Accelerated partial breast irradiation in early breast cancer: focus on intraoperative treatment with electrons (ELIOT)

Stefano Zurrida*[1], Maria Cristina Leonardi[2], Andrés Del Castillo[1], Roberta Lazzari[2], Paolo Arnone[1] & Piero Caldarella[1]

Wide tumor resection plus postoperative whole breast irradiation is standard treatment for early breast cancer. Irradiation decreases recurrence rates, but may cause poor cosmesis, breast pain, and cardiac and lung toxicity. Accelerated partial breast irradiation is increasingly used in the hope of increasing convenience, decreasing sequelae and maintaining cure rates. Intraoperative radiotherapy with electrons is an attractive accelerated partial breast irradiation technique because collimator placement is under the direct control of the surgeon who removes the tumor, the skin is spared, shielding protects the chest wall and complete irradiation can be given in a single intraoperative session (avoiding 5–7 weeks of whole breast irradiation). Intraoperative radiotherapy with electrons seems as safe as whole breast irradiation; however, long-term results on local control and survival are not available yet.

Wide excision followed by external whole breast irradiation (WBI) is the standard of care for patients with early (stage I–II) breast cancer [1]. This conservative approach ensures long-term local disease control and acceptable cosmetic results for most patients [2]. Randomized controlled trials show, after 20 years of follow-up, that this approach is equivalent to mastectomy in terms of survival, and that, compared with conservative surgery alone, the addition of radiotherapy significantly reduces the incidence of ipsilateral recurrence [3]. Local recurrence rates following WBI are less than 10% at 10 years compared with 25–30% following conservative surgery without radiotherapy.

Standard WBI delivers 45–50 Gy to the residual breast in 25 fractions over 5 weeks, usually followed by a 10–16 Gy boost to the tumor bed in 5–8 fractions over an additional week. Therefore, standard radiotherapy requires 5–7 weeks. This regimen may force women to miss work, and if they live distant from a radiotherapy facility, many will incur lodging and travel expenses [4]. For these reasons, many women who receive conservative surgery do not undergo radiotherapy or do not complete their course; some patients who are eligible for breast conservation receive mastectomy. The long-term toxicity of standard radiotherapy also remains a concern, particularly for the heart and lungs, although the problem appears to have been greatly reduced by modern techniques [5].

Clinical trials and observational studies on women who receive breast-conserving surgery indicate that approximately 80% of recurrences occur within the index quadrant, irrespective of whether or not the breast was irradiated [4]. The Milan III trial found, after 12 years of follow-up, that 85% of local relapses occurred close to the tumor bed; the remaining 15% occurred in different quadrants and were considered new ipsilateral carcinomas [6].

The NSABP B-06 trial, in which patients were assigned to lumpectomy with or without local irradiation, had similar findings: 75% of recurrences were at or near the lumpectomy site, while the other site ipsilateral breast recurrence rate was similar to the rate of contralateral breast cancer [7].

Since most local recurrences occur close to the surgical scar, it follows that most residual cancer cells in the breast after conservative surgery are present in this area. Thus, it may not be necessary to irradiate the whole breast, but only the part at greatest risk of harboring cancer cells; and if the irradiation volume is smaller, a higher dose can be delivered over a shorter period of time [8]. These considerations have given rise to the idea of accelerated partial breast irradiation (APBI) as an alternative to WBI. APBI offers several theoretical advantages over WBI. First, it simplifies and shortens the radiotherapy component of postoperative treatment, resulting in fewer patient transfers and less time off work. Second, it reduces the time

[1]Division of Senology, European Institute of Oncology, Milan, Italy
[2]Division of Radiotherapy, European Institute of Oncology, Milan, Italy
*Author for correspondence:
Diagnostic Breast Surgery Unit, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy
and
Breast Diagnosis & Surgery Unit, School of Medicine, University of Milan, Milan, Italy
stefano.zurrida@ieo.it

• accelerated partial breast irradiation • early breast cancer
• intraoperative radiotherapy
• intraoperative radiotherapy with electrons

lag between surgery and irradiation. Third, it reduces radiation to uninvolved parts of the breast and adjacent organs, raising the possibility of reduced long-term side effects. Finally, it resolves dilemmas related to the sequencing of radiation and chemotherapy [9].

There are also several disadvantages to APBI, including dependence on the experience of the radiation oncologist and possible lack of dose homogeneity in the target volume – particularly for brachytherapy. Furthermore, any additional surgical procedures that may be required will be complicated by prior irradiation [10]. The most obvious disadvantage is that occult cancer foci may be present in parts of the breast not irradiated, and be the source of future recurrence. In fact, in contrast to studies indicating that most recurrences occur within the index quadrant [4,6], Bartelink *et al.* found that 29% of local recurrences were outside the area of the original tumor and 27% were 'diffuse throughout the breast', while 47% were in the primary tumor bed and 9% in the scar [11]. These results are supported by a pathological study on mastectomy specimens which found that 63% of specimens had disease foci and 79% of these were distant from the index quadrant. The clinical significance of these malignant foci is unclear; however, it is likely that many remain inactive indefinitely [12]. These findings do suggest, however, that eligibility criteria for APBI need to formulated with care, as also emphasized by the American Society for Radiation Oncology (ASTRO) consensus statement [13].

