CME

Follow the link from the online version of this article to obtain certified continuing medical education credits

bmj.com Visit BMJ Group's Psychiatry portal http://www.bmj.com/specialties/psychiatry

Advances in radiotherapy

Saif S Ahmad,[1] Simon Duke,[1] Rajesh Jena,[1] Michael V Williams,[1] Neil G Burnet[2]

[1]Clinical Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK
[2]University of Cambridge, Cambridge
Correspondence to: S S Ahmad
saif.ahmad@nhs.net

Cite this as: *BMJ* 2012;345:e7765
doi: 10.1136/bmj.e7765

bmj.com
Previous articles in this series
- Generalized anxiety disorder: diagnosis and treatment (*BMJ* 2012;345:e7500)
- Resistant hypertension (*BMJ* 2012;345:e7473)
- Childhood constipation (*BMJ* 2012;345:e7309)
- Preparing young travellers for low resource destinations (*BMJ* 2012;345:e7179)
- Management of chronic rhinosinusitis (*BMJ* 2012;345:e7054)
- Salivary gland swellings (*BMJ* 2012;345:e6794)

Radiotherapy plays an important role in the care of patients with cancer and forms part of the management of 40% of patients cured of their disease.[1] Advances have been made in the past two decades, as improvements in engineering and computing have enabled technologies such as intensity modulated radiotherapy (IMRT), image guided radiotherapy (IGRT), and stereotactic radiotherapy (SRT) to be used in routine clinical practice.

This article explains newer radiotherapy techniques and aims to enable general practitioners and non-specialist clinicians to advise patients who come to them with questions. It will focus on external beam radiotherapy (EBRT), which is the most common form of treatment, delivered to 125 000 patients a year in England.[2]

How does radiotherapy work?

X rays are a form of electromagnetic radiation that deliver their energy through waves called photons. These photons are produced by accelerating a stream of electrons and colliding them with a metal target. High energy photons produce secondary electrons in human tissue. Electrons cause DNA damage which, if not repaired, proves fatal at cell division. Absorbed radiation doses are measured as joules per kilogram, expressed in the unit gray (Gy).

EBRT is administered using a linear accelerator. These machines are roughly the size of computed tomography (CT) scanners and, for radiation protection purposes, are housed in thick walled bunkers.

EBRT usually uses high energy x rays, which penetrate deep into body tissue while relatively sparing the skin. Electrons can also be used for superficial treatments. These electrons can be derived from most linear accelerators (by removing the metal target) and provide a high dose to a depth of a few centimetres, with little dose beyond. Electrons are therefore often used to treat skin tumours. Proton beams (discussed later) can also be used for EBRT; the dose builds up to a peak and then falls off steeply with no dose beyond their finite range.

EBRT is normally delivered over multiple sessions (or fractions) to exploit differences in repair and repopulation between tumour cells and normal cells. For example, treatment for prostate and head and neck cancer can extend to 40 fractions over eight weeks. By contrast, in palliative settings, single fraction treatment is common. This is because low doses of radiotherapy can provide tumour control for a short time (range of months) with minimal side effects.

Most EBRT is planned using CT imaging to locate the tumour and provide information on the patient's shape and tissue density. Correlation with diagnostic imaging is essential. The diagnostic imaging modality that provides the best possible information on the position and extent of the tumour is used. For many tumours this will be magnetic resonance imaging (MRI). For some sites such as the brain, computerised image fusion is used alongside the planning CT scan to improve the accuracy of tumour localisation. Positron emission tomography-CT can aid radiotherapy planning for lung cancers and lymphoma by showing which anatomical areas contain tumour. Over the past 20 years, techniques that can align treatment more closely to the tumour have been developed. This approach is known as three dimensional conformal radiotherapy (3D-CRT), and it enables oncologists to spare more healthy tissue and reduce toxicity.[3] IMRT represents a further development of this concept and will be discussed later.

Who needs radiotherapy?

A systematic review of national and international guidelines linked to detailed information on cancer incidence and stage estimated that 52% of patients with cancer should receive radiotherapy at some time during their illness, either for cure or palliation.[4] The authors developed an optimal radiotherapy utilisation tree for each cancer based on indications for radiotherapy taken from evidence based treatment guidelines and correlated this with epidemiological data.

In the curative setting, radical radiotherapy can be offered as the sole treatment. It can also be used with surgery, being given before (neoadjuvant) or after resection (adjuvant) (table).

Palliative radiotherapy plays a vital role in cancer care. A systematic review of 25 randomised controlled trials showed that it can reduce or eliminate pain from bone metastases in 60% of cases.[5] Radiotherapy can also be used to palliate brain metastases, spinal cord compression, compressive symptoms from visceral metastases, and uncontrolled bleeding—for example, haemoptysis or haematuria.

