Principles of cancer treatment by radiotherapy

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Abstract

Radiotherapy (or radiation therapy) uses ionising radiation aimed to selectively kill cancer cells, especially for solid tumours. Like surgery, it is meant to be a ‘local’ treatment, although its beneficial systemic effects are being discovered. It is most commonly used in addition to surgery (adjuvant, e.g. breast), but its role in the neoadjuvant setting in combination with chemotherapy for some cancers (e.g. rectum) is also established. In early stages of cancer, it can be the definitive treatment avoiding surgery and enabling organ preservation (e.g., larynx), while in late stages, it can provide excellent palliation (e.g. bone metastasis). Radiotherapy can be delivered at various energy levels (kiloVolts, megaVolts), with various subatomic particles (e.g. electrons, protons, and high energy electromagnetic radiation). The traditional bulky equipment (e.g. linear accelerator) needs to be housed in an underground bunker and uses complex imaging to improve precision and avoid radiation to normal tissues. Fractionated regimen spanning several days reduces individual doses. Modern techniques (e.g. TARGIT-IORT) using mobile devices can deliver radiotherapy during surgery with the ultimate precision and immediacy.

Keywords

radiotherapy; radiation therapy; linear accelerator; intraoperative radiotherapy; adjuvant;

Background

If there is a fun fact about radiotherapy – it is that radiation was discovered by Wilhem Roentgen who won the 1st ever Nobel prize and within the first few years, it was being employed for treatment of cancer.

How does radiotherapy work - the physics, radiobiology

Radiotherapy typically uses ionising radiation or high-energy particles. At the atomic level “ionising” radiation ionises atoms by disrupting the electrons out of their orbits. At a cellular level the most important effect this causes is breaks in the DNA. When such damage occurs in critical parts of the DNA, the cell cannot replicate. DNA-repair mechanisms in normal cells can repair almost all of such DNA damage, but such recovery is more difficult for cancer cells. This difference gives radiotherapy its therapeutic ratio. In addition, ionising radiation also releases free-radicals and cancer cells are more sensitive to such a toxic rise and succumb, while normal cells can counter this with robust mechanisms. The side effects can be so troublesome that the radiation oncologist always has to recognise the compromise necessary between giving the highest possible dose for best therapeutic effect, and troublesome toxicity, which can be permanent.

Different types of cancers react differently to radiotherapy - giving rise to the terms ‘radiation-sensitive’ cancer. One example of a highly radio-sensitive cancer is testicular seminoma, and Hodgkin’s lymphoma which virtually ‘melt’ before your eyes. On the other end of the spectrum, sarcomas in adults and melanomas are relatively ‘radio-resistant’ although radiotherapy is still useful as adjuvant to surgery, which remains its primary curative modality. Epithelial cancers fall somewhere in between, with squamous carcinoma being more sensitive than adenocarcinoma, in general.

The DNA and cellular damage caused by therapeutic radiation, can and does have side effects. Apart from acute damage to nearby tissues, long-lasting effects are caused by injury to the vasculature (e.g. the coronary vessels) and by inducing new cancers. The examples of the latter are sarcoma and lung cancer after whole breast irradiation, and breast cancers in those given mantle irradiation for lymphoma

in their young adulthood; such cancers are unsurprisingly more common in those with inherited deleterious gene mutations in breast cancer genes (eg. BRCA1 and BRCA2).

Character of therapeutic radiation and modes of delivery

Table 1 shows the common forms of energy / subatomic particles that are employed, and table 2 shows the common modes of their delivery.

Megavoltage and Kilovoltage are terms used to denote the energy of the radiation used. Gray or rads (100 rads = 1 Gy) are used to measure the radiation dose delivered to tissues.

As a rule of thumb, higher the energy of the radiation, deeper is the penetration. Traditional radiation employs photons - the same 'particles' that form visible light - but at a higher energy. These have been traditionally thought to be of low or zero mass. Photons can be given using linear accelerators (LINACs), or using radioactive materials such as iridium wires.

External beam radiotherapy (EBRT) is typically delivered using LINACs. LINACs are huge and occupy large rooms. Within large tubes, they create a series of electric potentials. When charged subatomic particles pass through such an oscillating field, they accelerate to a high speed and generate x-rays and high-energy electrons. This is the most common equipment in a modern radiotherapy department and takes care of bulk of therapeutic work. Typical photons penetrate deep so superficial layers such as the skin receive much lower dose, reducing skin toxicity. High-energy electrons transfer their energy to a smaller thickness of tissue (1-2 cms) so can be used for skin cancers or skin metastasis.

