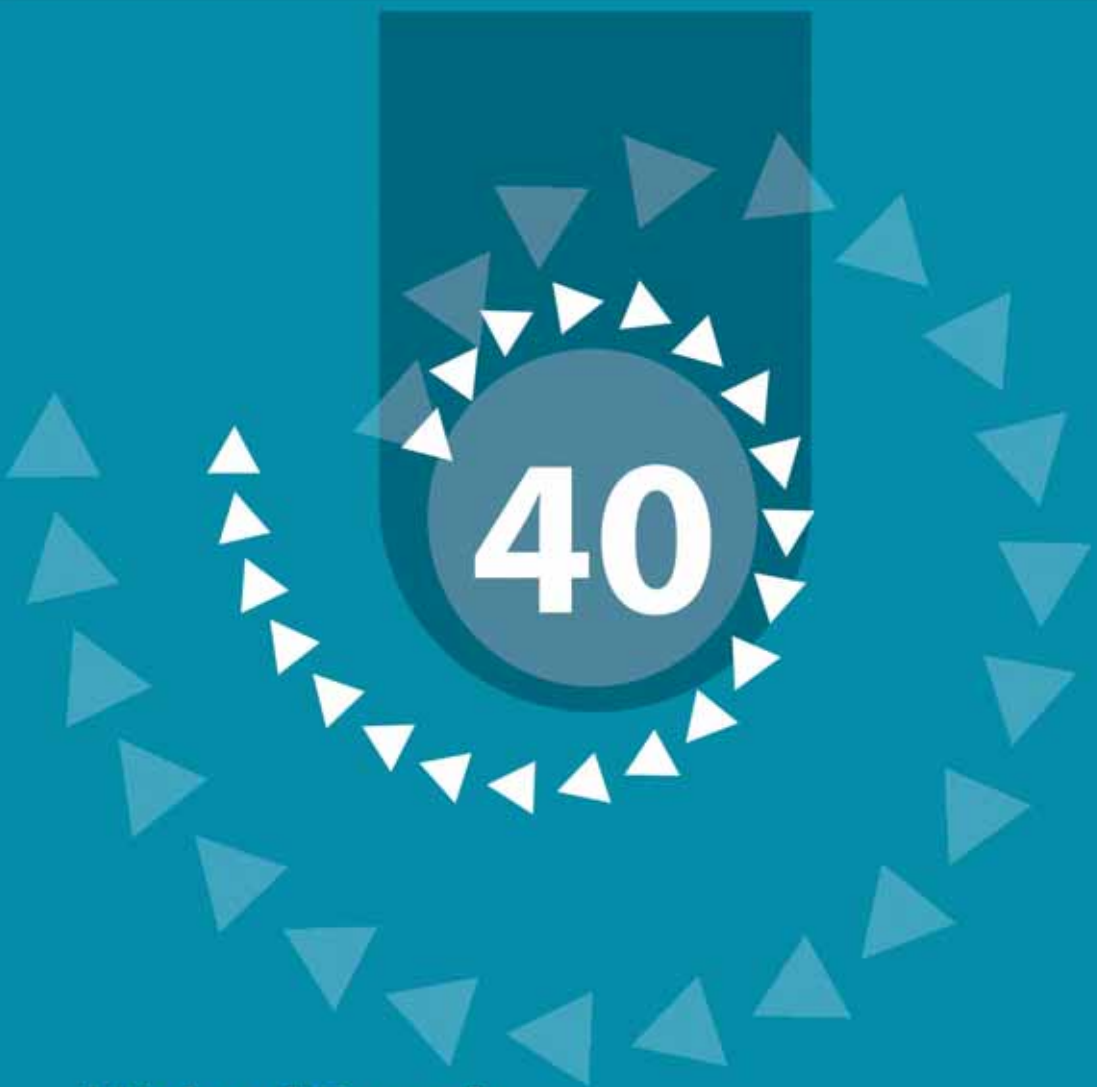
Recent Advances in Surgery



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Partial breast irradiation for cancer

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INTRODUCTION

Radiotherapy is an established component of multimodal treatment for most breast cancers. This is following evidence that breast irradiation after breast-conserving surgery significantly reduces both locoregional recurrence rates and deaths due to breast cancer [1,2]. Long-term follow-up of seminal trials also demonstrated the equivalence of this regimen to modified radical mastectomy in terms of disease-free survival and overall survival [3].

