T1 or T2,N0) laryngeal cancer: A pilot prospective cohort study. Head Neck. Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.22969.
10. Bibby JRL, Cotton SM, Perry A, Corry JF. Voice outcomes after radiotherapy treatment for early glottic cancer: assessment using multidimensional tools. Head Neck. 2008;30:600-610.
11. Jacobson BH, Jonson A, Grywalski C. The Voice Handicap Index (VHI):development and validation. Am J Speech Lang Pathol. 1997;6:66–70.

SURVIVING RADIOTHERAPY - WHAT THE FUTURE HOLDS

Greg Wheeler
Peter MacCallum Cancer Centre, Melbourne, Victoria.
Email: Greg.Wheeler@petermac.org

Abstract

The dramatic increase in the cure rates of malignancies over the last generation, especially in the paediatric population, has led to an increasing number of survivors. There is an increasing recognition of the late effects of the tumour, and its treatment whether it is surgery, radiotherapy or chemotherapy. Radiotherapy, being the oldest conventional cancer treatment, is the most studied and many long-term effects are known. There are significant impacts on patients' lives after treatment, including academic performance, ability to hold a job and even to obtain insurance. As the professions responsible for the cure of both children and adults, there is a medico legal and moral obligation to screen for, prevent and treat or mitigate the consequences of our treatment.

Most cancer patients' goal is to arrive at the point where their doctor tells them: "You're cured!". They can then get back to their normal life and forget that it ever happened. Of course this almost never occurs. The psychological trauma of facing a life threatening condition may have long-term implications for their mental health, and there is increasing recognition of the consequences of aggressive treatment. The concept of survivorship is relatively recent and has been championed through long-term follow-up clinics and adolescent and young adult cancer services. Curing significant numbers of cancers has been a recent phenomenon, in the last 35 to 40 years. When Faber first used methotrexate to treat children with leukaemia in 1948, short remissions resulted, but ultimately all patients succumbed. His initial report in the *New England Journal of Medicine* in 1948 was met with derision,[1] as the prevailing view was that leukaemias were incurable and that the children should be allowed to "die in peace". The use of multi-agent chemotherapy in the late 1960s led to the first reported durable remissions for children with acute lymphoblastic leukaemia. The 1970s saw a dramatic rise in cure rates for many malignancies. It is humbling to realise that many of these children are now in their forties and fifties, still relatively young. There have been significant, though not as impressive improvements in adult cancers too, and the number of long-term survivors continues to grow.

Before this, the only long-term survivors of cancers resulted from surgery or radiation. The numbers were small, but even then there was a cost seen with growth effects, neuro-cognitive and neuro-endocrine complications and the suggestion of increased second malignancies. In Blooms seminal paper on the role of radiotherapy in medulloblastoma,[2] children under two years old often required ongoing institutional care after receiving craniospinal radiotherapy. Prior to this, Lampe expressed concern regarding brain damage that could result from radiation to brains of younger patients.[3]

It was hoped that chemotherapy would eliminate the need for radiation and be free of long-term consequences, but unfortunately this was not to be. Until the 1990s, once a patient was deemed cured they were usually discharged and told to live normally with a reasonable expectation that they would. There has been an increasing recognition over the last 20 years of the many complications that may result from cancer treatments.

As a result of this improvement in treatment, it is now expected that 80% of childhood cancer patients will become long-term survivors.[4] In the general population, one in 640 young adults 20-39 are cancer survivors, with the average general practice expected to have at least two patients per physician. The overall survivor numbers are greater if adult patients are included. In the adult setting, many patients now survive decades after their treatment and their surveillance and follow up is equally necessary. About one third of the patients in our clinic are referred after having had therapy as an adult.

Physical effects from the cancer itself

Long-lasting problems can occur prior to any therapeutic intervention. In brain tumours, having a tumour itself can cause disturbance of the hypothalamic pituitary axis before any treatment.[5] Hydrocephalus is recognised as an independent cause of significant neurocognitive decline in patients, previously attributed solely to radiotherapy.[6] Damage to neurones may not be repairable, and so timely intervention is crucial in the setting of cord compression or the optic chiasm compromise.

Late effects from radiotherapy and chemotherapy

The most famous victim of radiation late effects was probably Marie Curie, who discovered radium along with her husband Pierre. Marie died of aplastic anaemia from her long-term radiation exposure. Her daughter Irene, also a Nobel Prize winning physicist, also died from acute leukaemia. Pierre Curie however, was spared a similar fate – he was run over by a horse drawn cart on the streets of Paris in 1906.

The first patients were treated with radiotherapy in the late 1890s and until the advent of chemotherapy, it was the only effective non-surgical treatment for cancer. However, from early on the effects of radiotherapy were appreciated.

> *"The dangers from the use of x-rays may be grouped as immediate and remote. During the actual exposure, the possibility of making contact with a high-tension lead carrying a very high voltage has to be guarded against. An accident of this kind may easily be fatal… Constitutional disorders, anaemia and sterility not infrequently arise in operators who are constantly exposed to x-rays."*[7]

In 1935, the concept of immediate and long-term or late-effects was very simple. Late-effects now refer to complications that arise many months to years after the completion of therapy.

Much of the early data regarding adverse effects from radiation isn't from treatment – rather from the Hiroshima and Nagasaki atomic bomb data, industrial accidents and use in benign conditions. For example, superficial irradiation was a commonly used treatment for tinea capitis with doses of 0.04-0.45 Gy used.[8] Reports from the 1960s suggested an increase in leukaemias, thyroid, brain and other head and neck cancers and interestingly 'mental disorders,' and in the large cohort of Israeli immigrants treated for tinea in the 1940s and 50s.[9]

Much of the current data regarding late effects of cancer treatments has been developed for the retrospective cohort of 10,000 patients with matched sibling controls in the Childhood Cancer Survivors Study group.[4,10-13] Much of this data and other published literature has been brought together in the long-term follow-up guidelines of the Children's Oncology Group.[14] These guidelines are used as the basis for many long-term follow-up programs. It is beyond the scope of this paper to exhaustively detail the physical effects of chemotherapy and radiotherapy, however a brief overview follows.

Head and neck region

Alopecia is physically the most insignificant side-effect of cancer treatment, but psychosocially one of the more distressing, particularly for teenage girls. Cranial radiation often leads to temporary hair loss, and the degree of permanent effect relates to total dose and concurrent chemotherapy

The lens is prone to cataractogenesis from both radiation (even very low dose) and steroids.[15] Anterior chamber exposure increases the risk of late glaucoma.[16]

Both surgery and radiotherapy to the hypothalamus can lead to hypothalamic-pituitary axis dysfunction, including hypothalamic obesity or metabolic syndrome. Late radiotherapy effects occur at a median time of three years post therapy. The thyroid stimulating hormone (TSH) is usually affected first, followed by growth hormone, the sex hormones and less commonly adrenocortocotropic hormone (ACTH), leading to Addisonian syndromes. The thyroid gland itself may suffer primary failure if it is in the radiation field. Central infertility may also result, however this may be negated by the use of gonadotrophic releasing hormone agonists to induce gonadal stimulation.[17-20]

The most devastating long-term effect is the functional neurological compromise suffered by patients who have had brain tumours.[21] Merchant et al have demonstrated that IQ decline is proportional to the volume and dose of brain irradiated, especially the temporal lobes.[22] Palmer et al found that there appeared to be a constant decline until age 12, after which the IQ remained stable. There is a progressive reduction in short-term memory and concentration span through the teenage years.[23] Some evidence suggests medications such as dexamphetamine and/or cognitive remediation programs may improve academic performance and overall quality of life in these patients.[24-27] Similar, but not as profound effects can be seen in patients who have had intrathecal methotrexate, especially if cranial radiotherapy is also given.[26] In adults, radiation "ages" the brain which may accelerate concentration and memory decline in later years.

There is also a small risk of focal radionecrosis in high dose regions,[27] and an increased risk of strokes. Radiation to the neck and mediastinum can increase the rates of cerebrovascular disease.[28] Thus, an aggressive approach to management of hypercholesterolemia, hypertension and other reversible risk factors for cerebrovascular disease is taken.

Cardiac effects

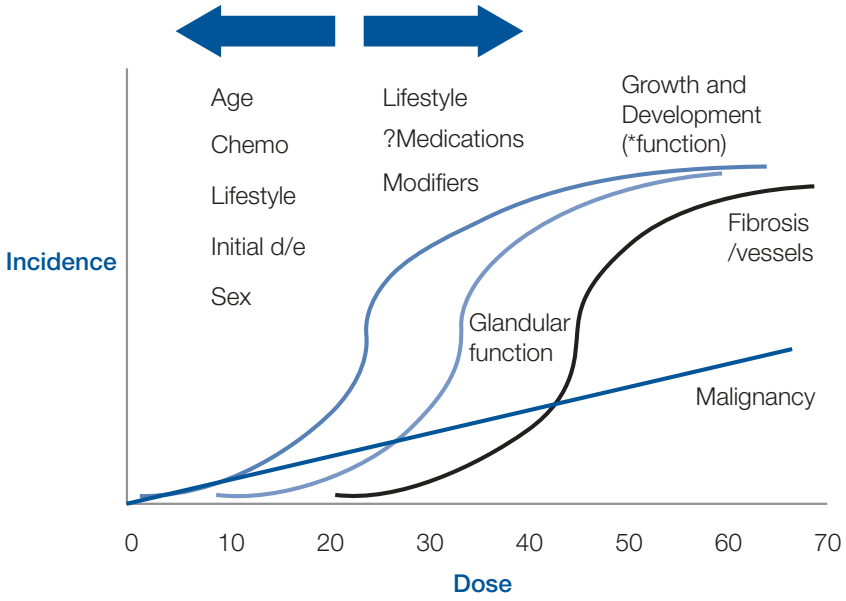
Radiotherapy and chemotherapy have significant impacts on cardiac function. Radiation itself can cause myocardial fibrosis leading to late cardiac failure. This is in addition to the effects of high-dose anthracyclines (eg. > 350 mg/m2 doxorubicin).[29-31] Cardiac failure may be unmasked during pregnancy, thus women with a history of cardiac irradiation or anthracycline chemotherapy should undergo cardiac function assessment during pregnancy and monitoring during labour and delivery. Radiotherapy to the chest increases the risks of ischaemic heart disease by 2-5%.[13,32] These patients also have an increased rate of valvular abnormalities – usually presenting with stenotic rather than incompetent valves. Renal irradiation may cause cortical scarring or fibrosis, increasing the risk of Angiotensin converting enzyme driven hypertension, aggravating both the cerebral and cardiac risk profile.[33]

Other effects

Radiation doses > 20 Gy induce variable degrees of pulmonary fibrosis in the radiation field, which may lead to a restrictive pattern on lung function testing and a decrease in overall diffusing capacity.[32,40] These problems are aggravated by Bleomycin chemotherapy, tobacco and marijuana smoking, so smoking cessation is essential.[34,35]

High dose irradiation may induce scarring in the bladder, causing reduced bladder volume with resultant frequency and urge incontinence. It reduces uterine blood flow, and above 16-20 Gy may induce hypoplasia and fibrosis, resulting in miscarriage or inability to carry a pregnancy to term. Radiotherapy doses of 2-4 Gy to the testes and 4-6 Gy to the ovaries may induce sterility, and at higher levels (~20 Gy) may result in loss of hormonal function.[36-39]

Figure 1: *Schematic representation of the late effects of radiotherapy.*



As depicted in figure 1, the threshold dose for hypoplasia induced by radiation appears to be about 16 Gy, with the plateauing of effect seen at about 25 Gy. If there is inhomogeneity across growth plates asymmetric growth may lead to impaired cosmetic outcomes, such as kyphoscoliosis, facial asymmetry and pelvic tilt. Impaired growth may also be due to decreased GH production. Radiation can lead to late osteoporosis in field and in some cases radionecrosis in high dose areas aggravated by steroids.

Second malignancies

One of the most concerning complications of cancer treatment is second malignant neoplasms.[40-49] Some primaries are associated with an increased risk of other malignancies, such as retinoblastoma or lymphoma. The second malignancy risk from radiotherapy has a dose response, with the exception of thyroid cancers (plateauing at ~15 Gy). Concurrent chemotherapy, particularly doxorubicin, increases the risk of developing a radiation induced second malignancy.

Mediastinal radiation increases the risk of breast cancer;[44] and cranial radiotherapy causes meningiomas or rarely gliomas in the central nervous system, especially with concurrnet antimetabolite maintenance chemotherapy.[49] Retinoblastoma patients who have had irradiation have a significant risk of osteosarcomas in the field, and the prognosis from these tumours is grim. Eighty per cent of secondary malignancies are either in or at the margins of the field, strongly implicating radiation in their pathogenesis.[40-49]

Psychological and social effects

Having had cancer can have a profound impact on psychosocial development. Survivors of cancer in childhood or adolescence are much less likely to marry, hold a job, reach the same socioeconomic status, hold insurance or complete tertiary education.[50-54] The most obvious impacts relate to failure to socialise due to brain injury. Damaged frontal lobe function often impacts on group play, and children may be ostracised as a result. More subtle impacts are seen when children lose touch with their peers during long absences caused by treatment. They are also often caught between wanting to be 'normal', yet having a life-changing event acknowledged in some way.

School absence can result in poor grades and if they need to repeat a year of school worsening social isolation.[55] Having a healthy body image and self-esteem relies on accepting physical appearances, which in the maelstrom of surgery, chemotherapy and radiotherapy, is hard for young people to achieve, especially with altered responses from peers. Permanent side-effects such as hair loss, amputation, scarring and fatigue can result in reactive depression, anxiety and in some situations post-traumatic stress disorder.[56,57] Increased prevalence of somatic symptoms, depression and/or anxiety, attention deficit and anti-social behaviour among young cancer survivors has been documented in many paediatric malignancies.[57,58]

Central nervous system patients in particular may have profound and often debilitating fatigue, which inhibits ability to work and socialise. In some patients, exogenous growth hormone or stimulants such as dexamphetamine may be useful. Of course, screening for hypothyroidism is an important part of surveillance. Other causes of fatigue may be an early sign of more significant issues such as a reactive depression, post-traumatic stress disorder or general anxiety, which many patients have about their health.[57] The wait for results can be particularly onerous, and returning to the same institution where their treatment was given can bring flashbacks or responsive nausea and vomiting. Often minor symptoms can bring on marked

agitation about the possible cause, and the caring team must put the risks of long-term problems in perspective. In other cases, patients may want to completely ignore what they have been through and refuse further follow-up. The extreme of this is to engage in risk taking behaviour such as tobacco and alcohol excess or illicit drug use.

Financial effects

Cancer survivors often find long-term consequences in later life that are not directly related to the direct physical effects of chemotherapy or radiotherapy. In many countries (such as Australia), there are enormous hurdles to cancer survivors joining the military and developing further trade opportunities that could carry on into civilian life. Short-term memory impairment and concentration span problems reduce patients' ability to complete tertiary education or vocational training.[50-54] More subtle issues such as altered cosmetic outcomes or personality affects may deny survivors promotion prospects or other advancement in their fields.