One form of intraoperative radiotherapy (TARGIT-IORT) uses x-rays generated at the tip of a miniature linear accelerator in which electrons are accelerated to the gold tip of a 3.5mm tube generating low-energy x-rays. For breast cancer, various sized spherical applicators can be inserted in the tumour bed immediately after a lumpectomy to give therapeutic radiation to the tissues at highest risk of local relapse. Smaller LINACs can be made mobile (with some difficulty) and can be used for intraoperative radiotherapy (IOERT) for delivering electrons through an open wound.

Protons are a very different type of radiation. They are much heavier nuclear particles, and are special because as they travel through tissues, the rate at which they deposit their energy into tissues is quick and it can be very precisely controlled. This means that while photons will cause a lot of scattered radiation, protons will stop after a certain and precise distance so that there is no radiation beyond that distance. This is particularly important in children as their normal tissues face the most danger from unnecessary irradiation causing stunted growth, cognitive impairment (for brain tumours), and secondary cancers. The reason why protons have been so much in the news is because protons are several orders of magnitude more expensive, and their access for treating cancer in children is naturally a very emotive subject.

Brachytherapy (literally, nearby - treatment) has been used almost from the outset of therapeutic radiation. Multiple radium wires were originally inserted in tissues at specific distances so that there is uniform dose distribution. Now, sophisticated after-loading systems protect the staff. So hollow plastic tubes are inserted at the right place using 3-D CT planning. The after-loading device then inserts the wires in these tubes precisely at the right depth while the staff is already out of the special lead-lined room. The need for such rooms, the need for patients to undergo an additional surgical procedure to insert the tubes, and the labour resource has made such treatment less popular.

Table 1 - character of therapeutic radiation

Character of radiation	Penetration	Typical examples
High-energy photons / x-rays / gamma rays	Deep - can spare superficial structures such as skin	Breast Prostate Rectum
Low-energy photons	Short reach - and low dose rate	Intraoperative use - breast, brain, spine, rectum
High-energy electrons	Superficial reach only (1-2cm)	Skin metastasis, skin cancers, superficial bleeding
Protons	Limits distal dose	Brain, skull base tumours, childhood, spinal tumours

Table 2 - modes of delivery of therapeutic radiation

Mode of delivery	Characteristics	Typical examples
External beam radiotherapy	Requires bulky equipment (LINAC) in underground bunkers. Very versatile. Intensity modulated/ 3-D planning as well as alteration of breathing can reduce but not avoid harmful scattered radiation (Siemens, Varian, General Electric, etc)	Breast Rectum Prostate Brain Head and neck Spine Oesophagus
Intraoperative radiotherapy	Mobile equipment which is much less expensive than LINAC (Zeiss Intrabeam)	Breast (TARGIT-IORT), Colorectal cancer, brain (INTRAGO), spine (Kypho-IORT)
Radioactive molecules	Highly targeted treatment due to tissue affinity. So can only be used for very specific types of cancers	Thyroid cancer with radio-iodine I^{131}
Radioactive wires/seeds	High dose-rate radiation for short distances	Cervix, prostate, sometimes breast

Intent of using radiotherapy

Radiotherapy can be used at various stages of cancer treatment as well as at various stages of cancer progression.

Radical radiotherapy

In early stage cancers, radiotherapy can be used as the only local therapy. It has the advantage of not needing any surgery. Such use has been mainly explored where complete organ preservation is valuable.

For example, a total laryngectomy for early stage laryngeal cancer is curative, but leaves the patient with no voice. Randomised trials comparing radical radiotherapy for early stage squamous carcinoma of the larynx and hypopharynx have confirmed that it can provide equivalent local control with preservation of voice and greatly improving quality of life.

Adjuvant radiotherapy

When given after curative surgery - an adjunct - adjuvant radiotherapy is the most common form of radiotherapy. A third of a modern radiotherapy department's workload consists of breast cancer - mainly given as an adjuvant treatment.

The original premise of such a treatment is that some cancer cells may be left behind even after radical surgery. The most commonly studied cancer for such treatment is for breast cancer. In the last 100 years, use of adjuvant radiotherapy has enabled breast conservation after it was shown in several randomised trials, collated by the Early Breast Cancer Trialists Group [1] that a wide local excision (lumpectomy) followed by whole breast radiotherapy yielded similar level of local control as a radical mastectomy. These randomised trials were fuelled by the concern about the detrimental effects of radical surgery, particularly as the size of cancers at diagnosis began to reduce with greater awareness. The excellent outcomes and widespread patient advocacy has led to breast conservation now being considered the standard of care.