SUMMARY POINTS

- Radiotherapy forms part of the management of 40% of patients who are cured of cancer
- Advances in technology mean that more patients now receive efficacious treatment with less toxicity
- Newer technologies are increasingly available in the UK
- These technologies include intensity modulated radiotherapy, image guided radiotherapy, stereotactic radiotherapy, stereotactic ablative radiotherapy, and proton beam therapy
- Toxicity can develop early or late, and non-specialist clinicians should be aware of the more common side effects, which typically relate to the anatomical site treated

SOURCES AND SELECTION CRITERIA

This article is an evidence based review of clinical radiotherapy. We searched PubMed and the Cochrane databases between 1990 and 2012 using the search terms radiotherapy, intensity modulated radiotherapy, image guided radiotherapy, stereotactic radiotherapy, and proton beam therapy to identify observational studies, randomised trials, meta-analyses, and systematic reviews.

Common indications for radiotherapy

Cancer	Role of radiotherapy	Example of indication	Comments	Outcomes
Breast	Adjuvant treatment	Early stage after wide local excisions	In selected cases may be given intraoperatively (mature data awaited)[w1]	Reduces first recurrence at 10 years (from 35.0% to 19.3%); reduces 15 year absolute risk of death from breast cancer by 3.8% (from 25.2% to 21.4%) compared with no radiotherapy[w2]
		High risk mastectomy patients		Reduces local recurrence at 5 years (from 23% to 6%) and reduces 15 year absolute risk of death from breast cancer by 5.4% (from 60.1% to 54.7%) compared with no radiotherapy[w2]
				After breast radiotherapy the hazard ratio for death from heart disease is 1.27 and lung cancer 1.78 compared with no radiotherapy (overall mortality still reduced)[w3]
Prostate	Primary treatment	Early stage	Radiotherapy alone (brachytherapy in some cases) as a treatment option rather than surveillance or surgery	Similar outcomes to surgery[w4]; 93% prostate specific antigen control with brachytherapy at 7 years in low risk disease[w5]
		Locally advanced	EBRT is often used in combination with androgen deprivation therapy	74.1% and 71.4% prostate specific antigen control and overall survival, respectively, at 10 years for inoperable tumours[w6]
Lung	Primary treatment	Locally advanced tumours or comorbidity	Optimal outcomes using CHART or chemoradiation; radical high dose treatment for small tumours	Concurrent chemoradiation improves 2 year survival by 8% compared with radiotherapy alone[w7]; CHART improves 2 year survival from 20% to 29% compared with conventional radiotherapy[w8]
	Stereotactic ablative radiotherapy	Medically inoperable tumours		Mature outcome data awaited
Head and neck	Primary and adjuvant treatment	Can be used in most cancers to aid organ preservation	Often given with cisplatin	5 year survival: 80-90% in stage 1-2 tumours, 60-70% in stage 3-4 tumours[w9]
Rectum	Neoadjuvant treatment	To downstage bulky tumours at risk of involved resection margins	Given as short course (5 days) or long course (5 weeks) treatment	Cochrane review shows improved overall survival (by 2%) and local recurrence rates (heterogeneous across trials) compared with no radiotherapy[w10]
Gynaecological	Primary and adjuvant treatment	Cervical cancer	Primary chemoradiotherapy is standard of care in all but early stage I cervical cancers	Concurrent cisplatin and radiotherapy improves 5 year survival from 60% to 66%[w11]
		Endometrial cancer		Adjuvant EBRT reduces locoregional recurrence from 8.5% to 2.5% compared with surgery alone but has no effect on survival[w12]
Brain	Primary and adjuvant	After debulking surgery	Concurrent temozolamide improves survival	At doses above 60 Gy improves median survival from 18 to 42 weeks compared with surgery alone[w13]

CHART=continuous hyperfractionated accelerated radiotherapy; EBRT=external beam radiotherapy.

What are the side effects?

With the exception of fatigue, toxicity is associated with the anatomical location of the radiotherapy fields. Common side effects are summarised in web table 1 (see bmj.com).[w1-w13] A detailed discussion of the side effects of treatment is outside the aims of this review.