Life insurance policies are often very difficult to obtain, frequently an issue when they start their own families. Many policies exclude any malignancy, even if it were to develop outside the treatment field and have no obvious link to the treatment given or the primary condition. Likewise, health insurance may be difficult to obtain and in many regions assisted fertility (eg. IVF) is not covered in public health programs. In regions where there is no universal health coverage, this can carry significant implications for patients, both for future health issues as well as the need for routine surveillance for long-term treatment related effects.

The increasing use of molecular genetics in the diagnosis of the primary tumour raises the spectre of future employers requesting the results as part of the employment process, potentially allowing discrimination. This is of most concern in jurisdictions where part of the employment conditions involves employer funded health insurance.

In the brain tumour survivor cohort who have suffered significant neuro-cognitively injury from the tumour or treatment, there is the heart-rending situation where patients are reliant on their now ageing parents for many of their activities of daily living. These parents often struggle with the issue of who will care for their children when they die or become unable to do it themselves.

Finally, one of the more insidious and common problems faced by patients is their, and their doctors, lack of knowledge about late-effects. There needs to be a balance between knowledge of risk and causing unnecessary concern. Many patients feel that they are a 'time bomb' waiting to develop a second cancer or other significant complication, when in fact most won't. The risks mandate an appropriate screening regimen, but an understanding of the risk is critical for peace of mind. In a busy oncology clinic, the needs of acutely unwell and newly diagnosed patients take precedence over those who are cured and healthy. In our practice, we find that a consult in our dedicated late effects clinic – with the same patient and the same room – is profoundly different in the scope of issues covered than in an acute clinic. We often see a correspondence trail between their GP asking for advice about issues and the oncology team answering that it is not related to their cancer and thus not appropriate for them to address. How should these patients be cared for now?

Future care models

At one end of the spectrum is where a patient is deemed cured and they are discharged into their GPs care. The other end is regular detailed follow-up in a multidisciplinary long-term follow-up clinic. The problems with the first option are that it places a lot of reliance on the family doctor to keep up-to-date with a wide range of potential issues for a small number of patients. Compounding this is the mobile nature of the young adult population and their own lack of knowledge about their treatment, let alone the likely toxicities. The second creates its own issues. A dedicated paediatric late-effects clinic can reach a steady state when patients that are discharged when they reach adulthood (18 years old), are replaced by patients entering the long-term follow-up period – a revolving door concept. However, an adult clinic is more like a bucket. Patients enter the clinic either directly from their oncology team or from the paediatric long-term follow-up unit and, due to the high cure rates and low mortality from late effects and with no ongoing plan, will stay there. Our own clinic initially ran alternate monthly, 10 years later is now a fully booked clinic every week.

Clearly a shared care model is appropriate.[59] The model that we are developing is based on a stratified shared care system. On entry to the clinic patients will be assessed as low, intermediate or high risk. Low risk patients would include such groups as a stage I Wilms tumour treated with surgery and simple chemotherapy. They would be discharged into their family physician's care with important provisos. The first is that the patients are given a survivorship care plan which outlines the treatment they have received, the risks identified as a result of the treatment and the recommended screening investigations and lifestyle modifications. This would enable a patient to change doctors without compromising their ongoing care, and would also give the family doctors guidance. The second proviso is the need to have a feedback loop so that the long-term follow-up clinic knows who the local doctor is, what tests have been ordered and what the results are. This is necessary to ensure that the appropriate care is being delivered and to allow contact with both the patient and the family doctor should new information about potential late-effects become apparent. In a survey of GPs from the Netherlands, 97% of GPs were willing to participate in the long-term care of survivors, and indeed 64% felt that it was their responsibility.[60]

The intermediate risk group would be patients who need regular surveillance and imaging, but not on an annual basis. This would include any patients who had had radiotherapy, high dose anthracyclines or endocrinopathies. Again, a passport and management plan is essential as is the feedback loop to a robust database. For instance, structural imaging for second malignancy surveillance or echocardiograms for delayed cardiotoxicity may be done every two to three years and subsequent review in a multidisciplinary could alternate with yearly bloods, blood pressure checks and lifestyle modification counselling by the GPs.

The high risk group would be those who need annual multidisciplinary review in a tertiary centre. Again, the passport and database would be essential to inform the GPs for care between visits to the long-term follow-up clinic. Patients in this group would include brain tumour/cranial irradiation patients and bone marrow transplant recipients.

In the Netherlands survey, GPs felt that to participate in a shared care program they needed availability of guidelines (64%), sufficient information about the patient's medical history (37%) and short communication lines (45%).[60] The main barriers to participation were felt to be workload (16%), lack of knowledge (15%), and lack of communication from the parent institution.

The challenge remains to plan the long-term care of cancers with high survival rates. Hopefully, a working model for childhood and adolescent cancer survivors will extrapolate easily to the appropriate care of cured adults such as breast, GI and head and neck tumours. It is often suggested that new techniques may reduce late-effects (eg. IMRT/protons) and hopefully this will be the case. However, a reduction in toxicity allows dose escalation to improve cure rates resulting in an isotoxic treatment.

As a profession we have only been curing childhood cancers reliably for only 30-40 years. This is the span of many of our senior colleagues working life. We need to provide robust and thorough follow-up, both for our current patients' sakes, and through surveillance and research, our patients that are yet to come. It may well be that in 200 years, our professional descendents look upon our crude therapies much as we look on the gross surgeries performed without anaesthesia 200 years ago. The question for us is how we will be viewed with regard to the care we have provided for our patients.

References

1. Farber S, Diamond LK, Mercer RD, Sylvester RF, Jr Soliff JA. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. N Engl J Med. 1948 Jun 3;238(23):787-93.
2. Bloom HJ, Wallace EN, Henk JM. The treatment and prognosis of medulloblastoma in children. A study of 82 verified cases. Am J Roentgenol Radium Ther Nucl Med. 1969 Jan;105(1):43-62.
3. Lampe I. Radiation tolerance of the central nervous system. Prog Radiat Ther.1958:224–36.
4. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Childhood Cancer Survivor Study. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006 Oct 12;355(15):1572-82.
5. Merchant TE, Williams T, Smith JM, Rose SR, Danish RK, Burghen GA, et al. Preirradiation endocrinopathies in pediatric brain tumor patients determined by dynamic tests of endocrine function. Int J Radiat Oncol Biol Phys. 2002 Sep 1;54(1):45-50.
6. Merchant TE, Lee H, Zhu J, Xiong X, Wheeler G, Phipps S, et al. The effects of hydrocephalus on intelligence quotient in children with localized infratentorial ependymoma before and after focal radiation therapy. J Neuro Surg. 2004Nov 10:1(2 suppl):159-68.
7. The Universal Home Doctor Illustrated, ODHAMS Press LTD 1935 pg 720.
8. Albert RE, Omran AR, Brauer EW, Dove DC, Cohen NC, Schmidt H, et al. Follow-up study of patients treated by x-ray for tinea capitis. Am J Public Health. 1966;56(12):2114-20.
9. Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B , Novikov I. Long-term follow-up for brain tumor development after childhood exposure to ionizing radiation for tinea capitis. Radiat Res. 2005 Apr 16;3(4):424-32.
10. Oeffinger KC, Hudson MM. Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. CA Cancer J Clin. 2004 Jul-Aug;54(4):208-36.
11. Friedman DL, Meadows AT. Late effects of childhood cancer therapy. Pediatr Clin North Am. 2002 Oct;49(5):1083-106.
12. Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME Jr, Ruccione K, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol. 2001 Jul 1; 19(13):3163-72
13. Gurney JG, Kadan-Lottick NS, Packer RJ, Neglia JP, Sklar CA, Punyko JA, et al. Stovall M, Childhood Cancer Survivor Study. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. Cancer. 2003 Feb 1;97(3):663-73.
14. Childrens Oncology Group Survivorship Guidelines, Version 3.0 c2008. Cited May 2012. Available from http://www.survivorshipguidelines.org
15. Ainsbury EA, Bouffler SD, Dörr W, Graw J, Muirhead CR, Edwards AA, et al. Radiation cataractogenesis: a review of recent studies. Radiat Res. 2009 Jul 17;2(1):1-9.
16. Yamada M, Wong FL, Fujiwara S, Akahoshi M, Suzuki G. Noncancer disease incidence in atomic bomb survivors, 1958-199: Radiat Res. 2004 Jun 16;1(6):622-32
17. Hameed R, Zacharin MR. Long-term endocrine effects of cancer treatment: experience of the Royal Children's Hospital, Melbourne. J Paediatr Child Health. 2005 Jan-Feb;41(1-2):36-42.
18. Duffner PK. Long-term effects of radiation therapy on cognitive and endocrine function in children with leukemia and brain tumors. Neurologist. 2004 Nov;10(6):293-310.
19. Rutter MM, Rose SR. Long-term endocrine sequelae of childhood cancer. Curr Opin Pediatr. 2007 Aug;19(4):480-7.
20. Cohen LE. Endocrine late effects of cancer treatment. Endocrinol Metab Clin North Am. 2005 Sep;34;(3):769-89.
21. Mulhern RK, Mercahnt TE, Gajar A, Reddick WE, Kun LE. Late Neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol 2004 Jul;5(7):399-408.
22. Merchant TE, Kienha EN, Li C, Shukla H, Sengupta S, Xiong X, et al. Modeling radiation dosimetry to predict cognitive outcomes in pediatric patients with CNS embryonal tumours including medulloblastoma. Int J Rad Biol Phys. 2006 May 1;65(1):210-21.Epub 2006 Feb 10.
23. Palmer SL, Gajar A, Reddick WE, Glass JO, Kun LE, Wu S, et al. Predicting intellectual outcome among children treated with 35-40 Gy craniospinal irradiation for Medulloblastoma. Neuropsychology. 2003 Oct;17(4):548-55.
24. Butler RW, Copeland DR, Fairclough DL, Mulhern RK, Katz ER, Kazak AE, et al. A multicenter, randomised clinical trial of a cognitive remediation program for Childhood survivors of a paediatric malignancy. J Consult Clinc Psychol. 2008 Jun;76(3):367-78.
25. Conklin HM, Khan RB, Reddick WE, Helton S, Brown R, Howard SC, et al. Acute neurocognitive response to methylphenidate among survivors of childhood cancer: a randomized, double blind, cross over trial. J Pediatr Psuchol. 2007 Oct;32(9):1127-39.
26. Iuvone L, Mariotti P, Colosimo C, Guzzetta F, Ruggiero A, Riccardi R. Long-term cognitive outcome, brain computed tomography scan, and magnetic resonance imaging in children cured for acute lymphoblastic leukemia. Cancer. 2002 Dec 15;95(12)2562-70.
27. Ruben JD, Dally M, Bailey M, Smith R, McLean CA, Fedele P. Cerebral radiation necrosis: incidence, outcomes, and risk factors with emphasis on radiation parameters and chemotherapy. Int J Radiat Oncol Biol Phys. 2006 Jun 1;65(2):499-508. Epub 2006 Mar 6.
28. De Bruin ML, Dorresteijn LD, van't Veer MB, Krol AD, van der Pal HJ, Kappelle AC, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. J Natl Cancer Inst. 2009 Jul 1;101(13):928-37.
29. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol. 2009 Jun 16;53(24):2231-47.
30. Jr Boucek RJ, Steele A, Miracle A, Atkinson J. Effects of angiotensin-converting enzyme inhibitor on delayed-onset doxorubicin induced cardiotoxicity. Cardiovasc Toxicol. 2003;3(4):319-29.
31. Van Dalen EC, Van Der Pal HJ, Kok WE, Caron HN, Kremer LC. Clinical heart failure in a cohort of children treated with anthracyclines: a long-term follow-up study. Eur J Cancer. 2006 Dec;42(18):3191-8. Epub 2006 Sep 20.
32. Green DM, Hyland A, Chung CS, Zevon MA, Hall BC. Green DM, et al. Cancer and cardiac mortality among 15-year survivors of cancer diagnosed during childhood or adolescence. J Clin Oncol. 1999;Oct;17(10):3207-15.
33. Maas MH, Cransberg K, van Grotel M, Pieters R, van den Heuvel-Eibrink MM, Renin induced hypertension in Wilms tumour patients. Pediatr Blood Cancer. 2007 May;48(5):500-3.
34. McDonald S, Rubin P, Phillips TL, Marks LB. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. Int J Radiat Oncol Biol Phys. 1995 Mar 30;31(5):1187-203.
35. Carver JR, Shapiro CL, Ng A, Jacobs L, Schwartz C, Virgo KS, et al. ASCO Cancer Survivorship Expert Panel. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. J Clin Oncol. 2007 Sep 1;25(25):3991-4008. Epub 2007 Jun 18.
36. Green DM, Sklar CA, Jr Boice JD, Mulvihill JJ, Whitton JA, Stovall M, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. J Clin Oncol. 2009 May 10;27(14):2374-81.Epub 2009 Apr 13.

37. Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. Int J Radiat Oncol Biol Phys. 2009 Apr 1;73(5):1304-12.
38. Kalapurakal JA, Peterson S, Peabody EM, Thomas PR, Green DM, D'angio GJ, et al. Pregnancy outcomes after abdominal irradiation that included or excluded the pelvis in childhood Wilms tumor survivors: a report from the National Wilms Tumor Study. Int J Radiat Oncol Biol Phys. 2004 Apr 1;58(5):1364-8.
39. Green DM, Whitton JA, Stovall M, Mertens AC, Donaldson SS, Ruymann FB, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol. 2002 Oct;187(4):1070-80.
40. Borgmann A, Zinn C, Hartmann R, Herold R, Kaatsch P, Escherich G, et al. Secondary malignant neoplasms after intensive treatment of relapsed acute lymphoblastic leukaemia in childhood. Eur J Cancer. 2008 Jan;44(2):257-68. Epub 2007 Nov 5.
41. Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med. 1996 Mar 21;334(12):745-51.
42. Tucker MA, Coleman CN, Cox RS, Varghese A, Rosenberg SA. Risk of second cancers after treatment for Hodgkin's disease. N Engl J Med. 1988 Jan 14;318(2):76.
43. Meadows AT. Risk factors for second malignant neoplasms: report from the Late Effects Study Group. Bull Cancer. 1988;75(1):125-30.
44. Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. N Engl J Med. 1996 Mar 21;334(12):745-51.
45. Meadows AT, Baum E, Fossati-Bellani F, Green D, Jenkin RD, Marsden B, et al. Second malignant neoplasms in children: an update from the Late Effects Study Group. J Clin Oncol. 1985 Apr;3(4):532-8.
46. Klein G, Michaelis J, Spix C, Wibbing R, Eggers G, Ritter J, et al. Second malignant neoplasms after treatment of childhood cancer. Eur J Cancer. 2003 Apr;39(6):808-17.
47. Breslow NE, Takashima JR, Whitton JA, Moksness J, D'Angio GJ, Green DM. Second malignant neoplasms following treatment for Wilm's tumor: a report from the National Wilms' Tumor Study Group. J Clin Oncol. 1995 Aug;13(8):1851-9.
48. de Vathaire F, Hawkins M, Campbell S, Oberlin O, Raquin MA, Schlienger JY, et al. Second malignant neoplasms after a first cancer in childhood: temporal pattern of risk according to type of treatment. Br J Cancer. 1999 Apr;79(11-12):1884-93.
49. Relling MV, Rubnitz JE, Rivera GK, Boyett JM, Hancock ML, Felix CA, et al. High incidence of secondary brain tumours after radiotherapy and antimetabolites. Lancet. 1999 Jul 3;354(9172):34-9.
50. Frobisher C, Lancashire ER, Winter DL, Jenkinson HC, Hawkins MM. Long-term population-based marriage rates among adult survivors of childhood cancer in Britain. British Childhood Cancer Survivor Study. Int J Cancer. 2007 Aug 15;121(4):846-55.
51. Crom DB, Lensing SY, Rai SN, Snider MA, Cash DK, Hudson MM. Marriage, employment, and health insurance in adult survivors of childhood cancer. J Cancer Surviv. 2007 Sep;1(3):237-45.
52. Gurney JG, Krull KR, Kadan-Lottick N, Nicholson HS, Nathan PC, Zebrack B, et al. Social outcomes in the Childhood Cancer Survivor Study cohort. J Clin Oncol. 2009 May 10;27(14):2390-5. Epub 2009 Feb 17.
53. Armstrong GT, Liu Q, Yasui Y, Huang S, Ness KK, Leisenring W, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2009 Jul 1;101(13):946-58. Epub 2009 Jun 17.
54. Schultz KA, Ness KK, Whitton J, Recklitis C, Zebrack B, Robison LL, et al. Behavioural and social outcomes in adolescent survivors of childhood cancer: a report form the childhood cancer survivor childhood study. J Clin Oncol. 2007 Aug 20;25(24):3649-56.
55. Thompson K, Palmer S, Dyson G. Adolescents & young adults: Issues in transition from active therapy into follow up care European Journal of Oncology Nursing. 2009; Jul;13(3):207-12. Epub 2009 Jun 17.
56. Hobbie WL, Stuber M, Meeske K, Wissler K, Rourke MT, Ruccione K, et al. Symptoms of posttraumatic stress in young adult survivors of childhood cancer. J Clin Oncol. 2000 Dec 15;18(24):4060-6.
57. Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer. Support Care Cancer. 2002 Nov;10(8):579-600. Epub 2002 Oct 24.
58. Zebrack BJ, Zeltzer LK, Whitton J, Mertens AC, Odom L, Berkow R, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study. Pediatrics. 2002 Jul;110(1 Pt 1):42-52.
59. Oeffinger K, McCabe M. Models for Delivering Survivorship Care. J Clin Oncol 2006;24:5117-5124.
60. Blaauwbroek R, Zwart R, Bouma M, Meyboom-de Jong B, Kamps I WA, Postma A. The willingness of general practitioners to be involved in the follow-up of adult survivors of childhood cancer. J Cancer Surviv. 2007 Dec;1(4):292-7. Epub 2007 Sep 27.



AWARDS

Medical Oncology Group of Australia Cancer Achievement Award

John Zalcberg
Peter MacCallum Cancer Centre, Melbourne, Victoria.
Email: John.Zalcberg@petermac.org

The Medical Oncology Group of Australia (MOGA), together with Novartis Oncology, presents the Cancer Achievement Award to recognise an outstanding Australian contribution to cancer research and control. The Award formally recognises the contributions made by scientists, clinicians and other health care professionals to the scientific study of cancer in Australia.

Since 1999 this Award has been presented to 10 leaders in the field of Australian Oncology. The winner of the 2011 award was Professor John R. Zalcberg OAM in recognition of his skills, commitment and achievement as an outstanding Australian medical oncologist. Professor Zalcberg is Chief Medical Officer and Executive Director at Peter MacCallum Cancer Centre, Melbourne.

The award was received by Professor Zalcberg at the MOGA Annual Scientific Meeting in Adelaide on 12th August 2011, at which he delivered the following address.

It's a great honour to be awarded the Medical Oncology Group of Australia / Novartis, Cancer Achievement Award. I'd like to acknowledge the prestigious group of Australians that have received this award in the past and am humbled to have been honoured by MOGA in this manner.

In thinking about a theme for this talk, a friend suggested that people may wish to know why I am, who I am. I thought the best way of telling you that might be by describing some formative experiences that have influenced my career. These experiences have taught me a lot, not only about medicine but about life and in so doing, have had a profound influence on how my career has developed. Some of these experiences were as a student and others as a doctor. But they've taught me about our profession as well as the essence of the practice of medicine.

Let me start by telling you some memories of being a medical student and intern at the Austin and the Repat in the mid-70s. The first was during a surgical outpatient clinic. There were lots of us hanging around, not quite sure where to go or what to do. As students, everything was a new experience. A young patient came in and said that he had an itchy anus. The consultant surgeon asked him to take down his pants. I remember being amused by the fact that almost before his pants were down, the sigmoidscope was inserted. Then, as fast as the sigmoidscope went in, the sigmoidscope came out again. The consultant dropped it onto the table and walked towards the door. I think we were almost as surprised as the patient, wondering what the hell was

Professor John R. Zalcberg OAM pictured with his wife Lynette.

going on. Suddenly the patient yelled out: "Well doc, what's the cause of my itch..?" To which the consultant somewhat cryptically replied: "You've got worms mate, you'll have to burn the house down…!". He then quickly exited – stage left. We glided out of the room behind him, glancing at the patient, not sure what to say or do.

A few months later, I was a medical student at the Repat and can remember a group of surgeons doing rounds at seven in the morning, which felt very early in those days. We would look at the x-rays, comment amongst ourselves and then move to the next patient. I vividly remember the surgeons looking at a young man who was all strapped up with counter-levers balancing various parts of his anatomy after a motorbike accident. They looked at the x-rays at the end of the bed, conferred amongst themselves and walked out of the room. We followed dutifully as medical students did in those days … and once again the patient yelled out: "What about me doc? What happens to me?" We looked at him soulfully but followed our consultants to their next set of x-rays.

And finally in this triptych, in 1976, I was an intern at the Austin. It was an incredibly exciting time. I was learning things I'd never really understood as a student, soaking up a huge amount of information. I remember one particular ward round which I like to call the "Bob Hope Ward Round". Bob Hope was actually a senior consultant – a very good and very experienced general physician. I was the excitable, fascinated intern who thought he knew it all, but actually knew very little. I especially remember one of these ward rounds. We'd finished seeing a patient in a wheelchair who'd had a stroke – we'd noted his speech deficit and difficulties in limb movement, and after examining him, I thought we'd sorted out the problem; what part of his brain had been affected, what artery was involved. We'd looked at his blood results, looked at his complicating factors, put in place a plan for the next few days … and I'd walked on to the next patient. I suddenly realised I was on my own, talking to myself. I looked back, and there was Bob Hope – bent over the patient, tying up his pyjamas. I was silently tapping my foot … there were patients to see, blood tests to order, x-rays to chase. After he finished doing up his pyjamas, he put on the patient's slippers (one by one), did up his dressing gown and then finally wheeled him into a spot of his choosing …. then we walked on to see the next patient. After my internship, I took the next year off. I did the backpacking thing around Europe and the US, but I kept on thinking about that Bob Hope ward round. What Bob Hope had just taught me – a lesson I continually relive was a lesson about the "practice of medicine", a lesson that continued to guide me for the next 35 years of my professional career.

In fact, when my son David graduated from medical school, we sat down at the kitchen table one night. It was quiet after the euphoria of the exam results, and we were both in a reflective mood. I said: "David, now that you've graduated, I'm going to tell you the secret of medicine. There are four secrets but the most important is the first one. If you know this secret, you'll know all there is to know about the practice of medicine. From my experience, this is the key that unlocks all the doors." David became quite fascinated by the conversation. "David, the secret of medicine, the real secret, is about treating other people as you would wish to be treated." He looked at me somewhat incredulously – is this for real, but I think the importance of what I was saying slowly dawned on him. Such a simple concept and yet so important, so basic and yet one that can be so hard to achieve in practice.

I have no doubt you all have your own version of the Bob Hope story that will have influenced you in various ways. However for me, the notion of putting the patient first, treating others as we'd want to be treated, is not just about tying up someone's PJs, it's about striving for new knowledge and knowing your limitations, about learning to listen and communicate, about respect and about compassion. It's a motto that's driven me since those early formative years, a lesson that's underpinned everything I've done and everything I've tried to do.

I want to talk a little about the concept of "suffering". I first learnt about this concept during my childhood, growing up in a home in which every moment of every single day I was reminded about the many hardships my parents had experienced during the second world war. Around the dinner table, my parents would tell me stories about their experiences as prisoners in the concentration camps of Auschwitz and Birkenau. I was barely able to grasp the meaning of their hardships, of their suffering on a day to day basis. I started – but only started, to understand this concept from a medical perspective whilst I was an intern. Late one night I was called to the ward to see a young man who was in severe pain. He was about my age at the time and he had a heroin infusion running to try and ease his pain. He was very cachectic and in a great deal of discomfort. To my innocent question about what was worrying him, he retorted: "Do you know what my real fear is 'doc, the thing that scares me most? It's the thought that I might wake up in the morning and still be here ….". There was silence in the room. Finally, I went out to the nursing station and adjusted his medication. Thankfully, his pain control improved …. and fate granted him his wish. He died the next day – for me, a memory that won't fade. Since then, through the past 15 years as a senior clinician at Peter Mac, I've often reflected on the meaning of suffering, on the degree of existential pain that our patients endure on almost a daily basis …the distress caused by the very diagnosis of cancer that envelops patients and their families.

The stories my parents had told us as kids led me to reflect on the fundamental desire of all human beings – indeed all living things, to live – often despite the desperate agony of unrelenting suffering. And in thinking through these principles, gradually I became more and more drawn into the debate on euthanasia. I took a strong – what I believed, moral position and because life and death issues are not confined to oncology, I soon found myself as Chairman of the Ethics Committee of the Montefiore Homes – an aged care facility for elderly people of Jewish background. I was appointed to try to develop a set of guidelines for addressing life and death issues, particularly around whether to artificially feed severely demented people. Some members of the committee were in favour of withholding all food as a matter of course, whereas others wanted to stave off death using every possible means. The committee was made up of secular, medical and religious individuals. We had deliberated for a year and it was crunch time with religious and medical views diametrically opposed. The night before the key meeting, I went to see a wise man, a Rabbi who had demonstrated great insight into the various extremes of the argument. We sat and talked for a few hours until finally he said: "Here's the bottom line. After all we've been through, nobody should intentionally be allowed to starve to death…."… Eureka, the basis upon which we could negotiate and move forward, all the opposing views dissolved by a key principle that informed practice from that time on.

Thinking about difficult issues in order to identify the key principles that can underpin decision making, is vital to the way I like to approach such moral and ethical dilemmas. But in order to define these principles, we need to articulate them, we need to challenge them, we need to modify and fine-tune and then we need to reach a decision and act accordingly. Then we need to stand up and be counted, stand up to critics or bureaucracies, however difficult, controversial or challenging such a stance may seem, because we are obliged to do so in the interests of our patients.

I've spent a lot of my career as a researcher, but have only recently understood how much it impacts on the practice of medicine. However, I came to research somewhat accidentally. Soon after completing my second year residency, I went to see a man I had always admired – Austin Doyle, then the Professor of Medicine at the Austin Hospital. To mere residents, Professor Doyle was a very important person. In what was our second meeting, he said: "John, I think you should do a PhD". I said: "Professor Doyle, I'm not really interested" and he said: "Yes, but you should do a PhD". I said: "I'm really only interested in clinical work" and he said: "Yes, but you really should do a PhD". That was a battle I lost but am so glad I did, because working at the bench as a PhD student was the most incredible experience. It taught me about myself, about other people as well as about science. It taught me how to think. It also ultimately lead me to the view that research is critical in improving the standard of medicine we practise and the quality of care for patients. I'll come back to that in a moment.

So I did a PhD with Ian McKenzie at Melbourne Uni and then went to Toronto, where I met the then head of the Ontario Cancer Institute, Ernest McCullough. He was a senior stem cell researcher to whom, late one afternoon, I pompously suggested how inferior I thought clinical research was and how "real research" was about the laboratory, about models, theories and hypotheses and how clinical research didn't come close to that ideal. He looked at me quizzically and after a brief pause, said: "Then you obviously don't understand clinical research". The impudent young man that had walked off in the ward round in so much haste to see the next patient several years earlier, had once again been put in his place.

When I eventually came back to Australia to a job at the Repatriation General Hospital, I had pretty minimal clinical research experience. Yet I lucked upon a strategy which I recommend to any of you who may be struggling to take those initial fateful steps towards embracing clinical trials, as a modus operandi. And that is, I joined an existing trial running at the hospital and as they say, "the rest is history".

It wasn't long before I became the PI of a study we ran through the Cancer Council. Having seen "incredible" responses to 5FU and folinic acid in advanced colorectal cancer -- which was then being used routinely at the Princess Margaret Hospital, as opposed to 5FU by itself – a few of us thought it was time we started an adjuvant study with this combination. The study only recruited 20-30 people before it was closed prematurely after the 1990 NCI consensus statement suggested that the standard of care for treatment of patients with Dukes' C colon cancer was adjuvant chemotherapy with 5FU and levamisole, a regimen some of you may never have heard of, unless you're a student of history or medical trivia.

But this experience stimulated a burgeoning interest in clinical research and I teamed up with a number of like-minded people such as John Simes and Bruce Gray. We formed a small group who wanted to start other adjuvant trials in GI cancer. That was the beginnings of the Australasian Gastro-Intestinal Trials Group (AGITG), which I'm proud to have chaired over the past 15 years. However, we were soon struggling to fund the day-to-day activities of the group. Fast forward to the early part of 21st century and it was becoming clearer than ever that to drive the clinical agenda forward, to address unanswered but important clinical questions, we needed a vibrant co-operative group structure. The Breast Group, Trans-Tasman Radiation Oncology Group and Australasian Leukaemia and Lymphoma Group were leading examples at the time but mostly surviving on a shoestring. So while I was the President of COSA in 2000-2001, I visited Bob Wittes who was then at the NCI in Washington. I can remember Bob sitting behind his desk and putting both his feet up and stroking his beard, looking at me and saying: "So, let me get this right John. You want the US Government to give you money for clinical trials groups, when the Australian Government won't?" It was very obvious and sensible that we needed to provide a detailed proposal to the Federal Government that would convince them to fund the infrastructure needs of the co-operative groups, so critical to the evolving clinical research paradigm in Australia. As a result, we formed a steering committee to develop an application ultimately known as the Wall Report, to submit to the Department of Health. During one of these meetings, a member of the Department of Health and Aging asked me – somewhat to my surprise, why should we actually do trials in Australia at all, given that we regularly receive publications about trials' results from international groups based in the US and Europe. In thinking that through – after my shock and horror that anyone, especially in government, had the gall to ask this question – I came to realise that it was not an unreasonable question at all but rather, one we needed to be able to answer.