However, these trials also found something intriguing. If the reason for effectiveness were killing of residual cancer cells, why would it work equally well (i.e., the same proportional reduction of local recurrence) even when the surgical excision is very wide and why should it be seen after a mastectomy? In fact, for large cancers with multiple positive nodes, the reduction in local recurrence by radiotherapy is so large in magnitude that it also improves overall survival. These and other findings (see below) have now established that radiotherapy has a beneficial effect on the tumour microenvironment[2]. There are also immune-modulatory effects - immune stimulation at high-single doses and immune-suppression at lower doses. These exciting findings are now prompting new studies to combine immunotherapy with radiotherapy.

Palliative radiotherapy

Radiotherapy can provide palliation in many situations. For spinal metastasis large single doses can provide pain relief in a large proportion of patients. When there is a risk of spinal cord compression, surgical stabilisation must be first considered. This is where a multidisciplinary approach is very important to consider the radiosensitivity of the tumour, the window of opportunity and general status of the patient. In this regard, use of intraoperative radiotherapy in conjunction with surgical spinal stabilisation (Kypho-IORT) [3] has been shown to give pain relief almost instantaneously. Palliative radiotherapy is also used for control of bleeding when surgery is not possible. Radiotherapy is also used for brain metastasis or primary brain tumours either to the whole brain or using more precise approaches such as a Gamma-Knife or intraoperative radiotherapy in combination with surgery.

Timing of adjuvant radiotherapy

Pre-operative (neoadjuvant radiotherapy)

Radiotherapy given in a neoadjuvant setting, i.e., adjuvant therapy given before curative surgery, is often used for rectal cancer and oesophageal cancer. This is most often done in conjunction with chemotherapy - called chemo-radiotherapy. There is some randomised evidence to suggest that this may yield better overall oncology outcomes. For advanced cervical cancer where surgery is no longer a curative prospect, chemo-radiotherapy can give excellent results, with long term control of the disease.

Intraoperative radiotherapy (IORT, TARGIT-IORT, IOERT)

This is the only type of radiotherapy that surgeons are intimately involved in delivering. It is given during the primary surgical procedure to remove the cancer – most commonly for breast cancer. Intraoperative radiotherapy is aimed to achieve a high level of precision and immediacy. It was historically difficult to deliver intraoperative radiotherapy IORT because radiotherapy equipment was typically very bulky and immobile. Technical advances in miniaturisation the early 1990s (and thanks to the infamous US Star Wars programme) has meant that it has been feasible to perform some forms of IORT during surgery in normal operation theatres.

IOERT[4] uses NOVAC-7/ Mobetron (rather bulky yet mobile LINACs) to deliver high-energy electrons directly to breast tissues. As these are delivered as beams, the breast gland needs to be dissected off the chest wall and separated from the superficial skin. Such a mobilised gland is then sutured together along with a radiation shield between the gland and the pectoral muscle. A cylindrical tube directs the electron beam towards the gland and irradiates the tissues. The ELIOT trial, the only randomised trial (n=1204) to test this type of IORT found that the local recurrence was much higher (4% vs 0.4%) with IORT, although in a subgroup of luminal A breast cancers, the local control was comparable to external beam radiotherapy.

TARGIT-IORT[5] (https://targit.org.uk) is delivered in a standard operation theatre without the need for lead lining because it uses low-energy low-dose rate radiation. The equipment is easily moveable and is called Intrabeam. TARGIT-IORT is delivered immediately after lumpectomy without the need for any further tissue dissection. Spherical applicators are inserted and positioned accurately in the tumour bed with a meticulously placed purse string suture. The applicators come in various sizes (2, 2.5, 3, 3.5, 4, 4.5 and 5cm) so depending upon the excised specimen, they can be inserted in place of the tumour specimen that was just excised. Over 20-35 minutes, therapeutic radiation is delivered to the tissues immediately surrounding the tumour, during which time, the surgical team may well have a well-earned break. The applicator is removed, and the glandular modelling and wound closure are performed as normal. There are no problems with wound healing because the skin can be well protected easily by ensuring a distance of 8-10 mm from the applicator surface. The TARGIT-A randomised trial (n=2298) compared TARGIT-IORT during lumpectomy with traditional external beam whole breast radiation and found no difference in local or distant control of breast cancer, breast preservation or breast cancer mortality. In fact, there was a significant and substantial reduction in deaths from causes other than breast cancer such as cardiovascular causes and from other cancers with TARGIT-IORT - so by 12 years, there was almost halving of the death rate (9.85% reduced to 5.41%). The most likely explanation for this is avoidance of scattered radiation that normally accompanies even modern EBRT.