Toxicity can broadly be divided into early and late. Early toxicity is generally reversible, but it must be managed appropriately to avoid unnecessary gaps in treatment. It begins around two weeks into treatment, but symptoms tend to peak at two to four weeks after completion. Late toxicity occurs at least six months after treatment and may present after many years. Unlike early effects, these late effects are often irreversible. A multinational peer reviewed collection of guidelines has been developed that details these risks and their relation to dose. The guidelines are limited by being based on pooled data from individual studies, but if interpreted appropriately during radiotherapy planning this information can help minimise toxicity.[6]

Fatigue occurs in around 80% of patients receiving radiotherapy and tends to peak in the second week, improving around four weeks after completing treatment.[7] A thorough but non-systematic review reported that fatigue persists in a chronic form in about 30% of cases.[7] Patients are advised to remain as active as possible. Exercise programmes may help, but robust data supporting fatigue prevention strategies are lacking.

Other toxicities are specifically associated with the area of the body treated. The skin is commonly affected during treatment for more superficial tumours. Early skin effects include erythema and desquamation, whereas late effects are characterised by atrophy and telangiectasia. For example, 23% of women who received adjuvant breast radiotherapy within the phase III trial, START B, at a dose of 40 Gy in 15 fractions (current UK standard of care) reported a change in skin appearance of the treated breast at five years.[8]

Pelvic radiotherapy—for indications such as urological, bowel, and gynaecological cancers—is associated with several early and late effects (see web table 1). The likelihood of certain side effects is largely dictated by the dose fractionation schedule, site treated, and any pre-existing comorbidities. Chronic symptoms such as dyspareunia, urinary incontinence, and faecal incontinence can have a serious impact on quality of life. Their management should be coordinated with the treating oncologist, and in some cases further specialist opinions may be needed.[9]

Does radiotherapy increase the risk of subsequent cancer?

The risk of second cancers after radiotherapy increases over the decades after treatment and depends on the treated volume and dose.[10] The risk is particularly relevant for younger patients with a good prognosis. A cohort study of more than 25 000 patients established that patients with stage I seminoma have a relapse rate of 4% but an excess second cancer risk of 6% at 25 years after radiotherapy.[11] Radiotherapy is now rarely used for these patients. For early treatment of breast cancer, the risks are lower. A cohort study of more than 180 000 patients that used the SEER (surveillance, epidemiology, and end results) database found an excess absolute risk of radiotherapy related second breast cancers and other solid cancers (such as lung cancer and sarcoma) of two and four cases per 10 000 person years, respectively.[12] This slight increase in second cancers is insignificant in most cases when compared with the risk of recurrence and death

from the primary lesion. Nevertheless, patients must be fully informed because these data might affect their decisions about radiotherapy when alternative treatments are available.

Breast screening by mammography or MRI is an important consideration for people at higher risk of second cancers. A UK based cohort study in young patients who received supradiaphragmatic radiotherapy for Hodgkin's disease found that the risk of breast cancer was similar to that of women with *BRCA* mutations.[13] This was especially true in women who were treated under the age of 20 years. The maximum absolute excess risk of breast cancer occurred at age 50-59 years (87.9 cases/10 000). In the United Kingdom, women given radiotherapy for Hodgkin's lymphoma under the age of 35 years are advised to have annual breast screening starting eight years after treatment. At the age of 50 years, they then join the national breast screening programme (mammography every three years) but, because this is the time of the maximum excess risk, it has been argued that more intensive screening may be needed.[13]

Increased risks of cardiovascular events and stroke are also important, and the evidence has recently been reviewed.[10] A key retrospective study of survivors of Hodgkin's disease showed a relative risk of 3.5 for death from myocardial infarction in patients receiving high dose radiotherapy.[14] The risk varies greatly according to dose and tumour site.[10] However, these findings are largely based on treatments using older techniques and may be overestimates. Smoking cessation and other lifestyle advice should be as standard. Moreover, the additional risk should be considered when using tools for estimating the risk of cardiovascular disease. Similarly, hypothyroidism occurs in almost 50% of patients after radiotherapy for head and neck cancer, necessitating regular thyroid function checks, at least annually, for 10 years or more.[15]

How safe is radiotherapy?

The potentially devastating effects of maladministration reinforce the need to avoid complacency.[16] The risk of death directly caused by radiotherapy errors is estimated at two per million courses in the UK and 15 per million courses in an international systematic review. For comparison, the risk of a crash on a commercial air flight is four per million departures.[17] Within the UK, detailed national checks and procedures are in place to ensure that the right patient receives the right treatment. In developed countries robust error reporting systems are an important learning tool.

Patients often ask if they will be "radioactive," but once the beam is turned off there is no radiation exposure. This makes the treatment environment safe for relatives and staff, although they must vacate the room while the beam is on.

How is radiotherapy initiated?