In my view, it is not only because the clinical trials process brings new treatments to patients and the community well before they'd otherwise be available through the results of international efforts. But it's because the very process of doing these trials changes the way we practise. One example I've used of late, relates to an AGITG trial involving the role of neoadjuvant radiotherapy in gastric cancer in which, to address the trial question, the standards of care against which experimental therapies need to be tested, must be resolved. Surgical standards based on best evidence need to be resolved….pathology standards (again based on best evidence) need to be defined. And hence, not only will the clinical trial potentially improve outcomes – depending on the results, but its very conduct changes the way we practise by redefining the standards of care. The trial process brings evidence-based medicine to the fore and improves the quality of care for our patients. So trials for trials' sake I don't see it as a bad thing, although in an environment of limited resources, it's becoming more difficult to do.

I'm pleased to say that I think governments are starting to get it and in some cases, hospital administrators are getting closer to understanding the role of clinical research. Clinical research is the way we must practise

medicine, although we can't continue to rely on a volunteer workforce of clinicians who sustain the academic co-operative groups. But whilst clinical research is the lifeforce of clinical medicine, we will need to work hard to make that message clear. We need to work even harder to ensure that an appropriate share of the research dollar is spent on clinical research and to ensure that a percentage of the dollars spent on service delivery via the Medicare Benefits Schedule and Pharmaceutical Benefits Scheme are used to enhance the quality of care through clinical research.

Finally, the last experiences I wanted to mention, relate to my learning about the importance of consumers in the health care system. When I first read about Herceptin in breast cancer, a disease I was no longer involved in managing, I wrote to a senior representative of the Breast Cancer Network of Australia and said: ".. what are the breast cancer advocacy groups doing about accessing this drug – arguably the most important new development in drug therapy for advanced breast cancer since Tamoxifen?" Not long afterwards, with a Federal election looming, we were sitting in the Minister for Health's office, trying to decide whether Her-2-positive breast cancer could be called "a rare disease." You see, depending on the definition of "rare", it might be eligible for a loophole in the approval process. "You'll need to talk to the Prime Minister", he finally retorted, "but I'll see what I can do". Several weeks later – on the Tuesday before the Federal election and unexpectedly, the Health Minister called me on my mobile: "I'm going to announce a special funding program for Herceptin. Can you find a patient receiving Herceptin for an interview?"

Some of you will know the Imatinib/Glivec story, but I will just briefly finish on that. Along with many others, I was involved in bringing the EORTC phase 3 trial for patients with GIST to Australia, not long after we'd heard that an Australian had gone to Boston to enter a similar trial and had been required to put down a deposit of $150,000. That's modern folklore and I still don't know if it's true but in any case, a number of us within the AGITG worked hard with Novartis to bring the trial to Australia. The trial was done but there's one aspect of this saga that you may not know. Once the trial was completed and showed the very dramatic impact on survival that you're all aware of, imatinib was approved by the Therapeutic Goods Authority and submitted for Pharmaceutical Benefits Scheme reimbursement. It was rejected twice and on the third occasion it was deferred so that without Pharmaceutical Benefits Advisory Committee (PBAC) approval, only the wealthy would be able to receive it. As a clinical community we were outraged, because we'd seen how valuable this drug had been for patients who would otherwise have died within months. One of the first patients that we treated was so sick that he actually started the drug whilst he was in ICU in Adelaide, only to walk out of hospital some weeks later. So oncologists understandably were quite emotional about access to this drug given its impact on patients. Now that it had been essentially rejected by the PBAC we didn't know where to turn, how to express our anger and frustration. At that time, we employed someone at the AGITG who had been active in the AIDS community and with his input, we organised a bus to take a group of patients from Sydney to Canberra. We planned to have a picnic on the Parliament House grounds to protest the PBAC decision. As the date got closer, we organised the patients who were going to join us on this protest – the bus was full. But I was starting to get very uncomfortable about this idea. This was not something we'd ever done before. I spoke to our organiser and said: "… I'm worried about this. What if someone gets sick along the way?" So he organised for a nurse to join the bus, in order to assist anyone who became ill en-route. But even so I was getting more and more nervous. Two days beforehand, we cancelled the bus trip. We just didn't feel we had enough experience to take this tack. But, we did not give in and instead, organised a national petition campaign. In two weeks, we had 30,000 signed petitions – that's similar to the initial response received by the Gillard government over the recent cattle export debacle – and remember too, this was in the days before Facebook and Twitter! I handed these 30,000 submissions to the consumer representative on the PBAC. Several weeks later, Department of Health representatives phoned Novartis and invited them back to talk about their PBAC submission. Once again, the rest is history.

I certainly learnt about the political process, more than I had ever previously understood it. Most importantly, I learnt the power of consumers in our efforts -- indeed our responsibility -- to alleviate the suffering of the community that we serve. I don't see consumers as patients with a history of cancer. Rather, I see the consumer as a partner in our efforts to improve cancer control. But just as we can't function in isolation, nor can consumers. I see it as our responsibility to stand with consumers, to work with governments, but always, to lobby and advocate for the patient. Sometimes it's a step into the unknown, but our knowledge, expertise and political influence as doctors, in partnership with the dedication and personal experiences of the consumer, is a very powerful force in health care. It's one we must help martial for all our sakes.

Shortly after the Glivec story, I tried to start a consumer advocacy network known as CAN. It had a Board full of consumers, some initial funds, mainly from the pharmaceutical industry, and a work plan. It took an enormous amount of effort, time and lobbying to get started. Unfortunately, despite a two year effort, it failed for a range of reasons, but I'm glad to see Cancer Voices has become a successful national force.

In concluding, I'd like to thank MOGA and the Award Committee, as well as Novartis for this award. I'd also like to thank the many colleagues with whom I've worked closely over the years, including those at Peter Mac who have all provided me with great mentorship, advice and feedback and without whom none of these initiatives would have succeeded. There are a number of people in the oncology community I would especially like to thank, including Michael Friedlander, David Goldstein and John Simes in Sydney, and Guy Toner and Danny Rischin in Melbourne …to name but a few. I'm pleased to call them colleagues and friends. I'd also like to thank my trusted secretary Emilia Agalianos. Finally, my heartfelt gratitude to my family – my wife Lynette (who's here today) and my two children Nicole and David for their tireless support, without which none of this would've been possible.

So that's the end of the personal anecdotes. These so called formative experiences have given me cause to reflect on our individual and collective roles as clinicians, as researchers and as participants in our efforts to continually strive to improve the health of our community.



REPORTS

AUSTRALIAN BEHAVIOURAL RESEARCH IN CANCER

Centre for Behavioural Research in Cancer (CBRC), Victoria

Lifestyle media message-testing: Finding the keys to successful public health campaigns promoting healthy weight and lifestyle

A team of investigators from CBRC and the Cancer Institute NSW has been awarded an Australian National Preventive Health Agency (ANPHA) grant ($348,093) for a two-year study that aims to determine how best to use mass media to promote healthy weight and lifestyle to Australians. This study, will initially identify existing mass media campaigns promoting healthy weight, physical activity and healthy eating from Australia and internationally. Potentially persuasive advertisements in each of these three domains will be shortlisted based on their concordance with content and executional characteristics known to exert beneficial influence in mass media advertising on other health topics (e.g. smoking cessation). Shortlisted advertisements for each domain will then be tested with target audiences using a combination of quantitative and qualitative techniques. Persuasive features of advertisements promoting healthy weight, physical activity and healthy eating will be identified and used to inform recommendations for developing and airing successful mass media campaigns on these health topics. The recommendations may identify existing campaigns with utility for airing to Australian audiences, or consist of a brief for developing successful advertising on these topics if development of new advertisements is deemed the most appropriate strategy.

Can mass media campaigns help prevent relapse in recent quitters?

Funded as part of an NHMRC project grant, this study aimed to determine whether greater mass media campaign exposure might help recent quitters avoid relapse. Using date of data collection and postcode, media market estimates of televised tobacco control advertising exposure measured by target audience ratings points (TARPs) were merged with a replenished cohort study of 443 Australians who had quit in the past year. Participants' demographic and smoking characteristics prior to quitting, and advertising exposure in the period after quitting, were used to predict relapse one year later. In multivariate analysis, each increase in exposure of 100 TARPs (ie. one anti-smoking advertisement for the whole population) in the three month period after the baseline-quit, was associated with a five per cent increase in the odds of not smoking at follow-up (OR=1.05, 95% CI 1.02-1.07, p<0.001). This relationship was linear and was unmodified by length of time quit prior to the baseline interview. At the mean value of 1081 TARPs in the three months after the baseline-quit interview, the predicted probability of being quit at follow-up was 52%, whereas it was 41% for the minimum (0) and 74% for the maximum (3541) TARPs. The results suggest that greater exposure to tobacco control mass media campaigns may reduce the likelihood of relapse among recent quitters. While the mass media campaign messages were primarily aimed at motivating quit attempts in smokers, these types of messages in the period soon after quitting also appear to assist recent quitters to remind themselves of the very good health reasons to quit smoking, resist urges to smoke and more generally reinforce the value of having quit.

Newcastle Cancer Control Collaborative (New-3C) NSW

Sun protection attitudes and behaviours among first generation Australians with darker skin types: focus group results

Exposure to ultraviolet radiation is an established cause of skin cancer. Australia is a multi-cultural society with a high proportion of individuals with darker skin types from Asian, Mediterranean, Middle East and Indian backgrounds. There is some suggestion that those with darker skin may not perceive themselves as being at risk of skin cancer, and may be adopting a positive attitude to tanning and sun exposure. Six focus groups were conducted to explore attitudes and behaviours towards sun exposure and protection among first generation Australians with darker skin types. Participants were 39 adults aged 18-49 living in NSW. The majority of participants had a university degree (59%), were never married or single (72%), and worked primarily indoors (72%). Overall, participants had reasonable levels of awareness and knowledge about the dangers of sun exposure and about appropriate sun protection behaviors. Participants correctly identified UV rays and the sun as a major cause of skin cancer. Many participants suggested that their darker skin type offered natural protection against the sun, burning and skin cancer. There was wide variation in participants' use of sun protection. Further quantitative research is needed to assess the impact of acculturation on solar behaviours in new Australians and their families and to determine whether sun protection messages need to be tailored and targeted to those with darker skin types.

Evaluation of the Cancer Council Legal Referral Service

Cancer Council NSW established the Legal Referral Service in February 2010 in response to the increasing number of requests from cancer patients and their carers for assistance with legal issues. The Legal Referral Service receives client referrals from social workers and matches these clients with law firms, individual solicitors and community legal centres who have agreed to provide pro-bono legal assistance. With funding from the Law and Justice Foundation, staff at Cancer Council NSW and University of Newcastle have commenced an evaluation of the acceptability and deliverability of the Legal Referral Service to the clients of the service as well as the pro bono legal service providers. Consenting clients complete a brief 15 minute structured telephone interview. Of these, two clients participated in an additional in-depth telephone interview to inform the development of client case studies. Consenting lawyers completed a 10 minute online survey. Two case studies will document the Legal Referral Service's experience engaging legal partners to provide pro-bono assistance. Although the response rate from clients has been lower than expected, there has been a surprisingly strong response from law firms. Preliminary analysis suggests that most clients are advanced or palliative stage cancer patients and are referred to the service for assistance with wills and estate issues. The evaluation findings will inform Cancer Council NSW about those areas of the service requiring improvement, and will inform the Law and Justice Foundation about one model for establishing pro bono legal services.

Breast Cancer Network Australia (BCNA)

BCNA's new CEO, Maxine Morand

Maxine Morand began as BCNA's new CEO in December last year. Maxine is a highly respected advocate for women and has extensive experience in the community, health sector and government.

A former Victorian Minister for Women's Affairs and Minister for Children and Early Childhood Development, Maxine has a background in health research and politics.

Maxine was diagnosed and treated for breast cancer in 2011, providing an intimate understanding of the issues facing women with breast cancer.

Strength to Strength: BCNA's National Conference for Women with Breast Cancer (at the Sydney International Breast Cancer Conference)

Registrations are now open for Strength to Strength: Breast Cancer Network Australia National Conference in Sydney on 25 and 26 October. The conference is part of the Sydney International Breast Cancer Congress (SIBCC).

This is the first time in Australia that health professionals, researchers and women with breast cancer will come together at one forum. The conference is an opportunity for women to:

- listen to international, world-leading authorities speak about the latest breast cancer research
- learn about treatment and care
- connect and network with more than 700 women, each offering a unique story, yet a shared experience
- feel empowered to make informed decisions about treatment, care and lifestyle choices
- find support in a warm and positive setting

For further information, including the program, visit www.bcna.org.au Early bird registration for $200 is available until 23 August.

DEXA bone density tests - survey of women with breast cancer

BCNA conducted an online survey of women with breast cancer to understand how frequently women were having DEXA bone density tests and their out-of-pocket costs.

The survey was targeted to women who had taken an aromatase inhibitor or tamoxifen for their breast cancer. The results will be published in *The Beacon*, through our website and by direct mail to health professionals and key breast cancer and cancer organisations.

MSAC MRI rebate review

Earlier this year the Medical Services Advisory Committee (MSAC) asked for public comment on the advantages and disadvantages of extending Medicare rebates for MRI to women with breast cancer.

The committee is expected to make a recommendation by mid-2012. To visit BCNA's submission on this issue, visit www.bcna.org.au

Fertility decision aid

BCNA is distributing a new resource for young women with breast cancer concerned about fertility issues. Fertility-related choices: a decision aid, was developed by Dr Michelle Peate at the University of Sydney, with input from an expert panel of advisors. McGrath Foundation has provided funding to print the resource, and BCNA is promoting and distributing it. For more information, visit www.bcna.org.au

Strengthen Your Recovery

BCNA has released a new, free resource: Strengthen your Recovery: A Pilates program following breast cancer surgery. It provides practical information and exercises for the 10 weeks following breast cancer surgery, and is provided in the free My Care Kit.

The program was developed by BCNA with breast cancer survivor and qualified Pilates instructor Fiona Eakin, in consultation with Kristi Smith, a specialist physiotherapist. For more information, visit www.bcna.org.au

Cancer Council Australia

$50m for cancer screening will save thousands of lives

Cancer Council refocused its advocacy efforts on the expansion of the National Bowel Cancer Screening Program to all Australians aged 50 and over in the lead-up to the May federal budget.

In March, the *National Bowel Cancer Screening Program Monitoring Report,* released by the Australian Institute of Health and Welfare, showed that between July 2008 and June 2011, the program detected more than 4000 cases of precancerous polyps and early-stage cancers that might otherwise have become fatal.

Cancer Council Australia CEO, Professor Ian Olver said 4000 cases was just the "tip of the iceberg". The results emphasised the program's life-saving potential and urgent need for expansion in the 2012-13 federal budget.