Postoperative radiotherapy

Most adjuvant radiotherapy is delivered a few weeks post-operatively. If adjuvant chemotherapy is required, data has shown that the outcomes are better when radiotherapy is given after chemotherapy because distant control is more important for survival.
Postoperative adjuvant radiotherapy typically uses LINACs and is called external beam radiotherapy. It needs to be delivered in small doses to reduce toxicity to skin and normal tissues, the principle being that normal tissues can repair themselves between these smaller doses, while cancer cells cannot.

Typically, individual single doses (called fractions) are 200 rads (2Gy) and the total doses can be between 40 to 60 Gy given daily over 3 to 7 weeks. Interestingly, it is rumoured that the French tradition of weekend holidays, rather than radiobiology, that has driven the current practice of radiotherapy scheduling of 5-days treatment and 2-days off. There have not been any comparative studies with continuous radiotherapy course - an obvious knowledge-gap! Recent studies suggest that larger fractions may be tolerated by breast and other tissues.

Brachytherapy using balloon applicators or wire can be used for adjuvant postoperative radiotherapy after lumpectomy for breast cancer. It is typically delivered over a course of 5 to 10 days, after an initial procedure to place the guiding tubes in the breast. While it has been shown to be as effective as whole breast radiotherapy, it still requires multiple doses including in-patient stay, leads to scars at the entrance of the wires and is accompanied by scattered irradiation of nearby organs.

Table 3 shows the various intents of radiotherapy for various types of cancers

Type of cancer	**Intent of radiotherapy**	**Character of radiation and modes of delivery**
Squamous carcinoma	Adjuvant or curative	EBRT, Brachytherapy
Adenocarcinoma	Neoadjuvant or adjuvant	EBRT, IOERT, TARGIT-IORT
Lymphoma	Curative	EBRT
Sarcoma	Adjuvant	EBRT, Brachytherapy

Table 4 shows the various intents of radiotherapy for cancers of various organs

Type of organ	**Intent of radiotherapy**	**Character of radiation and modes of delivery**
Breast	Adjuvant	EBRT, Brachytherapy, TARGIT-IORT
Oesophagus	Neoadjuvant, adjuvant, chemo-radiotherapy	EBRT
Head and Neck	adjuvant	EBRT
Thyroid	Adjuvant / palliative	EBRT, radio-iodine
Cervix	Adjuvant, neo-adjuvant	EBRT, brachytherapy

Urinary Bladder	Neoadjuvant, adjuvant	EBRT
Prostate	Radical, adjuvant	EBRT, brachytherapy
Rectum	Neoadjuvant, adjuvant, chemo-radiotherapy	EBRT, TARGIT-IORT
Spine	Palliative	EBRT, TARGIT-IORT
Paediatric cancers (Wilms, Neuroblastoma, Brain tumours)	Adjuvant, radical	EBRT, Protons

Breast cancer radiotherapy

This is discussed in slightly more detail as it is the single most common indication for radiation in any modern radiotherapy department. Furthermore, surgeons are involved in actually delivering intraoperative radiotherapy so an expanded discussion of radiotherapy for breast cancer is warranted in this article. Rather than a long text, the attached figures and tables are used to summarise the use of radiotherapy in breast cancer.

The Oxford overview[1] demonstrated the benefits of radiotherapy after breast conservation and after mastectomy. Radiotherapy reduced local relapse by 2/3rds. When the reduction in local recurrence was more than 10%, it also reduced mortality from breast cancer by about a quarter of that difference. For example, if the reduction in local recurrence was 16%, breast cancer mortality reduction was 4%. However, radiotherapy also increased the risk of deaths from other causes and in most cases, this nullified the survival benefit from reducing breast cancer deaths. Although modern radiotherapy, with techniques such complex CT-planning and manoeuvres such as ‘deep inspiration breath hold’ (DIBH) are meant to reduce dose to the heart and the lung, randomised evidence is yet to emerge supporting the hypothesis that the reduced dose leads to significantly reduced toxicity.