Once a patient has consented to treatment they will attend a "planning CT scan." Using these images, the precise arrangement of radiotherapy beams for treatment is planned, usually by an oncologist in conjunction with a radiographer and medical physicist. Simpler plans, such as single fraction palliative treatments, can be completed within an hour. More complex ones, such as those using IMRT, may take up to a week to allow for checking and verification of the plan. Each treatment session, or fraction, takes around 10-20 minutes, including time spent ensuring the patient is correctly positioned on the treatment couch. Patients receiving multiple fractions are usually reviewed, at least weekly, by a doctor to help manage treatment related side effects.

Newly introduced techniques in radiotherapy

IMRT, IGRT, and SRT are newer techniques that should be routinely available for all patients within the appropriate clinical context.

Intensity modulated radiotherapy (IMRT)

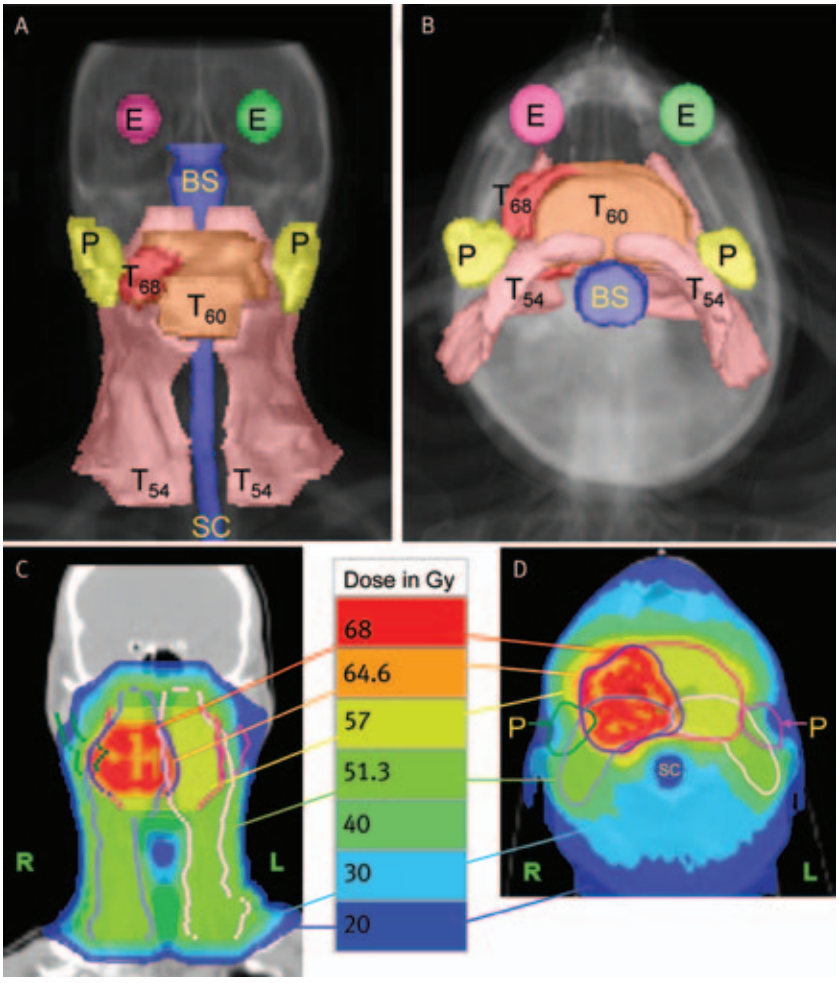
IMRT can create concave treatment shapes and steep dose gradients. This maximises the sparing of normal tissues, particularly if the tumour is wrapped around normal structures such as the spinal cord. Conventional radiotherapy typically uses a small number of beams, each with uniform intensity across the field. In contrast, IMRT uses multiple beams with a highly non-uniform dose across the field. This is achieved by dividing the beam into multiple "beamlets," so that doses of varying intensity can be delivered to different parts of the field (figure).

IMRT is particularly useful for head and neck cancers because of the high number of important normal tissue structures within close proximity to the tumour. A phase III study randomised patients with squamous cell cancers of the oropharynx to conventional 3D-CRT or parotid sparing IMRT. It found a significant reduction in dry mouth at two years (29% *v* 83%; P<0.0001) with IMRT compared with 3D-CRT.[18] A systematic review published in 2010 of the benefits of IMRT identified 61 studies that compared it with conventional radiotherapy.[19] It found similar benefits at many other treatment sites, including reduced rectal toxicity in patients with prostate cancer.