The National Institute for Health and Care Excellence (NICE) 2018 guidelines [4] advocate the utility of adjuvant radiotherapy in multiple contexts: after breast-conserving therapy for patients with clear margins, as a 'breast boost' for patients with a higher risk of local recurrence, post-mastectomy, and for supraclavicular nodal areas in specific patient groups. While external beam whole-breast radiation therapy (WBRT) has been generally accepted as the conventional irradiation technique in breast cancer, recent years have seen the pursuit of more localised treatment (partial breast irradiation) and shorter treatment plans, in order to maximise the therapeutic ratio of radiotherapy and to increase convenience. This resulted in a shift towards accelerated partial breast irradiation (APBI). APBI is a combination of two approaches: (1) a reduction in the number of radiotherapy treatments (i.e., hypofractionated or accelerated radiotherapy) and (2) a reduction in volume of breast irradiated (i.e., partial breast irradiation).

In APBI, only the predetermined index quadrant receives irradiation. Various studies have demonstrated compelling benefits in using APBI among patients with early-stage breast cancer, and the body of evidence is growing as newer techniques for delivering more focused therapy regimens, are introduced. This chapter outlines the rationale for APBI and appraises the range of techniques that are available in clinical practice today.

RATIONALE

Relative toxicity of whole-breast radiation therapy

Given the excellent survival rates of breast cancer, attempts to maximise quality of life have been considered with great interest. The ranges of systemic therapies used in cancer management are already known to be associated with a number of complications. For instance, endocrine therapy involving selective oestrogen receptor modulators (SORMs)

that also act as partial agonists in the endometrium, increase the risk of endometrial cancer, while cytotoxic drugs used in chemotherapy commonly result in anaemia and neutropenia, and in rare cases, may even lead to leukaemia. Irradiation to the whole breast, on the other hand, is associated with long-term side effects related to damage to residual normal breast tissue and overlying skin as well as damage caused by incidental irradiation to nearby structures like the heart, lungs, and oesophagus.

The association between whole-breast radiotherapy and subsequent major coronary events is well established. The risk of ischaemic heart disease is proportional to the mean dose of ionizing radiation to the heart; this increase in risk begins just a few years after radiotherapy and lasts at least 20 years [5]. It has been shown that patients who receive irradiation to the left breast (thus receiving a higher dose of incidental radiation to the heart) have significantly worse outcomes than those receiving radiotherapy to the right breast. This has implications of greater magnitude for patients with pre-existing cardiac risk factors. Although techniques such as prone breast radiotherapy and deep inspiration breath hold (DIBH) [6] have been beneficial in reducing radiation doses to the heart, the residue radiation remains clinically significant. This is where APBI proves instrumental in reducing radiation doses to the heart, especially in patients receiving treatment to the left breast [7].

With regards to the lungs, more grave complications include radiation-induced lung cancer, which has been shown to present > 10 years after radiotherapy. This is mainly relevant among smokers, who already have a significantly increased baseline risk of developing lung cancer. For smokers who have small, early-stage breast cancers, the absolute risks may outweigh the absolute benefits of adjuvant radiotherapy [8]. With APBI, individual treatment plans for at-risk patients may be arranged to prioritise lung sparing—this has shown favourable outcomes in terms of reducing both the risk of secondary lung cancer and cardiovascular toxicity [9].

Clinical outcomes: non-inferiority of partial irradiation compared to whole-breast irradiation

Non-inferiority trials are used in an attempt to display how a new, more conservative, treatment – in light of other benefits – may still be within an acceptable limit of 'inferiority' compared to the existing standard. Indeed, although it is sensible to expect that APBI is unlikely to be *more* effective than WBRT, it may still be considered as a suitable treatment alternative if the degree of its inferiority falls within a small, predetermined, margin.