Table 5 and Table 6 give the details of some modern trials of breast radiotherapy. It is clear from the latest long-term results of the PRIME-II trial comparing radiotherapy vs no radiotherapy in women super-selected for having the lowest possible risk of recurrence - over 65 years old, small ER positive, grade 1 or 2 tumours with uninvolved axillary nodes. It was clear that at 10 years, radiotherapy reduced the risk of local recurrence by 9%. Such a large increase in local relapse could impact on breast cancer survival and nullify the survival benefit of avoiding scattered irradiation and deaths from of the heart attacks and other cancers.

The one modality of radiotherapy that surgeons need to know well about is intraoperative radiotherapy, which is given during surgery. Thorough training for performing this procedure is essential, but it is relatively straightforward. The large international TARGIT-A trial[5] found that in a cohort of patients with medium-risk breast cancer patients, risk-adapted single-dose radiotherapy can effectively substitute whole breast radiotherapy in 8 out of 10 patients in typical modern breast cancer clinics who are suitable for breast conservation. For this medium-risk population, all breast cancer outcomes with TARGIT-IORT were comparable with whole breast radiotherapy and there was a substantial reduction in deaths from cardiovascular causes and other cancers (Figure 1). This reduction in deaths by TARGIT-IORT would be much more pronounced in patients who are smokers. TARGIT-IORT also leads to less pain, less acute and late toxicity, better cosmetic outcome and improve quality of life. For the health system, TARGIT-IORT is so much more convenient for patients and costs much less than any other form of breast radiotherapy. These data has prompted over 260 centres in 38 countries worldwide to offer TARGIT-IORT to over 45,000 patients (www.targit.org.uk/travel)

Figure 1 – Long-term outcome from the TARGIT-A trial of TARGIT-IORT during lumpectomy vs whole breast radiotherapy in typical patients in a breast clinic.

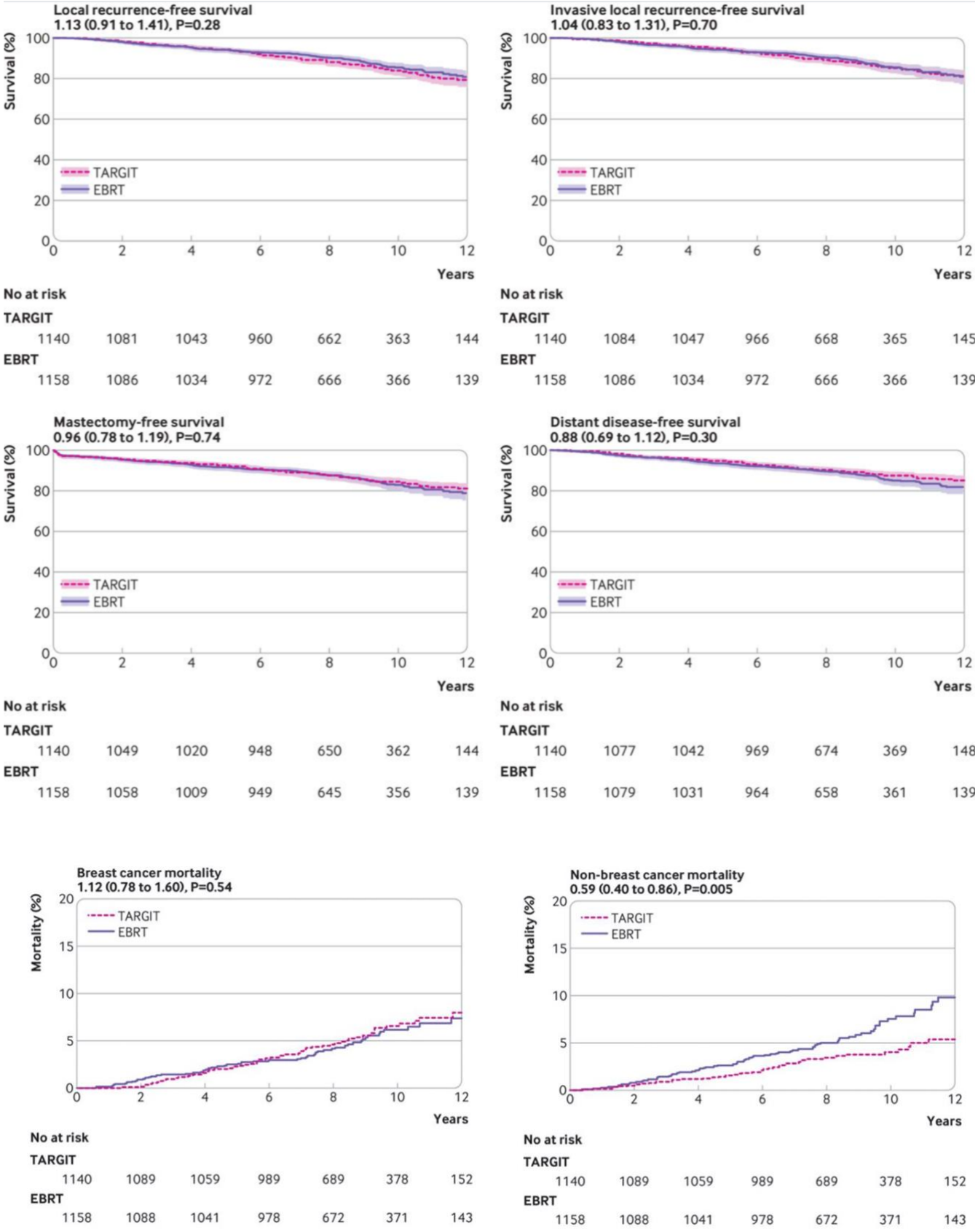
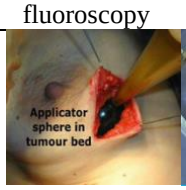
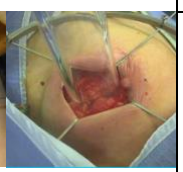
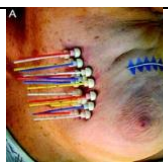
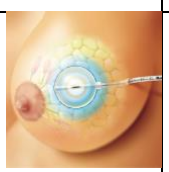