In breast cancer, improved dose distributions in patients with larger breasts decrease the risk of breast pain and improve long term cosmesis. Findings on local control and overall survival were generally inconclusive. However, consequent sparing of normal tissue means that higher and potentially more effective doses could be used without the risk of increased toxicity; this is being investigated in current trials.

IMRT does have disadvantages. A consequence of using multiple beams to deliver radiation is that despite normal tissue being spared higher doses, a greater volume of tissue receives a lower dose. As a result, it has been suggested that IMRT may increase the risk of a second cancer from 1% for conventional radiotherapy to 1.75% at 10 years.[20] It has been counter-argued that these figures are an overestimate and that risks from 3D-CRT and IMRT are similar.[21] Considerable uncertainty surrounds these estimates because they are generated from models of risk that are based on long term data obtained mainly from the follow-up of atomic bomb survivors. These people were exposed to a single whole body dose rather than fractionated high doses to specific parts of the body as used in radiotherapy.[21]

Provision of IMRT is variable worldwide, although availability is generally increasing. For example, a survey of all cancer centres in Canada showed that the proportion of centres offering IMRT rose from 37% to 87% between 2006 and 2010.[22] In the UK, it increased from 46% to 81% between 2007 and 2012.[23 24] The key indicator for patients is access to this treatment when needed: it has been estimated that about 33% of radically treated patients should receive IMRT.[25] In the United States, 50% of patients receive IMRT, whereas in the UK this



Example of an intensity modulated radiotherapy plan for head and neck cancer. Panels A and B: Target and normal tissue structures are outlined before preparation of the dose plan. The complex three dimensional shapes and anatomical associations can be seen. The tumour target is delineated into three parts, representing different levels of tumour burden. The primary gross tumour itself (T_{68} red) will receive 68 Gy, the surrounding area with high risk of direct tumour involvement (T_{60} light brown) will receive 60 Gy, and the nodal areas at risk of microscopic disease (T_{54} pink) will receive 54 Gy. Some of the important normal structures—the eyes, parotid salivary glands, brain stem, and spinal cord—are also shown. Other structures have been omitted for clarity. Panels C and D: Intensity modulated radiotherapy dose plan. Use of advanced computing techniques allows different doses to be "painted" on to different target areas, while minimising the dose to important structures. The high dose is delivered to the complex target, which is concave posteriorly, avoiding the spinal cord

figure is currently 19%.[23] Access in the UK is increasing rapidly and the 33% figure is expected to be reached by 2014.[23]

Despite its importance, there are few cost effectiveness data for IMRT and other newer radiotherapy techniques. A UK study reviewed 13 non-randomised studies in prostate cancer.[26] The authors estimated the additional staff costs of providing IMRT at £1100 (€1370; $1750) per case. Using models of clinical outcome, the authors concluded that if the higher doses possible with IMRT (up to 81 Gy) improve overall survival, then IMRT would be cost effective. At the lower dose of 74 Gy currently recommended by the National Institute for Health and Clinical Excellence, conformal radiotherapy is safe and the cost benefit depends on the size of the reduction in gastrointestinal toxicity that can be achieved by using IMRT rather than conformal treatment. The authors concluded that the size of the benefit and its cost are unclear, which makes cost effectiveness uncertain. Further studies investigating cost effectiveness are needed.

Image guided radiotherapy (IGRT)

All radiotherapy is delivered with imaging at the beginning and intermittently throughout treatment to ensure accuracy. IGRT uses imaging (often on a daily basis) just before radiotherapy is delivered to allow positional correction if necessary so that the dose is correctly delivered to the target.[27] This can be achieved with CT imaging or by implanting radio-opaque seeds, which allows the target to be identified using treatment x rays. This assures accurate treatment of the tumour and potentially allows smaller safety margins to be used, thereby sparing healthy tissue. The prostate, for example, is subject to a daily positional change of 15 mm or more in relation to bony landmarks; a recent review summarises evidence from the pre-IGRT era showing that this movement contributes to underdosage and reduced control of biochemical disease.[28]

Image guidance is crucial to the use of IMRT because steep dose gradients carry a risk of the target being given too low a dose and normal tissue being overdosed. Most machines that deliver IMRT also have IGRT capabilities, allowing imaging and treatment in a single session.

Lung cancers move with respiration and if this variation is great, four dimensional CT can be used to obtain a series of CT scans at different phases of the respiratory cycle.[28] The information can help define the motion of the tumour, which can then be targeted with respiratory gating. This involves tracking the patient's respiratory cycle, commonly using surface markers, and delivering treatment at specific phases of the cycle.

The provision of IGRT is increasing in the UK, but reliable national data on its availability are not yet available. There is an associated additional cost, but no robust cost effectiveness studies have yet been published.