Over 90% of local recurrences of cancer after breast-conserving surgery occur at, or in close proximity to, the original site of the operation. This means that while analyses of mastectomy specimens have found that the majority of additional cancer foci are found *outside* the index quadrant, the incidence of new breast cancers in other breast quadrants in the ipsilateral breast, remain similar to that of the contralateral breast [10,11]. A possible reason for this is that the local microenvironment may sometimes develop a tumour-promoting effect, perhaps due to the surgery (i.e., tumour seeding). This affirms the rationale towards using APBI, which offers more localised irradiation such that good control is preserved over the site that is most relevant despite the lower overall radiation dose.

A number of major clinical trials have since been conducted, comparing APBI to WBRT, with varying results due to the diversity of sample populations. Major multicentre trials conducted in the United Kingdom (UK IMPORT trial, 2017) [12] and in Canada, Australia,

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and New Zealand (RAPID, 2019) [13] found that APBI was non-inferior to WBRT. On the other hand, the NSABP B-39/RTOG 0413 2018 equivalence trial conducted in the United States concluded that APBI did not meet their equivalence criteria [14].

Meta-analyses have concluded that while APBI is associated with a small, statistically significant increase in local recurrence rates, other outcomes such as nodal or systemic recurrence, mortality rates, and overall survival were similar to that of WBRT [15,16]. Interestingly, studies which included only patients with low-risk characteristics saw comparable local recurrence rates between APBI and WBRT groups [17,18]. As expected, patients with larger tumours saw a lower degree of improvement in mortality and overall survival rates without recurrence. This is likely due to the fact that, even with APBI, more extensive radiation fields had to be used to account for larger tumours, thus diminishing the distinction in radiation field size between APBI and WBRT in the first place. This showed that there is, indeed, a specific population (i.e., patients with small, early stage, tumours) that may benefit optimally from APBI.

Quality of life

There has been an increasing emphasis on cosmesis in breast-conserving surgery, especially since satisfaction with cosmetic outcomes highly correlates with psychological morbidity [19]. Cosmetic outcomes after APBI have shown mixed results depending on the modality of APBI used. Initial reviews showed worse late radiation toxicity (e.g., subcutaneous fibrosis, telangiectasia, fat necrosis) with external beam APBI compared to WBRT [15]. However, many subsequent trials have shown very promising cosmetic outcomes, even with longer follow-up periods. This is likely to be due to the use of new techniques that have gained traction in the past few years, such as newer brachytherapy applicators, intensity-modulated radiotherapy (IMRT), as well as intraoperative radiotherapy (IORT) [20]. More research needs to be conducted with regard to cosmesis, especially with the emerging techniques that are quickly taking over the space.

Other significant outcomes affecting quality of life include fatigue, skin irritation, breast pain, and social functioning. Various studies have shown that women treated with APBI reported either similar or significantly better overall quality of life compared to those who had undergone WBRT [21–23]. APBI is generally well-tolerated, and even if temporary deterioration is experienced shortly after treatment, quality of life has been shown to return to baseline levels within 3 months [24].

Economics of cancer care: material and immaterial costs

The cost of treatment should never be a deterrent when presenting a more efficacious intervention to a patient. With this said, economic evaluation still has a place in medicine, especially when the clinical efficacy between two given interventions is deemed to be similar or only slightly different. In such cases, cost-minimisation strategies and cost-effectiveness need to be considered with great scrutiny [25]. Cancer care is incredibly complex in this regard because hidden costs permeate every aspect of the illness – this includes everything from managing side effects of treatment to potential disease progression or recurrence. Non-medical costs must also be taken into consideration, such as time lost travelling to additional hospital appointments, time taken off work, and childcare. Finally, in keeping with the recent emphasis on patient-centred care, it is paramount that non-material costs such as the psychological burden of repeated visits to the hospital, the perception of being a burden to

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family members, and general patient satisfaction must be taken into account since these can sometimes be the factors that matter most to patients.