The research was followed by independent MPs Tony Windsor, Rob Oakeshott and Andrew Wilkie calling on the Australian Government to expand the National Bowel Cancer Screening Program in the 2012-13 budget. They came together outside Parliament House, backing Cancer Council Australia's pre-budget call for the addition of Australians aged 60 and 70 to the program.

In May, the government announced its decision to expand the bowel cancer screening program and allocate $50 million in new funds.

Professor Olver commended the Australian Government on its decision, which he said would result in thousands of Australians avoiding a premature death due to bowel cancer.

An extra $49.7 million was allocated to extend bowel cancer screening to Australians turning 60 from next year, 70 year-olds from 2015, then progressively shifting to two-yearly screening of all Australians aged 50 to 74 from 2017-18.

"Along with initiatives like plain packaging for tobacco products and a record capital investment in regional cancer centres, this latest announcement reflects the Government's commitment to reducing cancer mortality and morbidity in Australia," Professor Olver said.

Find out more about Cancer Council's campaign here, www.getbehindbowelscreening.com.au

See Cancer Council's bowel cancer TV advert here, http://bit.ly/CCAbowelscreenTVadvert

New NHMRC approved clinical practice guidelines for surveillance colonoscopy

In March, Cancer Council Australia published new clinical guidelines to help the medical profession prevent, detect and manage bowel cancer.

According to Dr Cameron Bell, Chair of the Surveillance Colonoscopy Guidelines Working Party, the guidelines provide evidence-based information to help practitioners make decisions about the timing of surveillance colonoscopy.

"In the past 10 to 15 years, there have been major changes in thinking about colonoscopy and its effectiveness in reducing bowel cancer deaths," Dr Bell said.

The guidelines provide recommendations on:

- when to repeat colonoscopy after adenomatous polypectomy
- when to repeat colonoscopy after curative resection for colorectal cancer
- when to perform colonoscopy in patients with inflammatory bowel disease.

The guidelines were partially funded by the Australian Government Department of Health and Ageing under the National Bowel Cancer Screening Program and have been approved by the National Health and Medical Research Council.

"Bowel cancer is our country's second biggest cancer killer," Professor Olver said. "These guidelines will provide a useful resource for helping colonoscopists manage patients with bowel cancer and those at risk for it."

The guidelines are available through Cancer Council Australia's Clinical Practice Guidelines wiki http://clinicalguidelines.gov.au

Government must prepare for 40% increase in cancer cases in 2020.

Australian Institute of Health and Welfare analyses predict that 150,000 Australians will be diagnosed with cancer in 2020, a 40% increase on 2007 baseline data.

Professor Olver said that although population ageing was the main reason for the projected increase, decisions made by governments in regards to budget and funding could reduce cancer incidence and mortality, with immediate and longer-term benefits.

He added that more people quitting smoking, being active, eating a healthy diet, avoiding harmful UV radiation and limiting alcohol would also translate to fewer cancer cases and deaths.

Read the AIHW report, *Cancer incidence projections, Australia 2011 to 2020* at http://www.aihw.gov.au

Cancer Council applauds New Zealand move towards tobacco plain packaging

Cancer Council welcomed New Zealand's move towards the plain packaging of tobacco products, pending a public consultation process later this year.

"We note that the Government there will first hold a public consultation, but if the Australian experience is anything to go by, the public will support plain packaging and understand it is an important public health measure," Professor Olver said. "The most vocal opponents will no doubt be the multinational tobacco companies – which just shows that the tobacco industry also expects plain packaging to cut the numbers of new smokers."

"With New Zealand taking this decision and the UK Government also looking into the introduction of plain packaging, we could be at the forefront of a global push to end the use of glossy coloured packs to attract young people to tobacco use."

90,000 Australians face work-based cancer risk

More than 90,000 workers across four sectors could be at risk of occupational cancer as a result of Australia's fragmented approach to reducing exposure to workplace carcinogens, a forum in Melbourne heard in May.

Analyses presented at a national forum, hosted by Cancer Council Australia and the Australian Council of Trade Unions, showed the highest numbers of at-risk workers were employed in machinery manufacture (42,000), printing and allied industries (25,700), food (14,800) and plastics manufacturers (11,400).

ACTU Assistant Secretary, Michael Borowick, said fragmentation was evident in the absence of regulatory links between three of the key government agencies involved – SafeWork Australia, the National Industrial Chemicals Notification and Assessment Scheme and the National Pollutions Inventory.

Chair of Cancer Council Australia's Occupational and Environmental Cancers Committee, Terry Slevin said,"Australia is seen as a leader in cancer prevention, yet we lag well behind many comparable economies when it comes to protecting our workers from cancer risk.

"The Government is looking at ways to improve the system, so we hope the evidence presented at the forum encourages the establishment of an integrated national approach to reducing workplace cancer risk."

Reduced duty-free tobacco sales another world-leading public health measure

The Government's 2012-13 budget decision to cut inbound duty-free tobacco sales will help reduce the nation's cancer burden, according to Cancer Council Australia.

Professor Olver said enabling Australians to bring in large quantities of tobacco without paying duty was an anomaly.

"At present, inbound travellers can bring in in 250 cigarettes or 250 grams of cigars or tobacco products tax-free – an anomaly that encourages consumption of an extremely harmful substance," Professor Olver said. "Committing to slash the tax-free intake level to 50 cigarettes or 50 grams of cigars or tobacco products by 1 September will discourage people from purchasing bulk quantities of the world's most harmful carcinogen."

Clinical Guidelines Network

Cancer Council Australia's Clinical Guidelines Network is steadily increasing its portfolio of clinical practice guidelines that can be accessed on the Cancer Guidelines wiki at http://wiki.cancer.org.au/australia

Published clinical guidelines that are still current are also being transferred to the wiki in readiness for their revision phase.

Draft guidelines currently in development are also on the Cancer Guidelines wiki in an access restricted area for working party members' use only, before they are released for public comment.

Clinical practice guidelines for surveillance colonoscopy in adenoma follow-up, following curative resection of colorectal cancer, and for cancer surveillance in inflammatory bowel disease

These guidelines were approved by the National Health and Medical Research Council in December 2011 and were recently launched at http://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer/Colonoscopy_surveillance.

A summary flowchart based on the clinical guidelines will also be developed on the wiki for colonoscopists and general practitioners.

Clinical practice guidelines for the treatment and management of endometrial cancer

These guidelines, which focus on the management and treatment of apparent early stage low risk and high risk endometrial cancer, were developed with funding received from Cancer Australia. The current version can be accessed at http://wiki.cancer.org.au/australia/Guidelines:Endometrial_cancer/Treatment/Early_stage

Clinical practice guidelines for the treatment of lung cancer

The treatment section of the guidelines, comprising management of non-small cell lung cancer and small cell lung cancer topic sections, was released for consultation in April. Relevant organisations, experts and interested parties were consulted during the consultation phase. In coming months, following working party review of the submissions and Cancer Australia approval, the final guidelines will be available at http://wiki.cancer.org.au/australia/Guidelines:Lung_cancer

Clinical practice guidelines for the management of sarcoma

Literature searches have been completed and the search results sent to working party authors to develop their topic content. Relevant organisations, experts and interested parties will be consulted during the public commenting phase.

Clinical practice guidelines for the diagnosis and management of Barrett's oesophagus and mucosal neoplasia

Cancer Council Australia is planning development of guidelines for detection, assessment and management of Barrett's oesophagus and mucosal neoplasia in partnership with Cancer Council NSW. The multidisciplinary working party, chaired by Professor David Whiteman, held its initial meeting in November 2011. Working party membership is being finalised.

Clinical Oncological Society of Australia

In recent months, Clinical Oncological Society of Australia (COSA) led communication and advocacy to the government and pharmaceutical suppliers in response to the recent drug shortages, particularly those drugs affecting cancer patients.

COSA wrote to the Therepeutic Goods Adminstration (TGA) requesting a working group be established with representation from all relevant organisations to work with the TGA to implement a national strategy to mitigate the effects of the current drug shortages, and to devise a robust system for handling similar issues in the future.

COSA held the Cancer Care Coordination Conference in Melbourne in March. The conference attracted over 250 delegates, of which over 50% were working in care coordinator roles. Following the success of the conference and feedback from delegates, COSA plans to hold similar conferences every second year.

COSA will host a workshop titled *'Beyond bricks and mortar: cancer service development in regional and rural Australia'* on 3 August in Canberra. The workshop will bring together key government representatives and cancer care professionals to develop strategies to improve the provision of cancer services in regional and rural Australia. This follows on from the success of the 2009 workshop, which informed the development of regional cancer centres around Australia. The aim of the workshop is to discuss how to maximise the recent investment of $560 million in regional cancer centres made through the federal Health and Hospitals Fund. Attendees will discuss how the infrastructure will be resourced by appropriately skilled cancer care professionals, including the skill sets required, incentives for relocation, continuing education and involvement in research. The workshop will also focus on how best to develop links between regional centres and service providers in metropolitan and rural areas.

COSA made a joint submission with Cancer Council Australia to the Senate Community Affairs Committee regarding the factors affecting the supply of health services and medical professionals in rural areas. Our President, Professor Bogda Koczwara, was invited to attend as a witness at the hearing in Canberra in May. Together with Cancer Voices Australia, COSA also made a submission to the Senate Community Affairs Committees inquiry into Palliative Care in Australia.

The public consultation on the draft guidance aimed at GPs for the early detection of adolescents and young adults with cancer has closed and is now with the Department of Health and Ageing for review and endorsement. COSA plans to host another networking workshop for health professionals working with adolescents and young adults later in the year, possibly at the COSA ASM in Brisbane in November.

Leadership in improving cancer research

The Consumer Engagement in Clinical Cancer Research project funded by Cancer Australia gained a lot of traction in late 2011, and we are now moving into the next phase of the project, is the development and piloting educational resources and tools for consumers working in the Cancer Cooperative Trials Groups.

Together with Cancer Council Australia, COSA made two submissions to the McKeon review of health and medical research in Australia – one on clinical research (also in partnership with the Cancer Cooperative Trials Groups); and the other on public health research in cancer control.

COSA also made a submission to the recent White Paper '*Towards a National Cancer Research Plan'* by the Cancer Research Leadership Forum. The paper calls for development of an overarching national cancer research plan for Australia to coordinate investment in research, improve funding efficiency and accelerate progress to benefit people with cancer. COSA supports the plan and recommends that a significant proportion of a national cancer research plan focuses on support for clinical cancer research.

Following a successful pilot in 2011, COSA is again offering grants to fund visiting fellowships for up to 12 weeks for health professionals working in the Asia Pacific region. Applications are now open for visiting fellows and potential host institutions – visit the COSA website for more information www.cosa.org.au

Annual Scientific Meeting

COSA is partnering with the International Psycho-Oncology Society (IPOS) and their Australian collaborators, Cancer Council Queensland, to deliver an extensive psycho-oncology program for the Annual Scientific Meeting (ASM) to be held in Brisbane, 13-15 November. The COSA Program Committee has produced a sterling program which is now available on the website www.cosa-ipos.org. All session topics, themes, coordinators and many speakers are already confirmed.

One of the highlights of the ASM is the Presidential Lecture on the final day. We are pleased to announce that Professor Ian Frazer has accepted our invitation to give the lecture – Professor Frazer is very well known to the cancer community and we are honoured to have his involvement.

Marie Malica, Executive Officer

Medical Oncology Group of Australia

The Medical Oncology Group of Australia (MOGA) has continued its advocacy work addressing national oncology drugs and treatment issues, in addition to managing a range of important educational and professional programs.

Our 'Sciences of Oncology Program' in early May was attended by 50 medical oncology trainees. The program included sessions ranging from imaging and nuclear medicine to drug-drug and drug-herb interactions.

MOGA has also made a submission to the 'Strategic Review of Health and Medical Research' (The McKeon Review). The review provides a timely opportunity to identify how Australia can continue to grow and develop our health and medical research sector, culminating in the development of a 10-year strategic health and medical research plan. MOGA's submission aimed to ensure that the national health and medical research effort incorporates the full range of mechanisms to support the conduct of oncology health and medical research at international best practice standards.

Highlights from our submission include:

- National health system expenditure is expected to grow to $3.3 trillion by 2023. (Deloitte Access Economics, 2012). National health costs are projected to increase from 9.3% in 2003 to 12.4% of GDP in 2033, reflecting the ageing population and increased burden of diseases, such as cancer: 2010 Intergenerational Report (AIHW report: *Australia's Health 2010*). Without matching increases in investment in health and medical research, Australia will not be able to respond optimally to this looming demand and disease burden.
- Establishment of a coordinated strategic approach to the funding, planning and implementation of Australian cancer research through a National Cancer Institute to achieve greater efficiencies and ultimately better national outcomes in cancer control, management, patient care and clinical practice.
- Increased research on: population health and health services to support prevention, morbidity and mortality initiatives; clinical, health services and translational research to ensure best practice supportive care and services, along with innovative and efficient service delivery to cancer patients; and survivorship and palliative care.

Royal Australian and New Zealand College of Radiologists

I am pleased to provide this inaugural report from the Faculty of Radiation Oncology to the readership of *Cancer Forum.*

The Faculty of Radiation Oncology at the Royal Australian and New Zealand College of Radiologists is the peak bi-national body advancing patient care and the specialty of radiation oncology. We do so through setting of quality standards, producing excellent radiation oncology specialists, and driving research, innovation and collaboration in the treatment of cancer.

A strong radiation oncology sector is indispensable for an effective national cancer control strategy. Radiotherapy is estimated to contribute 40% of cancer cures and will remain a vital component of cancer care. Over half of all new cancer patients need radiotherapy as part of their treatment. Unfortunately, access to radiation oncology services remains a problem for many Australians.

National Strategic Plan for Radiation Oncology 2012-2022

Radiation oncologists work closely with our colleague radiation therapists and radiation oncology medical physicists. This collaborative approach applies to our professional organisations as well: the Radiation Oncology Tripartite Committee is a peak group in the radiation oncology sector and a conjoint committee between the Faculty of Radiation Oncology, the Australasian College of Physical Scientists & Engineers in Medicine), and the Australian Institute of Radiography.

In July 2012, the Radiation Oncology Tripartite Committee will be launching 'Planning for the Best: the Tripartite National Strategic Plan for Radiation Oncology (Australia) 2012-2022'.

The strategic plan will cover key areas in radiation oncology including quality, workforce, resources, rural and regional access, Aboriginal access and research.

In preparing the plan, an extensive stakeholder consultation was undertaken and we are grateful for submissions from groups such as Clinical Oncological Society of Australia, Cancer Nurses Society Australia, Medical Oncology Group of Australia, Cancer Voices Australia, and the Royal Australasian College of Surgeons, just to name a few.

Recommendations in the strategic plan are aimed at ensuring equitable access to quality care for all Australian patients who require radiation oncology treatment.

'Planning for the Best' is available to cancer professionals and the public at www.radiationoncology.com.au

Development of the plan, which is managed by the Faculty, is funded by a grant from the Australian Government Department of Health and Ageing.