Stereotactic radiotherapy (SRT)

SRT involves highly targeted treatment. It has been used for many years to treat a variety of brain lesions, using traditional fractionations such as 60 Gy in 30 fractions. More recently it has been used to treat small discrete lesions in a limited number (one to five) of higher dose fractions.[29] SRT is often administered using a frame to fully immobilise the patient, although frameless techniques are also available. Stereotactic radiosurgery refers to SRT delivered in just one session. SRT can be delivered using several different machines. These include specifically adapted standard linear accelerators, which use multiple beams from different angles centred on the tumour, and the Gamma Knife, which is designed exclusively to treat intracranial lesions.

Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiotherapy, refers to precise irradiation of extracranial lesions. As a result of improvements in image guidance, it is now increasingly offered for sites including the lung, prostate, liver, and pancreas.[30] It can be delivered using a standard linear accelerator, equipped for image guided IMRT. For mobile lesions tracking or gating technology can be used. The CyberKnife is a frameless robotic system consisting of a linear accelerator mounted on a robotic arm. It can deliver treatment with high accuracy and uses real time image guidance to track the tumour. To allow

TIPS FOR NON-SPECIALISTS

The term radiotherapy encompasses a wide range of different techniques. Establish precisely which has been used when discussing treatment and complications with patients

Newer techniques, such as intensity modulated radiotherapy and image guided radiotherapy, generally reduce toxicity

Because interruptions in treatment can lead to poorer outcomes in patients receiving curative radiotherapy, manage early toxicity promptly, coordinating with the treating oncologist

Late toxicity can sometimes occur years after radiotherapy, so determine the details of anticancer treatments in patients with a history of cancer

Long term effects include an increased risk of second cancer and cardiovascular disease

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

Begg AC, Stewart FA, Vens C. Strategies to improve radiotherapy with targeted drugs. *Nat Rev Cancer* 2011;11:239-53. Review of biological basis for combining targeted drugs with radiotherapy

Bortfeld T, Jeraj R. The physical basis and future of radiation therapy. *Br J Radiol* 2011;84:485-98. Summarises the importance of medical physics within radiotherapy

Towards safer radiotherapy (https://www.rcr.ac.uk/docs/oncology/pdf/Towards_saferRT_final.pdf)—Report detailing strategies to optimise radiotherapy safety

The Clinical and Translational Radiotherapy Research Working Group (www.ncri.org.uk/ctrad/)—National programme of collaborative radiotherapy research activity

Resources for patients

Cancer Research UK (www.cancerresearchuk.org)—Overview of current news stories in cancer and information on active research studies

Macmillan Cancer Support (www.macmillan.org.uk)—Information on cancer treatments and support networks

Patient.co.uk (www.patient.co.uk)—Lifestyle and cancer related discussion forums

this, most tumours require implantation of metal markers. This can lead to complications, including pneumothorax in lung cancers, but newer software can track some peripheral tumours without markers.[30]

Clinical outcomes for SABR within early phase trials are promising, particularly in the radical treatment of inoperable lung cancers. Trials have shown excellent local control but less of an impact on overall survival.[31] Similar results have been seen for other tumours. Accurate delineation of the tumour is essential, so lesions with unclear or infiltrative margins should be avoided. Because the volume of normal tissue within the periphery of the target is proportional to the cube of the target's radius, this treatment is most suitable for smaller lesions.

SABR has challenged our approach towards small volume metastatic disease. Selected patients can now be treated with high doses of SABR with the aim of achieving a long disease-free interval.[30] Small phase I-II studies of this technique have reported encouraging short term outcomes. Mature phase III comparisons with surgery, or other modalities, are needed to establish its place within clinical practice.[30]

At present within the UK, SRT and SABR are mainly available only at specialist cancer centres. Consequently, referral pathways are in place that allow patients from peripheral hospitals to be treated centrally. Robust cost effectiveness data are not available.

What is the role of proton beam therapy?

Proton beam therapy is an established technology that uses protons rather than photons to deliver the radiation dose. The physical properties of protons enable the dose to be deposited up to, but not beyond, a specific depth within tissue. When compared with photons, this limited range allows improved target volume coverage, with reduced doses to the normal tissue beyond.[32 33] This is expected to reduce the risks of late effects, including second cancers and cardiovascular risk, which are particularly relevant when treating children and young adults.[34]

A recent systematic review that summarised the current evidence base for proton beam therapy noted a lack of evidence from randomised phase III trials.[34] Current indications in adults include spinal and base of the skull tumours, although this is based on single institution cohort studies.[35] In the US this treatment is widely used for prostate cancer. Although excellent results can be obtained, the only clinical trials compared different doses given with protons, and there is no evidence from randomised trials that protons improve outcomes compared with photons when given at the same dose.[33]

In the UK, patients suitable for proton beam therapy can now be referred abroad under the NHS Proton Overseas Programme. The government has committed to fund two proton therapy units for children and adults with specific indications. It is intended that clinical provision will be combined with high quality research to help expand the evidence base for this treatment.[36]

What is the future of radiotherapy?