Whole-breast radiation therapy is ordinarily delivered daily over up to 7 weeks following breast-conserving surgery. Regrettably, this treatment duration was found to be less than ideal for a significant proportion of patients. There are reports of rates of up to 50% of patients declining adjuvant WBRT following breast-conserving surgery, due to a range of reasons, one of them being geographical location [26,27]. Other studies have found that patients, for reasons related to the nuisance of attending daily treatment, have declined WBRT or even opted for mastectomy simply to avoid this daily treatment [28]. This has led to trials exploring the merit of hypofractionated radiotherapy, which considerably reduces the dose and duration of adjuvant radiotherapy. The FAST-Forward trial recently found hypofractionated radiotherapy over 1 week to be non-inferior to the standard 3-week treatment course, in terms of local control, although there was a trend towards higher late normal tissue effects with the 1-week course reaching statistical significance in the group receiving 27 Gy [29]. APBI is another, possibly more cost-effective [30,31], way to deliver shorter courses of radiotherapy. One form of APBI, IORT, even enables patients to receive all the radiotherapy treatment during the surgery itself. This means that the patient does not have to return to the hospital for further radiotherapy treatment post-operatively, allowing patients who would ordinarily forgo adjuvant radiotherapy (perhaps due to financial or time restraints) to receive their treatment in its entirety without compromising clinical outcomes.

Those treatments requiring fewer hospital visits will prove to be of additional value in the new coronavirus disease 2019 (COVID-19) pandemic, where exposure to COVID-19 should be avoided as far as possible, especially among vulnerable cancer patients. Regardless, it is likely that APBI will dominate treatment for patients with early-stage cancers who benefit equally from shorter or longer regimens.

RECENT TECHNIQUES

Brachytherapy

One of the pioneering APBI techniques is *multi-catheter interstitial brachytherapy* (MIB), which has been in use for decades and has been shown to be non-inferior to WBRT in terms of local recurrence, in the GEC-ESTRO trial [18]. In MIB, radioactive catheters are positioned within and around the lumpectomy cavity either free-hand or by using a template. Radiation is delivered either in the form of high, low, or pulsed dose rates. Once the radiation has been delivered, the non-permanent catheters are removed in a relatively painless process requiring no anaesthesia. MIB has been evaluated extensively and is not just an attractive option among the standard APBI target population, but also has been described as an excellent compromise for elderly patients, who may not be physiologically fit for WBRT but can be treated with even a single fraction of MIB, if the alternative is to have endocrine therapy alone [32,33].

A technique that has gained popularity in the United States is *intra-cavity balloon brachytherapy*. In this technique, applicators are positioned within the lumpectomy cavity with balloons that are inflated with water or saline, along with some contrast. The core of the catheter contains radioactive seeds which then deliver the radiation to the target site. Out of the newer balloon brachytherapy techniques, the *Xoft Axxent® electronic*

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brachytherapy device [34] completely omits the use of radioisotopes through its use of miniaturised X-rays as a low-energy source. Apart from the undeniable benefit of not requiring shielding from radiation, its controller is portable, widening the scope for use in even outpatient clinics. However, neither technique has been evaluated within a randomised controlled trial and long-term outcomes are not known.

Non-invasive image-guided breast brachytherapy (NIBB) is also a newer technique allowing greater precision in delivering radiation to the tumour bed. It utilises breast compression and mammographic-like image guidance, and unlike all the other brachytherapy approaches, does not require any catheter placement. This completely non-invasive technique eliminates the risk of infection due to indwelling foreign objects. It may also be an attractive option for patients who are less tolerant towards the discomfort of having catheters placed in their breast. Research data is promising; NIBB is well-tolerated, associated with a low incidence of significant late toxicity, and results in favourable cosmetic outcomes [35,36].

Three-dimensional conformal radiotherapy and intensity-modulated radiotherapy

Traditional WBRT is typically carried out using the external beam approach, also known as external beam radiotherapy (EBRT). It is not a surprise, then, in the quest for a partial breast irradiation technique, researchers have come up with a modern approach using EBRT to target regions of the breast more selectively. The main merit of doing this is the fact that the process remains non-invasive. The process is also simpler and not as technically-challenging as brachytherapy.