Phase II and III studies in several parts of the world are investigating various APBI techniques in comparison to standard WBI [14].

Techniques of partial breast irradiation

APBI can be delivered using brachytherapy, hypofractionated conformal external radiotherapy, or intraoperatively with x-rays or electrons [12]. Each of these techniques is associated with its own benefits and limitations. The latter two techniques can be used to give the complete radiation dose or can be used as a boost in combination with WBI.

All have similar indications, but the volume of breast irradiated differs [12]. The appropriate clinical target volume (CTV) is controversial; however, many clinicians are of the opinion that defining a margin of 20–30 mm around the tumor bed should ensure that any microscopic margins are adequately irradiated in most patients [7,15].

Brachytherapy

Modern brachytherapy involves the insertion of radioactive sources into the breast tissue (interstitial) or their placement within the cavity (intracavitary) that remains after tumor removal [12,15,16]. Planning employs computed tomography, which identifies the 3D shape of the area to be irradiated, including the seroma cavity, internal postoperative scars and surgical clips, when present.

Multicatheter interstitial brachytherapy

In multicatheter interstitial brachytherapy (MIB), the radioactive sources can be designed to deliver low dose rate (LDR) or high dose rate (HDR) irradiation [15]. Approximately 6–12 weeks after conservative surgery, flexible afterloading catheters are inserted into the breast tissue surrounding the tumor bed. To ensure homogeneous coverage of the cavity and its margins, 14–20 catheters are inserted at 1–2-cm intervals in several parallel planes. The exact number of catheters is determined by the size and shape of the target using established brachytherapy guidelines [17].

With LDR irradiation, a dose of 45–50 Gy is delivered to the CTV at 30–70 cGy/h, necessitating hospitalized of the patient for approximately 4 days [10]. With HDR irradiation, where delivery exceeds 12 Gy/h, a total dose of 32–35 Gy is delivered in twice-daily fractions of 3.4 Gy over 5 days. HDR irradiation is more common because it is given on an outpatient basis [10,18].

Pulsed-dose-rate brachytherapy is a relatively new technique with biological effects similar to LDR. The dose per pulse is approximately 0.4–1 Gy, and total dose is 50 Gy. Pulses are administered for approximately 10 min every hour over 24 h for approximately 5 days (typical times). A computer-controlled afterloader moves the source in steps through the catheters. When the source is not stepping through the implant, it is retracted into the afterloader [19].

Disadvantages of MIB are its strong dependence on the experience of the irradiation oncologist: it is an invasive technique and surgical skill is required to place the catheters correctly; there are also risks arising from lack of dose homogeneity within the target volume [10,13,16,20]. In addition, many patients find the appearance of the brachytherapy catheters disturbing. The main advantage of MIB is that a highly localized area around the tumor bed is irradiated. The dose and volume of irradiation can, in fact, be adapted to the shape, volume

and site of the tumor bed by differential loading of the catheters, to also spare nearby critical structures. Thus, the dose inhomogeneity characteristics of the technique can be advantageous. Furthermore the pathologic characteristics of the tumor and axillary status are known at the time of irradiation [16,21]. Although fibrosis and induration may occur, rendering subsequent routine examination of the breast problematic, long-term follow-up – among the longest of the APBI techniques – indicates that cosmetic results are excellent in 90–95% of cases [22,23,18].

Recent studies with careful quality assurance and patient selection indicate local control rates above 80% [9,10,13,18]. A randomized multicentric trial (GEC-ESTRO study) to compare MIB (HDR or pulsed-dose-rate) with WBI (50 Gy WBI plus 10 Gy electron boost) was initiated in May 2004. The primary end point is local recurrence at 5 years. It is a noninferiority trial and requires the recruitment of 1170 patients to detect a difference of 3% in local recurrence rates between the arms. Secondary end points are overall, disease-free and distant metastasis-free survival; contralateral breast cancer; early and late side effects; cosmesis; and quality of life. Eligibility criteria include unifocal ductal carcinoma *in situ* (DCIS) and invasive disease up to 3 cm, and an age of 40 years or more [24].