Patient access to modern radiotherapy techniques

The Faculty believes that timely patient access to appropriate radiotherapy treatment techniques is of paramount importance.

We have developed a horizon scan for current and upcoming radiotherapy techniques and technologies and put forward the view of the radiation oncology profession with regards to their priority for patient access.

This work is presented in the Faculty position paper: 'Techniques and Technologies in Radiation Oncology, 2011 Horizon Scan' and is available at: www.ranzcr.edu.au/advocacy/consumers/764-radiotherapy-technologies

The paper will be of interest to all professionals who wish to better understand the diversity of radiotherapy treatment techniques and to all members of the public who wish to understand priorities in terms of patient access to treatments.

Supporting quality practice

As the peak standards setting body in the field of radiation oncology, the Faculty has developed position papers and guidelines. Recent papers of interest include:

- Position paper on breast cancer and late effects following Radiotherapy and Chemotherapy for Hodgkin's Lymphoma.
- Position paper on the Evidence Base for Multiple Volumetric Modulated Arc Therapy – A Quality Perspective.
- Position paper on Image Guided Radiation Therapy (IGRT) – A Quality Imperative.
- Faculty Guidelines for Informed Consent.
- Faculty Guidelines for Medical and Dosimetry Record Storage.

These documents and others are available at: www.ranzcr.edu.au/organisation/faculty-radiation-oncology

As part of the Radiation Oncology Tripartite Committee, we launched the Radiation Oncology Practice Standards in 2011 for radiotherapy facilities. The standards support best practice by providing a framework of requirements. A copy of the standards can be found at: www.ranzcr.edu.au/quality-a-safety/radiation-oncology/tripartite-radiation-oncology-practice-standards

We would be happy to receive your questions and comments about radiation oncology and the work of the Faculty of Radiation Oncology or the Radiation Oncology Tripartite Committee. Please write to me at faculty@ranzcr.edu.au

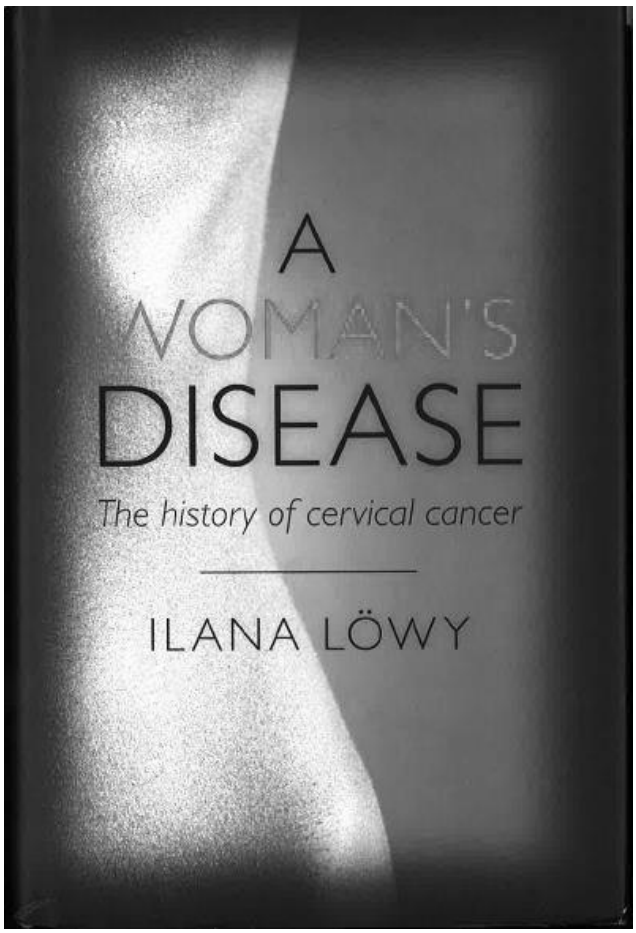
A/Prof Chris Milross, Dean, Faculty of Radiation Oncology

A Woman's Disease: The history of cervical cancer

Illana Lowy
Oxford University Press (2011)
ISBN: 9780199548811
220 pages
RRP: $28.95

The author, Ilana Lowy, is a biologist and historian of medicine, and a Senior Research Fellow at the French National Institute for Health and Medical Research. The history of cervical cancer is introduced in the prologue introducing three women; computing pioneer Ada Lovelace (1815-1852), First Lady of Argentina Eva Peron (1919-1952) and UK television personality Jade Goody. The book reflects on each woman's journey with cervical cancer and the treatment they received.

The book highlights the early struggle that women who had the misfortune of developing a gynaecological cancer in the 19th and 20th centuries endured. There is particular focus on the social stigma and attitudes of the time. The author explores: the evolution of the medicine and science involved in treating cervical cancers; the subsequent advancements in surgical, radiotherapy treatment and pathology; and the development of early awareness, pap smears, prevention advertising campaigns and HPV vaccination.



This book predominantly presents an American and European experience. Australian cervical cancer treatments and developments do not feature except in the mention of western countries. A notable omission from the book was the work of prominent Australian clinical immunologist professor Ian Frazer for his pioneering work in developing the HPV vaccine.

The book is an easy to read, historical account of the advances in diagnosis, treatment and prevention of cervical cancer and the change in society's attitudes toward this disease. It is well referenced and the chapters are arranged in a logical sequence. I would recommend the book for those who have an interest in the history of women's health and gynaecological cancer. It would have appeal to both health professionals and avid readers without a healthcare background. By example, my mother started reading this book and would like it back when I have finished!

Taryn Robinson, Department of Gynaecological Oncology, Peter MacCallum Cancer Centre, Victoria.

Human Radiation Injury

Dennis C Shrieve, Jay S. Loeffler
Wolters Kluwer, Lippincott Williams Wilkins (2011)
First Edition
ISBN 978-1-60547-011-5
533 pages
RRP: US$205.00

This is a comprehensive and well referenced textbook focusing on the impact of radiation on normal tissues. It is clearly written and well-illustrated with graphs, colour drawings and photographs.

The book starts with chapters on the radiobiology of normal tissues and the cellular and tissue pathology of radiation damage. It also explores the impact of dose and fractionation and of other agents and conditions which have a role in radiosensitivity. This section will be useful for trainees, a resource for teachers and a reference for practitioners.

Although the book is clearly aimed at providing background information for therapeutic radiation, it has interesting

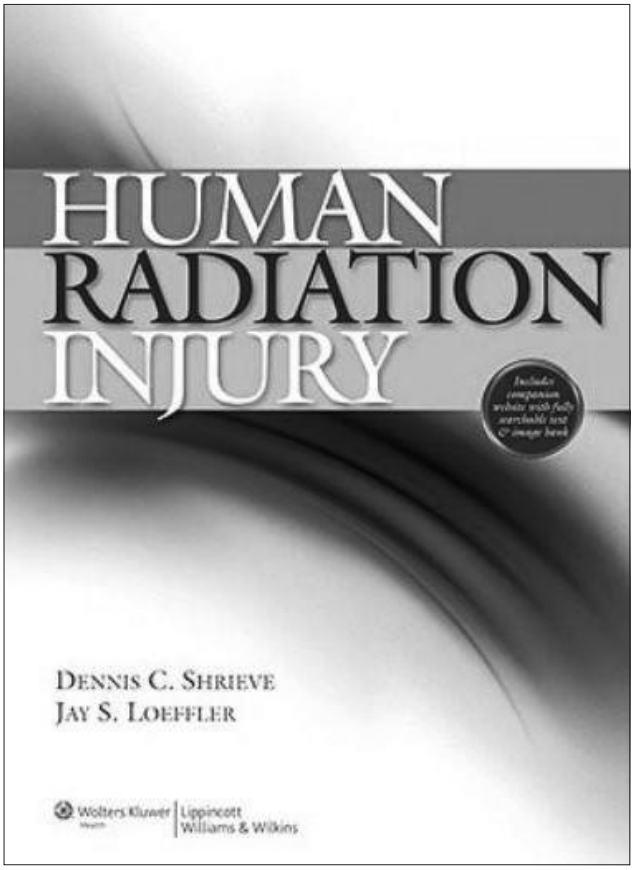
chapters on the late effects of radiation on atomic bomb survivors, radiation injuries in nuclear power plant disasters, the response to nuclear terrorism and space travel radiobiology.

The bulk of the chapters in the book (29 chapters) summarise the information of radiation effects on specific organs. There is an additional chapter on radiation effects on the embryo and foetus. Starting with the anatomy of the organ, the chapters progress to the radiation sensitivity of the organs, as recorded from animal and human data, including immediate and late effects, the diagnosis of radiation injuries and strategies for minimising the toxicity of radiation, or treatment strategies if they exist. In keeping with the rest of the book the text in these chapters is well complemented by illustrations and comprehensively referenced.

The book finishes with a chapter on the treatment of late radiation injury, which is so important as part of survivorship after radiotherapy.

The text will be useful for radiation oncologists, trainees and other oncological specialists who want a working knowledge of this area as they care for patients who have had multimodality treatment. There is a website which (via an access code in each copy of the book) gives access to the contents online that are fully searchable. This enhances the usability of the textbook. I would recommend this book to radiation oncologists, trainees, therapy radiographers, and medical physicists who make daily use of this information, however it will also be of great interest to other cancer specialists.

Ian Olver, Cancer Council Australia, NSW.



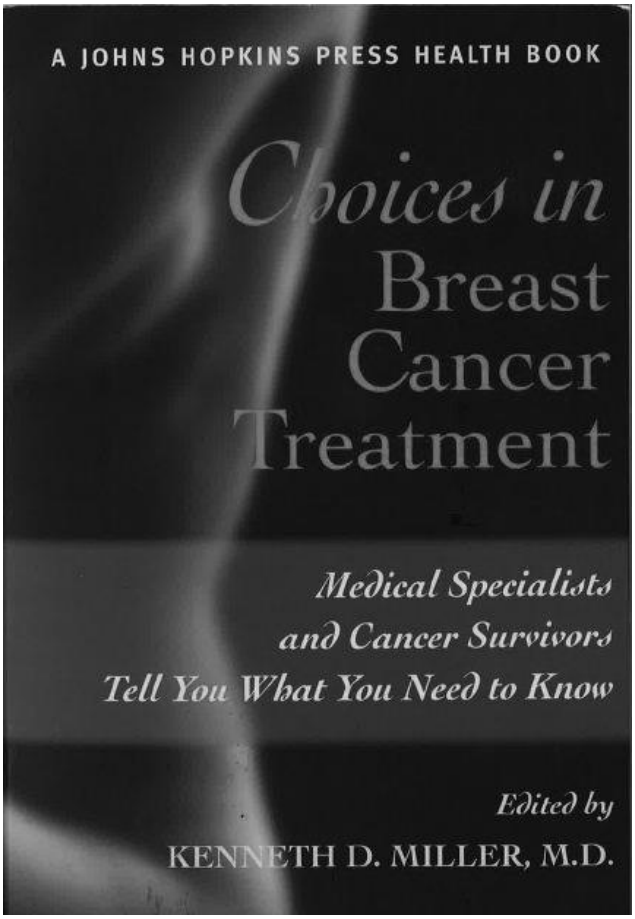
Choices in Breast Cancer Treatment

Kenneth D Miller MD (Editor)
John Hopkins Press Health Book (2008)
ISBN: 978-0-8018-8685-0
403 pages
RRP:$19.95 paperback

This book is written for women who have received a diagnosis of breast cancer. It endeavours to simplify and remove a lot of misconceptions around breast cancer and its treatment and covers everything from the process of diagnosing breast cancer to the different treatments available. There are testimonials from women with early breast cancer, as well as women with advanced disease. There are also testimonials from health professionals who have been diagnosed with breast cancer.

There are five sections in the book, starting with an overview of what cancer is, risk factors and decision making. This is followed by a section on understanding the treatment options from a doctor's perspective. The perspectives of medical oncologists, radiation oncologists and surgeons are also discussed. Section 3 is about the experience of having breast cancer. This is followed by two sections of testimonials from cancer survivors and cancer specialists with cancer.

While this book has been written for the US market, the choices in treatment are essentially the same and give a woman with a new diagnosis a reasonably good insight into what to expect from surgery through to chemotherapy



and radiotherapy. The language is easy to read and the descriptions of treatments relatively straightforward, however it does tend to repeat itself a lot.

The chapters written by cancer survivors were interesting to read, they offered a good insight into how it feels to be diagnosed with cancer and the emotional rollercoaster that most women with breast cancer feel they are on during their cancer journey. Some of the personal stories were a little long-winded and I found my attention starting to waver at times. Overall, the stories were interesting and insightful. The personal stories were divided into categories of cancer survivors with early breast cancer, advanced breast cancer and cancer professionals with breast cancer, making it possible for a woman newly diagnosed to read only the chapters that she feels are relevant.

This book provides a good overview about breast cancer diagnosis and treatment, as long as the reader remembers that it is written for the US market and that some of the terminology is different. It would benefit from a glossary of terms at the back, which would also be a good reference for the reader. This is quite a good reference book providing both factual and emotional insights into the breast cancer journey. I believe that if a woman with a new diagnosis of breast cancer were to read this book, she would gain quite a good insight into the processes around treatment decisions.

Jo Beven, McGrath Elders Breast Care Nurse, Royal Flying Doctor Service, Broken Hill NSW.

Practical Geriatric Oncology

Arti Hurria and Harvey Jay Cohen (Editors)
Cambridge University Press (2010)
ISBN:978-0-521-5131-97
448 pages
RRP: £70.00

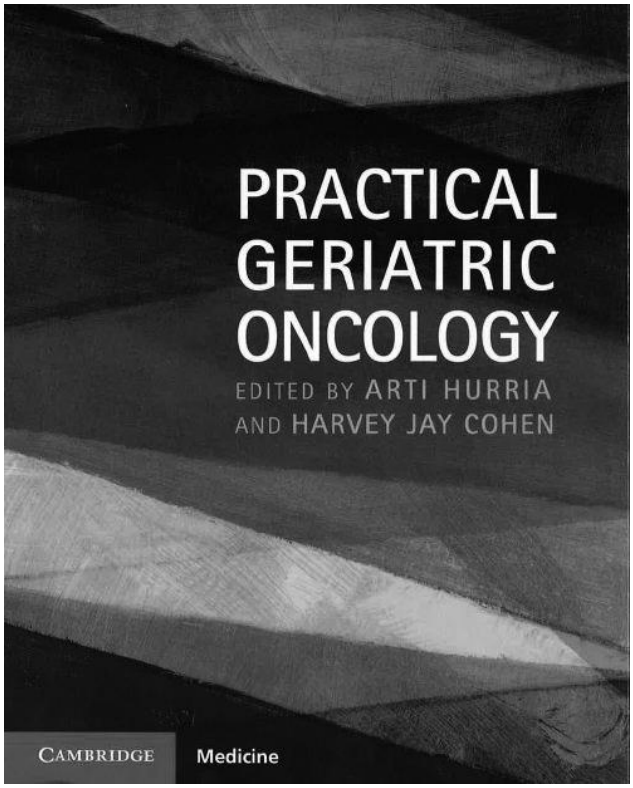
It is well recognised that cancer incidence and prevalence increases with age and, as such, geriatric oncology is becoming an increasing area of interest for health care providers. The challenge of achieving optimal outcomes from treatment, while still focusing on quality of life, requires knowledge of complex age-related factors that invariably present management dilemmas. Despite the merger of geriatric medicine and oncology being in its infancy, there is a growing body of knowledge to guide and inform clinicians regarding the holistic care of this vulnerable population.