The initial product that emerged was *three-dimensional conformal radiotherapy* (3D-CRT), which involves multiple beams of radiation being directed to the lumpectomy cavity in various different planes. 3D-CRT quickly garnered widespread use since many hospitals already utilised this technique for other cancers.

A newer EBRT technique which shortly succeeded 3D-CRT is *intensity-modulated radiotherapy*. IMRT is a more complex form of 3D-CRT which allows more precise modulation of radiation doses as it involves computerised inverse planning and permits non-uniform intensity of radiation beams. IMRT has been shown to result in favourable outcomes in terms of dosimetric analysis, while maintaining comparable or reduced toxicity and improved cosmesis [37,38]. It also allows more homogeneous dose distribution among larger-breasted women [39]. However, duration of treatment is still 3 weeks and IMRT suffers from the same drawbacks of EBRT related to late normal tissue effects.

Intraoperative radiation therapy

Intraoperative radiation therapy is unique in that irradiation occurs during the breast-conserving surgery itself. It allows very accurate delivery of radiation to the target site, since this occurs by direct visualisation of the lumpectomy cavity during surgery itself. IORT was evaluated for breast cancer treatment since the late 1990s [40]. The TARGIT-A randomised controlled trial of IORT, randomised its first patient in March 2000 and demonstrated non-inferiority against EBRT [41], with long-term follow-up [42]. IORT is also currently being explored for its use in colorectal cancer (CRC) [43], glioblastoma multiforme (GBM) [44], and head and neck cancers, with very promising results to date.

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Since IORT is defined by the circumstance in which radiation is delivered (i.e., intraoperatively), and not by the irradiation technique used, there are a wide range of techniques that fall within the definition of IORT, some of which also fall under the categories mentioned previously. The most relevant IORT techniques are summarised in **Table 10.1**.

Overall, the evidence for IORT is very good. The obvious benefit is that a more accurately demarcated target area is irradiated during the surgery itself. Irradiation in this manner avoids inaccuracy caused by inconsistent displacement of breast tissue after surgery and misleading positional relation of breast scars from the actual lumpectomy site [50]. IORT may also prove beneficial in populations with breasts that are smaller in size, as it has been noted that EBRT techniques such as 3D-CRT have been unsuccessful at effectively targeting medial tumours without unnecessarily exposing the contralateral breast to additional radiation [51,52]. Another significant advantage is the fact that there is no time delay between resection of the tumour and the delivery of radiotherapy. This is significant because there is a statistically significant increase in local recurrence with

Table 10.1 Intraoperative radiation therapy (IORT) techniques

Technique	Major trials
Low-energy X-rays (Intrabeam) A single dose of around 20 Gy of low-energy X-rays is delivered using a spherical applicator of a chosen size that is anchored to position in the lumpectomy cavity. Beyond the surface of the applicator, up to 6 Gy of radiation is delivered at a 1-cm depth. The treatment lasts for around 20–35 minutes	• *TARGIT-A* [41,42] There was a slightly higher rate of recurrence with IORT, but this was within the 2.5% non-inferiority margin. There was no significant difference in overall survival, local recurrence-free survival, mastectomy-free survival, distant disease-free survival, and breast cancer mortality. Mortality from other causes was significantly lower with IORT. IORT was also cheaper than EBRT • *TARGIT-B* [45] This ongoing trial explores the utility of IORT in delivering a tumour bed boost after breast-conserving surgery, in comparison to EBRT. The population being studied is patients under 45 years of age or those with a higher risk of cancer recurrence
Intraoperative electron radiotherapy (IOERT) (Lilac, Novac7, Mobetron) Electron radiation is delivered with a mobile linear accelerator at a uniform dose of around 10–25 Gy in a single fraction. The accelerators are able to deliver radiation at higher rates, so the procedure only lasts around 15–20 minutes	• *ELIOT* [46] There was a significantly higher rate of local recurrence with IOERT compared to EBRT, but this difference was within the 4.5% non-inferiority margin • *HIOB trial* [47] This is another ongoing trial investigating the use of IOERT tumour bed boost followed by hypofractionated whole-breast radiation therapy (WBRT). Preliminary results after a short/mid-term follow-up show excellent tolerance of the regimen. Cosmetic appearance was also well-preserved after 3 years
^{192}Ir high-dose-rate (HDR) brachytherapy Iridium-192 (^{192}Ir) is delivered via multiple catheters positioned using a flexible template applicator. Approximately, 18 Gy is delivered at a 1-cm depth, with the process taking around 20–40 minutes. Shielding is required, where only the patient remains in the shielded room during the delivery of treatment	• *Maranzano et al.* [48] *and Gaudet et al.* [49] HDR brachytherapy in women with early-stage breast cancer is associated with local control, survival rates, and cosmetic outcomes that are comparable to that in WBRT