Balloon catheter brachytherapy

Several balloon-based brachytherapy devices are available, including MammoSite® (Hologic, Inc., Bedford, MA, USA), Axxent® Electronic Brachytherapy (Xoft, Inc., Sunnyvale, CA, USA) and Contura® (SenoRx, Inc., Tempe, AZ, USA). The MammoSite brachytherapy system consists of a silicone balloon connected to a 15-cm-long double-lumen catheter of 6-mm diameter. The MammoSite catheter can be inserted at the time of surgery into the open cavity, which is then closed. It can also be inserted postsurgically under ultrasonic guidance through a small separate lateral incision into the closed cavity, or directly through the scar [25,26].

The catheter contains a small inflation channel and a channel to allow entry of the HDR ^{192}Ir source into the center of the inflated balloon. The balloon is inflated to a recommended minimum of 5 mm with saline solution mixed with a small amount of contrast (to aid visualization) so as to completely fill the cavity. The ^{192}Ir source material is inserted through the catheter into the center of the balloon by means of a computer-controlled remote afterloader. The prescribed dose of 32–35 Gy is delivered to a spherical volume in 8–10 fractions over 5 days (3.4 Gy per fraction, twice daily, with a minimum of 6 h between fractions on the same day) [25,27].

The minimum distance between the skin and the balloon surface must be 5 mm: 7 mm is recommended. Greater skin–balloon distance is associated with better breast cosmesis [28].

The main advantages of MammoSite are a shorter operator learning curve than for MIB, a reproducible technique and good patient tolerability. However, a substantial drawback is that the dose distribution is spherically symmetrical and cannot be adapted to individual target volumes; this can result in unfavorable cosmetic results, since overdosage to the skin is not always avoided [9]. The therapeutic radiation range is 10 mm, so residual disease beyond this limit will not be irradiated [9]. MammoSite is best suited to delivering irradiation when margin status, tumor characteristics and lymph node status are known, to ensure that the patient is indicated for the technique. The system may be unsuitable for small breasts or when the disease is in the upper-inner quadrant as skin-to-cavity and skin-to-chest wall distances are less likely to be adequate [29].

External-beam techniques

Our experience is that external-beam approaches to APBI are more acceptable to patients and more reproducible than brachytherapy techniques. A critique of the American Brachytherapy Association recommendations is consistent with our affirmation and, in particular, emphasized the need for reproducibility [16]. There are two kinds of modern external-beam technique: high-dose conformal radiotherapy and intraoperative radiotherapy (IORT).

High-dose conformal external radiotherapy

3D conformal external-beam radiation and intensity-modulated radiotherapy are modern alternatives to WBI [30]. Planning employs computed tomography, which identifies the 3D shape of the area to be irradiated, including the seroma cavity, internal postoperative scars and surgical clips, when present. The optimal CTV is a matter of controversy, but typically incorporates the surgical cavity with a 1.0–1.5 cm margin trimmed to spare the skin and chest wall. An additional margin of 0.5–1.0 cm is added to account for respiratory motion and

setup variation. To specify the CTV, the tumor cavity should not be sutured, or when it is sutured, must be marked with metal clips [26]. External-beam conformal approaches to APBI have been described using supine and prone positioning, and simple and multifield arrangements. The breast may be irradiated with photons, photons plus electrons, or protons [30]. The clear advantage of 3D conformal external-beam radiation/intensity-modulated radiotherapy over brachytherapy is its noninvasiveness. Furthermore, irradiation begins after definitive information on the tumor, resection margins and lymph nodes is available; technical aspects and quality assurance are less demanding than for brachytherapy; dose homogeneity is intrinsically more likely, so cosmetic outcomes may be better than with brachytherapy. Finally, high-dose conformal external radiotherapy is potentially more widely available since most radiation therapy centers already use these techniques for other cancers.

Disadvantages of 3D conformal external-beam radiation/intensity-modulated radiotherapy are that metal clips are sometimes left in the breast to help define the target, and there is always the possibility that they may become displaced so that the irradiation volume changes [31]. Furthermore, identifying the surgical cavity can be difficult, leading to considerable interobserver variability in definition of the target volume, further contributing to the uncertainties in defining treatment volume [32].

The RTOG 0413/NSABP B-39 randomized trial is comparing conventional WBI to APBI (either 3D conformal irradiation, intracavitary balloon brachytherapy or interstitial brachytherapy) in women undergoing lumpectomy for DCIS or stage I–II (up to 3 cm) breast cancer. Patients considered at high risk of recurrence are eligible: young age (≥18 years), DCIS, extensive intraductal component and ≤3 involved lymph nodes. The main end point is ipsilateral tumor recurrence on long-term follow-up. The trial aims to recruit 4300 patients within 2–3 years and recruitment is ongoing [101].