Table 5 Details of trials of no -radiotherapy, short course intensive radiotherapy and TARGIT-A trial[6, 7]

	CALGB No RT vs WBRT	BASO 2 No RT vs WBRT	PRIME 2 No RT vs WBRT	FAST-FORWARD WBRT vs Shorter WBRT	TARGIT-A trial Risk-adapted single-dose TARGIT-IORT vs WBRT
Number for comparison	636	1135	1326	2562	2298
Number at 6 yrs follow up	<500	N/A	<600	1025	1967
Age limits	>=70 0%<70	>=65 0% < 65	>=65 0% < 65	>18 84% < 70	>=45 60% < 65 85% < 70
T Size limits	<=2cm	<=2cm	<=3cm	T1-T3	<=3.5cm
Grade limits		Grade 1	Grade 1 or 2, only 2% were grade 3	No restriction 28% grade 3	No restriction 20% grade 3
Nodes limits	Negative	Negative	Negative	N0-N1 19% node positive	No restriction 22% node positive
LV invasion		Negative	Neg if Gr 3	No restriction	No restriction
ER status	Positive	Positive	Positive	No restriction	No restriction
Additional hospital visits	1	1	1	7 to 15	None in 80 to 85% of cases *15-20% will need WBRT
5-year local recurrence rates	4% vs 1%	6% vs 2%	4.1% vs 1.3% Difference 2.9% (upper 95%CI 4.8%)	2.1% vs 1.4% (including 7% post-mastectomy radiotherapy) No difference	2.11% vs. 0.95% Non-inferiority confirmed with complete 5-year follow up Difference 1.16% Upper 95%CI 2.09%
5-year LR in the experimental arm	1 in 25	1 in 17	1 in 25	1 in 46 (including 7% Mastectomy patients)	1 in 48
Long term outcomes	10-yr OS 60% LR 8% vs 2% 10-yr LRFS ~53% vs ~61%	10-yr LRFS ~89% vs ~97%	SABCS 2020 abstract: 10-yr local recurrence 9.8% vs 0.9% Estimated binomial rate of non-breast cancer deaths estimated 3.9% vs 6.1%, total deaths 13.2% vs 12%.	Not available	At median follow up of 9 years (max 19 years): No difference in local/distant control/breast preservation/breast cancer mortality Significantly fewer deaths from other causes (5.41% vs 9.85% at 12 years)
Significant scattered radiation to vital organs?	No	No	No	Yes	No
Mortality	No difference	No difference	No difference	No difference	Significantly reduced non-BC mortality with TARGIT-IORT No difference in BC mortality
Toxicity in experimental arm	Not reported	Not reported	Not reported	Higher	Reduced
Quality of life with experimental treatment	Not reported	Not reported	Lower emotional & total functionality Higher insomnia No improvement in QOL	Worse	Improved breast related QOL Improved cosmetic outcome Reduced pain