The evolution of radiotherapy will continue, fuelled by improvements in imaging, computing, and engineering, combined with a greater understanding of tumour biology. Radiotherapy trials currently recruiting within the UK are shown in web table 2 (see bmj.com). Ensuring the availability of newly established techniques to patients who would benefit from them poses an important challenge, particularly in the face of economic constraints. It is hoped that more precise delivery of radiotherapy coupled with strategies to enhance tumour cell killing, such as chemoradiation, will enable more cancers to be cured with fewer side effects. As these strategies are developed, it is vital that their implementation is supported by evidence from intelligently designed phase III trials.[37]

Thanks to Kate Burton (consultant radiographer at Addenbrooke's Hospital, Cambridge) for help in revising this article.

Contributors: SSA did the literature review, wrote the initial draft, and collated subsequent revisions; SD helped design the figures and tables; RJ developed the IMRT image figure and provided the first review of the text; MVW oversaw all subsequent reviews and contributed to all sections of the text; NB conducted all subsequent reviews, contributed to all sections of the text, and contributed the IMRT image figure. NGB is guarantor

Funding: NGB is supported by the NIHR Cambridge Biomedical Research Centre.

Competing interests: None declared

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Tubiana M. The role of local treatment in the cure of cancer. *Eur J Cancer* 1992;28A:2061-9.
2 Department of Health. Radiotherapy dataset annual report 2009/2010. 2011. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_128357.
3 Dearnaley DP, Khoo VS, Norman AR, Meyer L, Nahum A, Tait D, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet* 1999;353:267-72.
4 Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. *Cancer* 2005;104:1129-37.
5 Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. *Clin Oncol (R Coll Radiol)* 2012;24:112-24.