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delays in commencing radiotherapy [53]. This means that, with IORT, irradiation can occur before the tumour cells start to proliferate. There is considerable interest also in the role of IORT as a tumour bed breast boost, for which findings have been promising so far. Another possible application of IORT may include settings where nipple-sparing mastectomies are performed in order to preserve cosmetic outcomes; in such cases, IORT should be explored further as a possible option in order to maximise oncological outcomes [54,55].

To date, the British Association of Surgical Oncology (BASO) has produced guidelines for the practical management of breast cancer during the COVID-19 pandemic; these guidelines recommended that, where possible, targeted intraoperative radiotherapy (TARGIT-IORT) be offered to patients who are either suitable for breast conservation or patients who are considering mastectomy in order to avoid EBRT.

Among the IORT techniques listed above, Intrabeam® was found to be cheaper than EBRT, which may tip the balance in its favour. However, out of the above-listed techniques, only high-dose-rate (HDR) brachytherapy is routinely performed in conjunction with intraoperative image-guidance [i.e., computed tomography (CT) scan], which allows identification of errors in applicator positioning, dosimetric analysis to the target area and adjacent structures, and documentation of other actionable findings [56].

Given the meaningful benefits of IORT and its clinical non-inferiority to WBRT in low-risk patients, there has been an increase in the implementation of IORT around the world, especially following the publication of the American Society for Radiation Oncology (ASTRO) APBI guidelines and the TARGIT-A trial. In order to encourage widespread use of this APBI modality, further fine-tuning of patient selection criteria for IORT and greater awareness outside academic centres, are required.

CONCLUSION

The current paradigm in breast cancer treatment is to strive to deliver the 'minimum effective treatment' to patients, including hypofractionated or accelerated adjuvant radiotherapy and partial breast irradiation. APBI techniques should now be considered as an alternative to EBRT for selected patients, in line with published evidence. With some techniques such as IORT, the risk of local recurrence should be discussed with patients and considered along with evidence on breast cancer and non-breast cancer mortality and the great advantage of a single-fraction radiation treatment.

Key points for clinical practice

- The recent publication of numerous long-term studies have corroborated the preliminary findings supporting APBI and validated its use in lower risk, early-stage breast cancers
- Although APBI can be used as an exclusive modality of radiotherapy following breast-conserving surgery, there is also potential for its use in the context of a breast boost following whole-breast irradiation, or in addition to post-surgical EBRT
- Most systematic reviews to date have displayed heterogeneity in the APBI modalities used. It may be beneficial for comparisons to be made *between* different APBI modalities in order to delineate the specific settings in which some techniques may be better suited than others

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Recent Advances in Surgery 40

Recent Advances in Surgery 40 is the latest volume in this well-known series which reviews current topics in general surgery. The editors have chosen topics which cover the whole clinical range of general surgery, along with professional issues which are currently of relevance to all surgeons. No publication after 2020 would be complete without the inclusion of a chapter relating to COVID-19 and the editors have chosen to address the issue of facemasks in the first chapter. Other references to COVID-19 are made in subsequent chapters where relevant. Many readers are involved in surgical training, either as trainers or trainees, and therefore the editors have continued to include a section on surgical training topics. The aim of the book is to update the busy surgeon on the front line and also help surgeons in training prepare for examinations. The authors of individual chapters come from a wide geographical background which gives an international perspective to many of the topics. The editors hope that every reader will find something of interest to help improve their clinical practice, enhance their knowledge of emerging themes in surgery and stimulate further development and advancement of surgical practice.



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