Table 6 Modern trials of partial breast irradiation vs whole breast radiotherapy[6]

	Intraoperative		**Post-operative 2nd procedure interstitial**			**Post-operative external beam**	
	TARGIT-A Risk-adapted TARGIT-IORT during lumpectomy[5]	**Electron IORT during lumpectomy ELIOT**	**TARGIT-A Delayed second-procedure TARGIT-IORT[8, 9]**	**Interstitial wires x 5 days GEC-ESTRO**	**NSAPB-B039 Balloon (6% of exp. arm)**	**NSAPB-B39/ RAPID /Florence 3DCRT /IMRT**	**IMRT IMPORT-Low**
Patients							
Total	2298	1305	1153	1184	811	2193/ 1754/ 520	1343
At 6-yr FU	**1967**	**676**	**1068**	**784**	**708**	**1915/ 1548/ 503**	**661**
KM curves to	12 years	9 years	12 years	6.5 years	10 years	10/9/10.5 yrs	7 years
Tumours	Medium risk	Medium risk	Low risk	Low risk	Low risk	Low risk	Low risk
Grade 3 (%)	20%	20%	6%	9%	1%	1%/15%/11%	9%
Pos. nodes (%)	22%	26%	6.5%	0%	10%	10%/1%/ 10%	3%
5-year Local recurrence	2.11% vs. 0.95%	4.4% vs. 0.4%	3.96% vs. 1.05%	1.44% vs.0.92%	2.8% vs. 2.1%	2.8/2.3/2.5% vs 2.1/1.7/1.3%	0.5% vs. 1.1%
Non-inferiority Margin and whether achieved?	2.5% (bkgr 6%) Non-inferior	Equivalence margin 4.5% (bkgr 3%) (4.4% v 0.4%)	2.5% (bkgr 6%) No. Non-inferior in HR+HER-, ET	3% (bkgr 4%) Non-inferior	NA Not equivalent	NA/ 2.75% (bkgr 4%)/ 2% (bkgr 3%) Not equivalent/Non-inferior/Non-inferior	2.5% (bkgr 2.5%) Non-inferior
Breast cancer control similar to WBRT?	Yes	No	Yes	Yes	No	No/Yes/Yes	Yes
Toxicity/ QOL less or more than WBRT?	Less toxicity, better QOL	Not reported	Less toxicity, better QOL	Less toxicity, but wire-entry scarring not reported	More toxicity, QOL not reported	Generally more toxicity, QOL not reported	No major difference
Deaths from other causes different?	Sig. reduced (HR0.59); by 4.4% at 12y	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference
Significant scatter radiation to vital organs?	No	Possibly, if lead shield is not properly used	No	Yes	Yes	Yes	Yes
Additional hospital visits and time?	**No additional visits for 80%**; 20% had supplemental WBRT (~16 half days)	**No additional visits**	Additional surgical procedure for 1 dose single dose **1 full day**	Additional procedure 10# over 5 days, 2# /day as inpatient **5 full days**	Additional procedure 10 # over 8 days 2#/ day **5 full days**	10# twice per day over 5-8 days or 5# over 2 weeks **5.5 full days or 6 half days over 2wks**	16 hospital visits **16 half-days**
Where is it done?	Standard OR like c-arm fluoroscopy	Lead-lined walls	Standard OR like c-arm fluoroscopy	Lead-lined walls	Lead-lined walls	Lead lined bunker	Lead lined bunker
How it is done?	 Given during lumpectomy surgery	 Given during lumpectomy surgery. Needs extensive dissection + deep lead shield	 Given as a second-procedure by re-opening the lumpectomy wound	 Given as second-procedure and radioactive wires remain in place for 4 days (in-patient)	 Given as second procedure and the baloon remains in place for 8 days (in-patient)	 Given as twice daily treatments over 8 days or 5 non-consecutive days over 2 weeks	 Given as daily doses for 15 days over 3 weeks