6 Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010;76(3 suppl):S10-9.
7 Jereczek-Fossa BA, Marsiglia HR, Orecchia R. Radiotherapy-related fatigue. *Crit Rev Oncol Hematol* 2002;41:317-25.
8 Hopwood P, Haviland JS, Sumo G, Mills J, Bliss JM, Yarnold JR. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *Lancet Oncol* 2010;11:231-40.
9 Andreyev J. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. *Lancet Oncol* 2007;8:1007-17.
10 Travis LB, Ng AK, Allan JM, Pui CH, Kennedy AR, Xu XG, et al. Second malignant neoplasms and cardiovascular disease following radiotherapy. *J Natl Cancer Inst* 2012;104:357-70.
11 Travis LB, Curtis RE, Storm H, Hall P, Holowaty E, Van Leeuwen FE, et al. Risk of second malignant neoplasms among long-term survivors of testicular cancer. *J Natl Cancer Inst* 1997;89:1429-39.
12 Berrington de Gonzalez A, Curtis RE, Gilbert E, Berg CD, Smith SA, Stovall M, et al. Second solid cancers after radiotherapy for breast cancer in SEER cancer registries. *Br J Cancer* 2010;102:220-6.
13 Swerdlow AJ, Cooke R, Bates A, Cunningham D, Falk SJ, Gilson D, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a national cohort study. *J Clin Oncol* 2012;30:2745-52.
14 Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. *JAMA* 1993;270:1949-55.
15 Miller MC, Agrawal A. Hypothyroidism in postradiation head and neck cancer patients: incidence, complications, and management. *Curr Opin Otolaryngol Head Neck Surg* 2009;17:111-5.
16 Marks LB, Rose CM, Hayman JA, Williams TR. The need for physician leadership in creating a culture of safety. *Int J Radiat Oncol Biol Phys* 2011;79:1287-9.
17 Williams MV, Frew TL. How dangerous is radiotherapy? *Int J Radiat Oncol Biol Phys* 2011;79:1601.
18 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;12:127-36.
19 Staffurth J. A review of the clinical evidence for intensity-modulated radiotherapy. *Clin Oncol (R Coll Radiol)* 2010;22:643-57.
20 Hall EJ, Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys* 2003;56:83-8.
21 Ruben JD, Davis S, Evans C, Jones P, Gagliardi F, Haynes M, et al. The effect of intensity-modulated radiotherapy on radiation-induced second malignancies. *Int J Radiat Oncol Biol Phys* 2008;70:1530-6.
22 AlDuhaiby EZ, Breen S, Bissonnette JP, Sharpe M, Mayhew L, Tyldesley S, et al. A national survey of the availability of intensity-modulated radiation therapy and stereotactic radiosurgery in Canada. *Radiat Oncol* 2012;7:18.
23 Mayles WP, Cooper T, Mackay R, Staffurth J, Williams M. Progress with intensity-modulated radiotherapy implementation in the UK. *Clin Oncol (R Coll Radiol)* 2012;24:543-4.
24 Jefferies S, Taylor A, Reznek R. Results of a national survey of radiotherapy planning and delivery in the UK in 2007. *Clin Oncol (R Coll Radiol)* 2009;21:204-17.
25 Williams MV, Cooper T, Mackay R, Staffurth J, Routsis D, Burnet N. The implementation of intensity-modulated radiotherapy in the UK. *Clin Oncol (R Coll Radiol)* 2010;22:623-8.
26 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.
27 Verellen D, De Ridder M, Linthout N, Tournel K, Soete G, Storme G. Innovations in image-guided radiotherapy. *Nat Rev Cancer* 2007;7:949-60.
28 Button MR, Staffurth JN. Clinical application of image-guided radiotherapy in bladder and prostate cancer. *Clin Oncol (R Coll Radiol)* 2010;22:698-706.
29 Short S, Tobias J. Radiosurgery for brain tumours. *BMJ* 2010;340:c3247.
30 Martin A, Gaya A. Stereotactic body radiotherapy: a review. *Clin Oncol (R Coll Radiol)* 2010;22:157-72.
31 Chi A, Liao Z, Nguyen NP, Xu J, Stea B, Komaki R. Systematic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: clinical implications. *Radiother Oncol* 2010;94:1-11.
32 Schulz-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. *J Clin Oncol* 2007;25:953-64.
33 Allen AM, Pawlicki T, Dong L, Fourkal E, Buyyounouski M, Cengel K, et al. An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. *Radiother Oncol* 2012;103:8-11.
34 Brodin NP, Vogelius IR, Maraldo MV, Munck Af Rosenschold P, Aznar MC, Kiil-Berthelsen A, et al. Life years lost-comparing potentially fatal late complications after radiotherapy for pediatric medulloblastoma on a common scale. *Cancer* 2012;118:5432-40.
35 DeLaney TF. Proton therapy in the clinic. *Front Radiat Ther Oncol* 2011;43:465-85.
36 Maughan TS, Illidge TM, Hoskin P, McKenna WG, Brunner TB, Stratford IJ, et al. Radiotherapy research priorities for the UK. *Clin Oncol (R Coll Radiol)* 2010;22:707-9.
37 Burnet NG, Billingham LJ, Chan CS, Hall E, Macdougall J, Mackay RI, et al; on behalf of the National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group Executive Group. Methodological considerations in the evaluation of radiotherapy technologies. *Clin Oncol (R Coll Radiol)* 2012; published online 12 July.

Accepted: 08 November 2012

ANSWERS TO ENDGAMES, p 46

For long answers go to the Education channel on bmj.com

PICTURE QUIZ

A case of loin pain: a cause close to the heart

1 This is an arterial phase contrast enhanced computed tomogram of the abdomen. Contrast is absent beyond the proximal segment of the left renal artery, with non-enhancement of the left kidney. A wedge shaped area of non-enhancement is also seen in the right kidney, consistent with a renal infarct. The findings are consistent with bilateral renal emboli.
2 Transthoracic echocardiography.
3 Atrial fibrillation is the most common cause of intracardiac thrombosis. Ventricular thrombus formation may occur after acute myocardial infarction, in a left ventricular aneurysm, and in dilated cardiomyopathy.
4 Silent myocardial infarction in a patient with type 2 diabetes complicated by intracardiac thrombosis, with embolism to the kidneys and spleen.
5 Conservative management is with anticoagulation to minimise the risk of further embolic events. Revascularisation of the ischaemic kidney may be attempted by localised or systemic thrombolysis, thrombectomy, or surgical embolectomy.

ANATOMY QUIZ

Magnetic resonance imaging of lumbar spine

A: Facet joints
B: Right L4 nerve root (exiting nerve)
C: Right L5 nerve root (transiting nerve)
D: L4/L5 disc
E: Cerebrospinal fluid
F: Cauda equina rootlets

STATISTICAL QUESTION

Parametric statistical tests for independent groups: numerical data

Student's *t* test (answer *b*) would most likely have been used to compare the treatment groups in the mean difference in mean change in BMI z score over three years from baseline.