Practical Geriatric Oncology is edited by Arti Hurria and Harvey Jay Cohen, both of whom are extremely well published and respected oncologists within the geriatric and oncology communities worldwide. This book is a comprehensive, evidence-based text that encapsulates the current literature while providing clinically relevant guidelines concerning the care of older adults with cancer. This text is divided into four parts, beginning with key principles in geriatric oncology, progressing to the management of solid tumours and the management of haematological malignancies, and finishing with symptom management and supportive care issues. The segregation of these subjects allows the reader to conveniently review specific topics of interest.

Part one covers the issues of geriatric assessment, pharmacology, principles of surgical and radiation oncology. This section is dominated by pharmacological issues that are discussed over three of the six chapters. Part two contains chapters on specific solid tumours prevalent in the elderly. These include management of cancers of the breast, lung, head and neck, oesophageal and gastric, colorectal, renal and bladder, prostate, ovarian and endometrial. Part three is dedicated to haematological malignancies, namely myelodysplasia, chronic leukaemia, acute myeloid leukaemia, haematological transplantation, non-Hodgkins lymphoma and multiple myeloma. Part four includes nine chapters covering elderly specific symptom management and supportive care needs. This section contains chapters examining the issues of quality of life, functional status, myelosuppression and the management of common toxicities of treatment and/or disease. Included in part four are chapters examining the issues of depression and anxiety, pain, fatigue, dyspnoea and gastrointestinal changes in the elderly cancer population.

This text does not cover every nuance of the management and treatment of solid tumours or haematological disorders. However, it provides readers with a well referenced, concise, easy to read text, with up-to-date, elder specific information and practical management advice for clinicians caring for older people affected by cancer. Most importantly, it informs the reader about the differences between older and younger cancer populations, as well as their similarities. It is targeted at oncologists and haematologists, however it would also be a useful resource for other healthcare professionals who provide oncology care, including surgeons, radiation oncologists, palliative care doctors, primary care providers, pharmacists, geriatricians and nurses.

Janette Prouse, Nurse Practitioner Candidate, Royal Adelaide Hospital Cancer Centre, Adelaide, South Australia.



Cancer in Pregnancy and Lactation: The Motherisk Guide

Gideon Koren and Michael Lishner (Editors)
Cambridge University Press (2011)
ISBN: 978-1-107-00613-3
211 pages
RRP: £60.00

This book had immediate appeal to all my obstetric colleagues who eyed it with envy.

A diagnosis of cancer in pregnancy presents difficult challenges for the woman and the health professionals involved in her care yet, to date, succinct data on the management of cancer in pregnancy has been scarce. The publishing of *Cancer in Pregnancy and Lactation: The Motherisk Guide* has addressed this gap.

The Motherisk program is based at the Hospital for Sick Children, Toronto, Canada and the book is complemented by the Motherisk On-line Cancer in Pregnancy Consultative Forum. The on-line forum is a place where clinicians can share their clinical experiences and have access to expert guidance.

The book is a comprehensive guide which addresses a variety of issues in pregnancy, including maternal diagnosis, treatment, prognosis and the impact on the unborn child. It is compact, evidence-based, concise and divided into four sections which have been authored by 29 contributors from Canada and Israel.

Section 1 is titled 'Specific tumours during pregnancy'. Cancers covered in this section include: bone malignancies, breast cancer, cervical cancer, hepatocellular carcinoma, Hodgkins lymphoma, intracranial tumours, treatment of acute and chronic leukaemia, lung cancer, malignant melanoma, Non-Hodgkins lymphoma, ovarian tumours and thyroid cancer.

For the rarer cancers in pregnancy such as bone malignancies, hepatocellular carcinoma and intracranial tumours, the chapters are only two to three pages in length, while chapters on the most commonly diagnosed cancers are more detailed.

Section 2 is titled 'Fetal effects of cancer treatments and interventions'. This section covers pregnancy and radiation, chemotherapy during pregnancy and non-obstetrical surgical interventions during pregnancy.

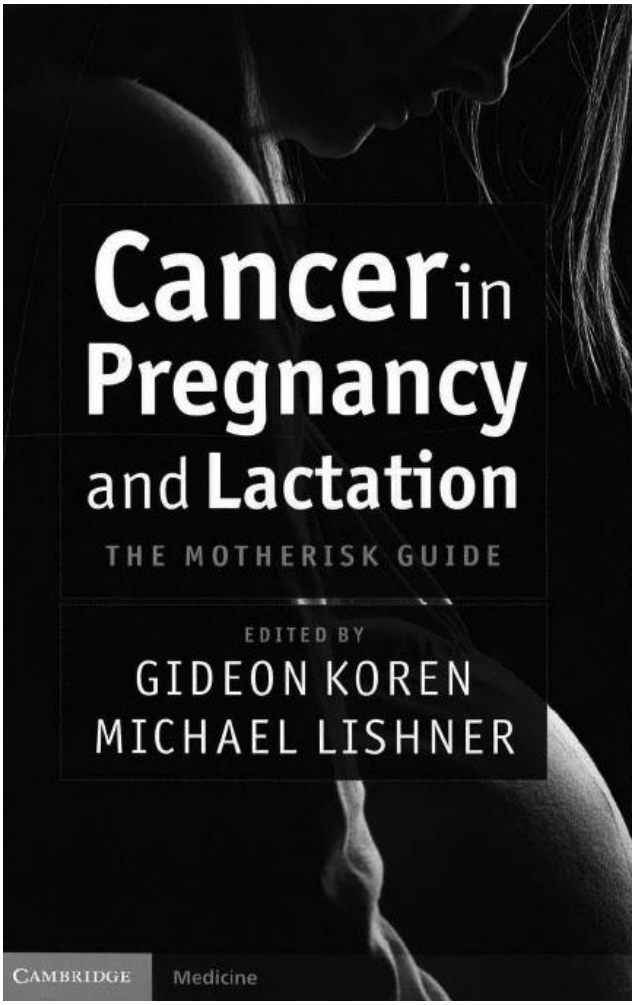
The chapter on pregnancy and radiation looks at radiotherapy for breast cancer, Hodgkins disease and cervical cancer and considers the risk to the fetus for the treatment of each of these cancers. Chemotherapy during pregnancy and breastfeeding presents difficult dilemmas which need to be individualised to determine the best outcome for the mother and fetus. The authors of this chapter have provided tables which summarise studies of commonly prescribed cytotoxic agents and pregnancy outcomes.

Section 3 is titled 'Management of maternal complications during treatment'. It looks at the management of complications associated with cancer or neoplastic treatment during pregnancy, the management of nutritional problems in the pregnant cancer patient, pharmacological and non-pharmacological treatment of chemotherapy induced nausea and vomiting, fertility considerations and methods of fertility preservation in patients undergoing treatment for cancer.

Section 4 is titled 'Long-term effects of in-utero exposure on children'. Topics covered here include long-term neurodevelopment of children exposed in-utero to treatment for maternal cancer, fertility of children exposed in-utero to chemotherapy, lactation and cancer chemotherapy, breast cancer and pregnancy – critical review of the effects of prior and subsequent pregnancy on the prognosis of young women with breast cancer and effects of the placenta on metastatic breast cancer.

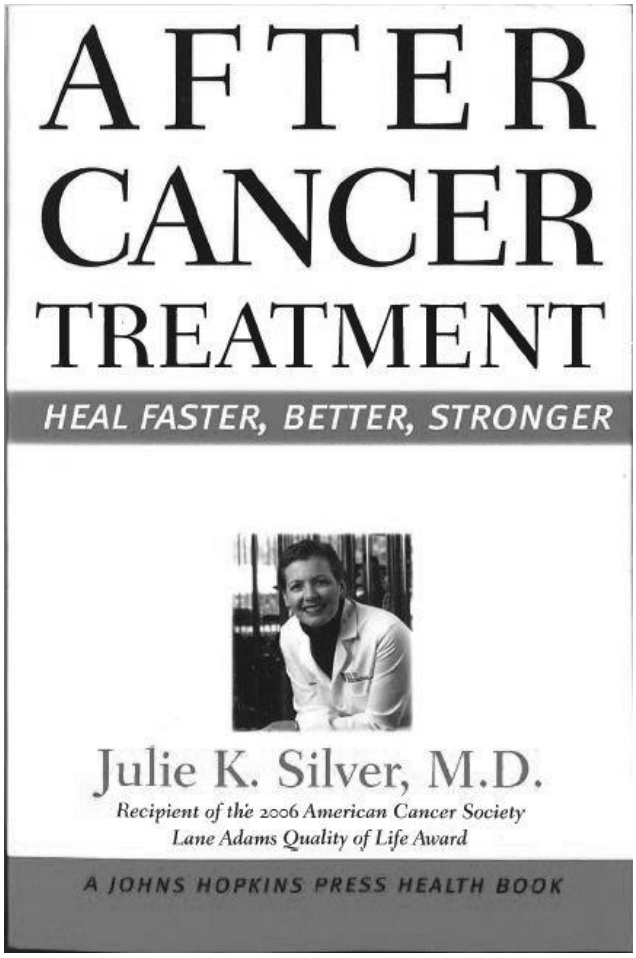
The editors have produced a quality guide to cancer in pregnancy and I would highly recommend it as a valuable resource for all health professionals involved in the care of these women. At a cost of $125 my obstetric colleagues considered that the book was value for money and one deserving of a place on their bookshelf.

Jayne Maidens, Department of Gynaecological Oncology, Royal North Shore Hospital, Sydney, New South Wales.



After Cancer Treatment: Heal Faster, Better, Stronger

Julie K Silver MD
John Hopkins Press Health Book (2006)
ISBN: 978-0-8018-8438-2
269 pages
RRP: $17.95



This sensible text of some 269 pages is written by Julie Silver, a doctor in rehabilitation medicine in the US. Using her own and others' experiences the content contains factual and practical information focusing on physical, emotional and spiritual healing for people who have experienced cancer.

Written in an easy to read style, the book consists of 15 chapters, each covering a particular topic. It begins with some basic facts about cancer, treatments and the healing process leading into recovery and setting goals. Personal anecdotes reiterate the fact that life does not return to what it was prior to diagnosis, but ascribes to building and 'finding a new normal.'

The causative factors of treatment related symptoms along with strategies to regain fitness and health are well presented. Chapter 7 in particular, titled 'Dance, skip and walk; exercise your way back to health', provides the reader with clear benefits on the value and importance of exercise in varying degrees on physical and psychological wellbeing. Readers are reminded to seek medical advice prior to the commencement of any exercise program. The inclusion of tables throughout the text reminds the reader of the focus on each chapter by succinctly summarising the key points being addressed.

I would recommend this book to patients and family/care providers as well as health professionals. However, from a patient perspective it would be helpful to provide state and territory based information and resources as the section on where to find help is solely American based.

Liz Zwart, Royal Adelaide Hospital Cancer Centre, Adelaide, South Australia.

CALENDAR OF MEETINGS

AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
July			
25	Painful truths: A workshop for primary care practitioners working with people in pain	Canberra, ACT	Chronic Pain Australia Website: www.nationalpainweek.org.au Email: Contact form on website Phone: 1800 218 921
18-20	2012 PHC Research Conference	Canberra, ACT	Primary Health Care Research & Information Service Website: www.phcris.org.au/conference/2012 Email: conference@conlog.com.au Phone: +61 2 6281 6624
26-28	Cancer Nurses Society of Australia 15th Winter Congress 2012	Hobart, Tasmania	Cancer Nurses Society of Australia (CNSA) Website: www.cnsa.org.au Email: info@cnsa.org.au Phone: +61 2 8063 4100
31-3 August	13th Australasian Prostate Cancer Conference 2012	Melbourne, Victoria	Australian Prostate Cancer Research Website: www.prostatecancerconference.org.au Email: info@prostatecancerconference.org.au Phone: +61 3 9682 0244
August			
2-4	4th Modelling of Tumours Meeting	Adelaide, South Australia	Royal Adelaide Hospital Website: www.rah.sa.gov.au/cancer/mot.php Email: christine.robinson2@health.sa.gov.au Phone: +61 8 8222 4000
23-24	Shaping the future of Palliative Care Conference	Melbourne, Victoria	Palliative Care Victoria Website: www.pallcarevic.asn.au Email: info@pallcarevic.asn.au Phone: +61 3 9662 9644
23-24	35th Annual Oncology Nurses Group Conference	Cairns, Queensland	Cancer Council Queensland Website: www.ongconference.org.au Email: info@cancerqld.org.au Phone: 13 11 20
23-25	4th Australian Lung Cancer Conference	Adelaide, South Australia	The Australian Lung Foundation Website: www.alcc.net.au Email: info@alcc.net.au Phone: +61 (0) 7 3251 3600
September			
6-8	Australasian Gastro-Intestinal Trials Group 14th Annual Scientific Meeting	Sydney, New South Wales	Australasian Gastro-Intestinal Trials Group Website: www.agitg2012.com.au Email: agitg2012@arinex.com.au Phone: +61 2 9265 0700
9-15	Australia and Asia Pacific Clinical Oncology Research Development (ACORD) Workshop 2012	Sunshine Coast, Queensland	Australia and Asia Pacific Clinical Oncology Research Development (ACORD) Website: www.acordworkshop.org.au Email: moga@moga.org.au Phone: +61 2 8247 6210
26-28	Sydney Cancer Conference 2012	Sydney, New South Wales	Cancer Research Network Website: www.sydney.edu.au/cancer-research/SCC2012 Email: nadine.caisley@sydney.edu.au Phone: +61 2 9114 1943

CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
October			
23-26	Sydney International Breast Cancer Congress 2012	Sydney, New South Wales	Sydney International Breast Cancer Congress 2012 Managers Website: www.sydneybreastcancer2012.com Email: sydneybreastcancer2012@arinex.com.au Phone: + 61 2 9265 0700
25-27	GP12 – The Conference for General Practice	Gold Coast, Queensland	Royal Australian College of General Practitioners Website: www.gpconference.com.au Email: events@racgp.org.au Phone: +61 3 8699 0533
November			
11-15	14th World Congress of Psycho-Oncology	Brisbane, Queensland	International Psycho-Oncology Society (IPOS) and Clinical Oncological Society of Australia (COSA) Website: www.ipos-society.org/ipos2012 Email: cosa@cancer.org.au Phone: + 61 8063 4100
13-15	Clinical Oncological Society of Australia 39th Annual Scientific Meeting	Brisbane, Queensland	Clinical Oncological Society of Australia (COSA) Website: www.cosa.org.au Email: cosa@cancer.org.au Phone: +61 2 80634100
November			
10-11	Palliative Care Nurse Australia Conference	Melbourne, Victoria	Palliative Care Nurses Australia Website: www.pcna.org.au/conference Email: pcna@palliativecare.org.au Phone: (02) 6232 4433
2013			
March			
7-8	International Meeting on Psychosocial Aspects of Hereditary Cancer	Sydney, New South Wales	International Meeting on Psychosocial Aspects of Hereditary Cancer (IMPAHC) 2013 Website: www.impahc2013.com.au Email: info@impahc2013.com.au Phone: +61 2 9382 3440
13-16	13th St.Gallen International Breast Cancer Conference 2013	St.Gallen, Switzerland	St. Gallen Oncology Website: www.oncoconferences.ch Email: info@oncoconferences.ch Phone: +41 (0) 71 243 00 32
2014			
November			
8-11	Biannual Meeting of the International Gyneacological Cancer Society	Melbourne, Victoria	The International Gynecologic Cancer Society (IGCS) Website: www.igcs.org Email: adminoffice@igcs.org Phone: +1 502 891 4575
9-10	12th Queensland Palliative Care Conference 2012	Sunshine Coast, Queensland	Palliative Care Queensland Website: www.palliativecareqld.org.au/qld-conference-2012 Email: enquiries@palliativecareqld.org.au Phone: +61 7 3211 2299

INTERNATIONAL

Date	Name of Meeting	Place	Secretariat
July			
7-10	22nd Biennial Congress of the European Association for Cancer Research	Barcelona, Spain	European Cancer Organisation (ECCO) Website: www.ecco-org.eu Email: eacr22@ecco-org.eu Phone: +32 2 775 02 01
11-13	6th International Cardiff Conference on Paediatric Palliative Care	Cardiff, United Kingdom	International Children's Palliative Care Network (icpcn) Website: www.icpcn.org.uk Email: admin@icpcn.co.za Phone: +27 0 78 802 3986
11-15	Singapore Palliative Care Conference 2012	Singapore	Singapore Palliative Care Conference (SPCC) Website: www.cvent.com/events/singapore-palliative-care-conference-2012/event-summary-a3deae3ccda54505b4133c70de1a13b5.aspx Email: dt-spcc2012@globewerks.com Phone: + 65 6513 7321
12-13	2012 Best of American Society Clinical Oncology Chicago	Chicago, United States of America	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
23-24	31st Sapporo International Cancer Symposium 2012	Hokkaido, Japan	Sapporo Cancer Seminar Foundation Website: scsf.info Email: shirato@med.hokudai.ac.jp Phone: 81 11 706 5977
25-27	Cancer in Never-Smokers	Rio de Janeiro, Brazil	International Association for the Study of Lung Cancer Website: www.lalca2012.org Email: lalca2012@icsevents.com Phone: +1 604 681 2153
26-28	Beyond the Global Standard of Medical Oncology – Perspectives from Asia.	Osaka, Japan	Japanese Society of Medical Oncology (JSMO) Website: www.square.umin.ac.jp/jsmo2012/en/index.html Email: jsco@gakkai.net Phone: +81 3 6809 1250
August			
1-4	XIV World Congress on Cancers of the Skin	Sao Paulo, Brazil	Skin Cancer Foundation Website: www.skincancer2012.com Email: atendimento@intimeeventos.com.br Phone: +1 212 725 5176
3-4	2012 Best of American Society Clinical Oncology Boston	Boston, United States of America	American Society of Clinical Oncology (ASCO) Website: www.boa2012.asco.org Email: membermail@asco.org Phone: + 1 571 483 1300
10-11	2012 Best of American Society Clinical Oncology San Diego	San Diego, United States of America	American Society of Clinical Oncology (ASCO) Website: www.boa2012.asco.org Email: membermail@asco.org Phone: +1 571 483 1300
27-30	Union for International Cancer Control World Cancer Congress	Montreal, Canada	Union for International Cancer Control (UICC) Website: www.worldcancercongress.org Email: congress@uicc.org Phone: +41 22 809 1811

Date	Name of Meeting	Place	Secretariat
September			
4-7	Australian and New Zealand Society of Palliative Medicine conference	Queenstown, New Zealand	Australian and New Zealand Society of Palliative Medicine (ANZSPM) Website: www.willorganise.com.au/anzspm2012/ Email: anzspm@willorganise.com.au Phone: +61 2 4973 6573
6-8	The 2nd World Congress on Controversies in Hematology	Barcelona, Spain	Comtec MED Medical Congress Website: www.comtecmed.com/cohem/2012 Email: Info@comtecmed.com Phone: +97 2 3 5666166
13-15	2012 Breast Cancer Symposium	San Francisco, United States of America	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: + 57 1 483 1300
14-16	International Liver Cancer Association Sixth Annual Conference	Berlin, Germany	International Liver Cancer Association (ILCA) Website: www.ilca2012.org Email: info@ilca-online.org Phone: +32 (0)2 789 2345
28-2 October	37th European Society Medical Oncology Conference	Vienna, Austria	European Society for Medical Oncology (ESMO) Website: www.esmo.org Email: registration@esmo.org Phone: +41 91 973 19 26
October			
3-5	Global Summit on International Breast Health: "Breast Cancer – Quality of Life"	Vienna, Austria	The Breast Health Global Initiative (BHGI) Website: www.bhgi.info/ Email: mhartman@fhcrc.org Phone: + 1 (206) 667-3538
6-8	Ethics and Compliance in Oncology Research	Houston, United States of America	MD Anderson Website: www3.mdanderson.org/calendar/tool/event/Ethics_and_Compliance_in_Oncology_Research_ECOR_16538.html Email: ecor@mdanderson.org Phone: +1 713 563 5450
9-12	19th International Congress on Palliative Care	Montreal, Canada	Palliative Care McGill Website: www.palliativecare.ca/en/ Email: secretariat@pal2012.com Phone: +1 450 292 3456 ext. 227
10-12	Symposium on Breast Cancer Prevention: Models for Breast Cancer Prevention from Innovation to Action	West Lafeyette, United States of America	International Breast Cancer and Nutrition (IBCN) group Website: www.purdue.edu/breastcancer/ Email: kw@purdue.edu Phone: +1 765 494 2758
11-12	Management in Radiology (MIR) Annual Scientific Meeting 2012	Milan, Italy	Management in Radiology Website: www.mir-online.org/cms/website.php Email: office@mir-online.org Phone: +43 1 533 40 64
11-13	17th World Congress on Advances in Oncology and15th International Symposium on Molecular Medicine	Crete, Greece	Spandidos Publications Ltd Website: www.spandidos-publications.com/ Email: conference@spandidos-publications.com Phone: +30 210 722 7809
12	European Society of Breast Imaging (EUSOBI) 2012 - Annual Scientific Meeting	Barcelona, Spain	European Society of Breast Imaging (EUSOBI) Website: www.eusobi.org/ Email: office@eusobi.org Phone: +43 1 535 89 25
18-19	Cancer Care in the Older Population	Cairo, Egypt	South & East Mediterranean College of Oncology (SEMCO) Website: www.semco-oncology.info Email: atef.badran@gmail.com Phone: +20 2 25 35 14 24

CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
October			
25-27	European Society Cardiac Radiology 11th Annual Scientific Meeting	Barcelona, Spain	European Society Cardiac Radiology (ESCR) Website: www.escr.org/cms/website.php Email: office@escr.org Phone: +43 1 535 50 93
25-27	50th Japanese Society Clinical Oncology Annual Meeting	Yokohama, Japan	Japan Society of Clinical Oncology Website: www.congre.co.jp/jsco2012/english/index.html Email: jsco2012@congre.co.jp Phone: +81 6 6229 2555
26-27	12th Meeting of the International Society of Geriatric Oncology	Manchester, United Kingdom	Société Internationale d'Oncologie Gériatrique (SIOG) Website: www.siog.org Email: info@siogweb.org Phone: +31 70 30 67 200
26-28	Society for Immunotherapy of Cancer 27th Annual Meeting	North Bethesda, United States of America	Society for Immunotherapy of Cancer (SITC) Website: www.sitcancer.org/2012/annualmeeting Email: education@sitcancer.org Phone: +1 414 271 2456
November			
1-2	2012 American Institute for Cancer Research Annual Research Conference on Food, Nutrition, Physical Activity and Cancer	Washington, United States of America	American Institute for Cancer Research (AICR) Website: www.aicr.org/cancer-research/conference/ Email: aicrweb@aicr.org Phone: +1 202 328 7744
4-7	National Cancer Research Institute Cancer Conference	Liverpool, England	National Cancer Research Institute (NCRI) Website: www.ncri.org.uk/ncriconference Email: ncriconference@ncri.org.uk Phone: +44 (0)20 3469 5453
8-10	BCY1 – Breast Cancer in Young Women	Dublin, Ireland	European School of Oncology (ESO) Website: www.eso.net/events-2.html Email: eso@eso.net Phone: +39 02 8546451
9-10	2nd International Conference on Cancer and the Heart	Houston, United States of America	MD Anderson Cancer Center Website: www.mdanderson.org Email: register@mdanderson.org. Phone: + 1 713 792 2223
22-25	2nd International Multidisciplinary Forum on Palliative Care	Florence, Italy	International Multidisciplinary Forum on Palliative Care Website: www.imfpc.org Email: secretariat@imfpc.org Phone: +41 0 22 533 0948
30-1 Dec	American Society of Clinical Oncology's Quality Care Symposium	San Diego, United States of America	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: + 1 571 483 1300

CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
2013			
January			
24-26	2013 Gastrointestinal Cancers Symposium	San Francisco, United States of America	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: + 1 571 483 1300
February			
14-16	2013 Genitourinary Cancers Symposium	Florida, United States of America	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: + 1 571 483 1300
March			
12-16	13th International Conference of Primary Therapy of Early Breast Cancer	St Gallen, Switzerland	St Gallen Oncology Website: www.oncoconferences.ch Email: info@oncoconferences.ch Phone: +41 (0) 71 243 0032
20-22	Reach to Recovery International Breast Cancer Support Conference	Cape Town, South Africa	17th RRI Conference Secretariat Website: www.reachtorecovery2013.org/ Email: form on website Phone: +27 21 683 2934
May			
30-2 June	13th World Congress of the European Association for Palliative Care	Prague, Czech Republic	European Association for Palliative Care Website: www.eapc-2013.org Email: eapc2013@interplan.de Phone: +49 0 89 548234 73
31–4 June	2013 American Society Clinical Oncology Annual Meeting	Chicago, United States of America	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: + 1 571 483 1300
October			
10-12	Global Breast Cancer Conference	Seoul, Korea	INTERCOM Convention Services Inc. Website: www.gbcc.kr Email: gbcc@intercom.co.kr Phone: +82 2 501 7065

CANCER COUNCIL AUSTRALIA

Cancer Council Australia is the nation's peak cancer control organisation.

Its members are the leading state and territory Cancer Councils, working together to undertake and fund cancer research, prevent and control cancer and provide information and support for people affected by cancer.

MEMBERS

Cancer Council ACT
Cancer Council New South Wales
Cancer Council Northern Territory
Cancer Council Queensland
Cancer Council South Australia
Cancer Council Tasmania
Cancer Council Victoria
Cancer Council Western Australia

AFFILIATED ORGANISATIONS

Clinical Oncological Society of Australia

CEO

Professor I Olver AM

COUNCIL

Office Bearers

President
Hon H Cowan

Vice President
Mr S Foster

Board Members

Ms C Brill
Professor R Gardiner
Mr G Gibson QC
Professor C Saunders
Ms O Stagoll OAM
Mr B Hodgkinson SC
Professor B Koczwara
Ms R Martinello
Mr S Smiles
Mr S Roberts
Ms J Brown
Ms J Fenton

CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA

The Clinical Oncological Society of Australia (COSA) is a multidisciplinary society for health professionals working in cancer research or the treatment, rehabilitation or palliation of cancer patients.

It conducts an annual scientific meeting, seminars and educational activities related to current cancer issues. COSA is affiliated with Cancer Council Australia.

EXECUTIVE COMMITTEE

President
Professor B Koczwara

President Elect
Associate Professor S Porceddu

Executive Officer
Ms Marie Malica

Council Nominees
Associate Professor I Davis
Associate Professor M Krishnasamy
Dr H Dhillon
Professor I Olver AM
Profesor J Zalcberg OAM

MEMBERSHIP

Further information about COSA and membership applications are available from:
www.cosa.org.au or cosa@cancer.org.au

Membership fees for 2012

Medical Members: $160
Non Medical Members: $100 (includes GST)

PROFESSIONAL GROUPS

Breast
Cancer Nurses Society of Australia
Cancer Pharmacists
Cancer Biology
Clinical Research Professionals
Epidemiology
Familial Cancer
Gastrointestinal
Gynaecology
Lung
Medical Oncology
Melanoma and Skin
Neuro-oncology
Nutrition
Palliative Care
Paediatric Oncology
Psycho-oncology
Radiation Oncology
Regional and Rural
Social Work
Surgical Oncology
Urologic Oncology

Information for contributors

Cancer Forum provides an avenue for communication between all those involved in the fight against cancer and especially seeks to promote contact across disciplinary barriers.

To this end articles need to be comprehensible to as wide a section of the readership as possible. Authors should provide sufficient introductory material to place their articles in context for those outside their field of specialisation.

Format

Cancer Forum welcomes original articles about medical, scientific, political, social, educational and administrative aspects of cancer control. All manuscripts should be submitted by email to info@cancerforum.org.au as MS Word documents.

Length: 2000-2500 words.

Font: Arial - 20pt for title, 12pt for headings and 10pt for text.

Following the title, include your full name, organisation and email address.

Include an introductory heading and sub-headings that describe the content.

Number pages in the footer.

Abstract

All manuscripts must include an abstract of approximately 200 words, providing a summary of the key findings or statements.

Illustrations

Photographs and line drawings can be submitted via email or on disk, preferably in tiff or jpeg format, or as transparencies or high quality prints.

If images are not owned by the author, written permission to reproduce the images should be provided with the submission.

Referencing

Reference numbers within the text should be superscripted and placed after punctuation.

The list of references at the end of the paper should be numbered consecutively in the order in which they are first mentioned and be consistent with the National Library of Medicine's International Committee of Medical Journal Editors' *Uniform Requirements for Manuscripts Submitted to Biomedical Journals.*

> eg. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002 Jul 25;347(4):284-7.

A full guide is available at www.nlm.nih.gov/bsd/uniform_requirements.html

The Editorial Board will make the final decision on publication of articles and may request clarifications or additional information.

Manuscripts should be emailed to:

Executive Editor
Cancer Forum
GPO Box 4708
Sydney NSW 2001
info@cancerforum.org.au

GPO Box 4708, Sydney NSW 2001
Telephone: 02 8063 4100
Facsimile: 02 8063 4101
Website: www.cancer.org.au