Footnote to tables 5 and 6. *bkgr = expected background risk in the control arm. ET = Endocrine therapy. For NSABP-39 overall LR used for balloon. External beam days includes half a day for planning. QOL= quality of life. The very old or small trials with less than 500 patients or those with less than 5-year follow up - from Leeds (EBRT over 28 days, n=174, published 2005) and Christie (EBRT 10 days, n=708, published 1995) both with worse outcome for PBI, Budapest (interstitial wires twice a day over 7 days, n=258, published 2013) with similar outcome for PBI and trials with no published cancer outcome data are not included in this table. Tables 5 and 6 reproduced and slightly modified from Vaidya JS et al, Intraoperative radiotherapy for breast cancer: powerful evidence to change practice, Nature Reviews Clinical Oncology; 2021; DOI 10.1038/s41571-021-00471-7 and Vaidya JS et al Single-dose intraoperative radiotherapy during lumpectomy for breast cancer: an innovative patient-centred treatment British Journal of Cancer, February 2021 https://doi.org/10.1038/s41416-020-01233-5
Numbers are for patients with invasive breast cancer.

Side effects

As with any therapy, radiotherapy causes some side effects and depending on their timing are called either acute or late toxicity.

Acute toxicity

Acute toxicity can be local or systemic. Local toxicity is usually in the skin, causing erythema, oedema, desquamation, which can be painful. Head and neck irradiation can cause mucositis and hair loss. Unlike chemotherapy, with radical radiotherapy, the irradiated skin may never grow back any hair. When parts of the bowel are irradiated, it can cause diarrhoea, nausea and vomiting. Irradiation of large areas of bone that includes active bone marrow can lead to marrow suppression, neutropenia and its consequences. Irradiation near the lung can cause pneumonitis.

Late toxicity

One hallmark of radiotherapy is that its effects last a lifetime. These are cumulative and permanent. Therefore, when an area has been given therapeutic radiation, the course cannot generally be repeated. One exception is if one of the treatment volumes is very small such as TARGIT-IORT which can be given even after whole breast radiotherapy and EBRT can be given after TARGIT-IORT is given.

Long term side effects can start as early as 6 months and may continue to worsen over years or decades.

In the long-term the irradiated skin may never sweat or grow hair and mouth may remain permanently dry. Fibrosis of the breast tissues is another common form of long-term toxicity and is increased when individual doses are higher as seen in the highly compressed whole breast radiotherapy Fast-Forward regimen for breast cancer.

One form of late toxicity is the result of long-term effects of the remnant of damage to DNA leading to neoplastic changes - secondary cancers. Another form is due to damage to the vasculature. Telangiectasia are vascular abnormalities leading to relatively minor annoyance of small visible subcutaneous vessels. But when such lesions cause severe bleeding, it can be difficult to treat, for example when it occurs within a urinary bladder irradiated 20 years ago! Another well-known vascular effect is on coronary vessels when the breast is irradiated leading to an excess of heart attacks.

Worryingly, these effects seem to be synergistic with other risk factors. For example, it is estimated that even modern radiotherapy leads nearly a quarter of patients to die from lung cancer and heart attacks, if they were smokers and had EBRT for breast cancer[10].

Avoiding radiation toxicity

Manipulating the dosage, scheduling and accurate targeting are all aimed at reducing side effects. Definition of the target volume has been greatly advanced with the era of modern diagnostic imaging techniques such as high quality CT, MRI and PET scanning.

People react differently to radiotherapy and predicting who will suffer more side effects is an active area of research. Some anatomical features may increase the risk of side effects. For example, if the size of the breast is large there can be higher risk of erythema, desquamation - the acute skin toxicity - are more common.

If suitable patients receive TARGIT-IORT during their lumpectomy acute toxicity to the skin is avoided and as there is almost no scattered irradiation, deaths from cardiovascular causes and other cancers are also reduced. No other form of radiotherapy can achieve such complete reduction of unnecessary radiation to normal tissues.

Future of radiotherapy

Radiotherapy[11-14] has evolved greatly since its first use more than 100 years ago. Novel ideas such as combination with chemotherapy and new drugs such as immune checkpoint inhibitors are gaining ground. Improved technology has meant that radiotherapy can be delivered during surgery. Planning using CT is being overtaken in some areas with MR- planning which could offer the ability for much better delineation and contouring the dosimetry. In addition to radiation oncologists, surgeons are being involved in delivery of radiotherapy and medical oncologists in combining it with chemotherapy and immunotherapy. Such multidisciplinary approach is not only beneficial to the patient, but it greatly increases the pleasure in practicing the art and science of medicine.

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