Intraoperative radiotherapy

IORT is single-fraction irradiation of the tumor bed. It is given by a mobile accelerator that delivers either electrons or low-energy x-rays to the breast tissue. Both methods can give the full irradiation dose in the operating room or can provide a boost that is followed by a shortened course of conventional WBI. The most important advantage of full-dose IORT is its rapidity: the entire intraoperative irradiation procedure lasts 10–25 min. Thus, IORT can potentially solve the logistical and similar problems associated with the 5–7 weeks of conventional WBI. Another advantage is that there is no longer any delay in administering chemotherapy. Furthermore, IORT machines can be installed in any operating room without major structural modifications, provided mobile radiation screens are used [33].

Potential disadvantages are that both IORT techniques require expensive specialized equipment operated by highly trained personnel, and the final pathological status of margins and lymph nodes is not available at the time of treatment delivery; thus, patients should be carefully selected [33]. There is also the possibility of increased risk of late effects, such as fibrosis, with poor cosmetic results. IORT with electrons is not suitable for tumors located near the skin, and IORT with x-rays is not suitable for large or irregular tumor cavities [33]. Finally, when irradiation is delivered in a single large dose, reoxygenation and reassortment of cancer cells through the cell cycle do not occur (these effects occur with fractionation and enhance the radiosensitivity of cancer cells).

IORT with low-energy x-rays

Intrabeam® (Carl Zeiss Surgical, Oberkochen, Germany) is the only system available for delivering x-rays intraoperatively. A miniature gun plus accelerator direct a beam of electrons down a conical tube and hit a target within a sphere connected to the tapered end of the tube. The sphere (available in sizes of 2.5–5.0-cm diameter) is placed within the tumor bed. A shielding cap is placed between the sphere and the chest wall. The target emits soft x-rays (50 kV) over approximately 25 min. The prescribed dose is 20 Gy close to the applicator sphere, which is equivalent to approximately 70 Gy in conventional fractionation [34]. The low energy radiation attenuates quickly, so damage to normal tissues is minimal, and the irradiation can be performed in a standard operating room.

Early results of the TARGIT-A trial were published in 2010 [32]. This multicentric trial randomized over 2200 patients undergoing breast-conserving surgery to either IORT with x-rays or to conventional WBI. Patients under 45 years of age, with tumors over 4 cm, multifocal disease or preoperative diagnosis of lobular carcinoma were excluded. Postoperative discovery of risk factors such as lobular carcinoma indicated subsequent addition of external-beam

radiotherapy with 50 kV x-rays. The primary outcome was local recurrence in the conserved breast. The early results suggest that IORT with low-energy x-rays may be able to substitute WBI in selected patients with early breast cancer. However, the early concern that penetration of the low-energy x-rays was too low, so that insufficient breast volume was irradiated [34] – and more local recurrences would occur – has not been laid to rest because the follow-up is too short, and longer term results are necessary before IORT can become the new standard.

IORT with electrons in early breast cancer

The technique we call ELIOT (IORT with electrons) is an APBI modality that delivers a single intensive dose of radiation directly to the tumor bed, in the operating room, immediately after surgical removal of the tumor [35,36]. The electrons are delivered by a mobile linear accelerator (Mobetron®, IntraOp Medical Corp., Sunnyvale CA, USA; Novac7®, Hitesys, Aprilia, Italy) (Figure 1). The electron beam is collimated by a 'hard docking' system, part of the accelerator's robotic arm, one end of which is managed by the radiation oncologist. The other end (the applicator) is sterile and applied by the surgeon to the tumor bed. Applicators are 5-mm-thick Perspex® cylinders, available in different diameters (4–12 cm) and head angles (at 90° or beveled at 15–45° to the applicator axis). Applicator diameter is selected according to breast size and the site of the tumor bed, and is the main determinant of the area of the exposed breast to receive irradiation.

After quadrantectomy, the breast is temporarily reconstructed and detached from the underlying fascia. A circular aluminum–lead disc is inserted between the pectoral muscle and the gland to protect the chest wall. The skin is retracted away from the gland, out of the way of the radiation. The energy of the electron beam is selected based on gland thickness, as measured by a needle after the temporary reconstruction. The applicator is then positioned onto the exposed breast tissue.

Radiation protection is ensured by mobile 1.5-cm-thick lead shields. All operating room personnel leave the room during the brief period that radiation is delivered.

The theoretical relationship between fractionation of radiation dose and tumor response can be estimated by several models, although the linear quadratic model is the most commonly used. The linear quadratic model appears best when dose fraction is below 6–8 Gy, but may be reasonable for dose fractions up to 18 Gy [37]. According to this model, and assuming an α/β (fractionation) ratio for mammary gland cells of approximately 10 [38], the dose required to achieve a given reduction in cell survival with a single fraction is half to a third less than the dose given by conventional fractionation. Thus, an ELIOT dose of 21 Gy should produce the same local control as conventionally fractionated 60 Gy. The dose of 21 Gy was corroborated by our Phase I/II dose-escalation study [35].

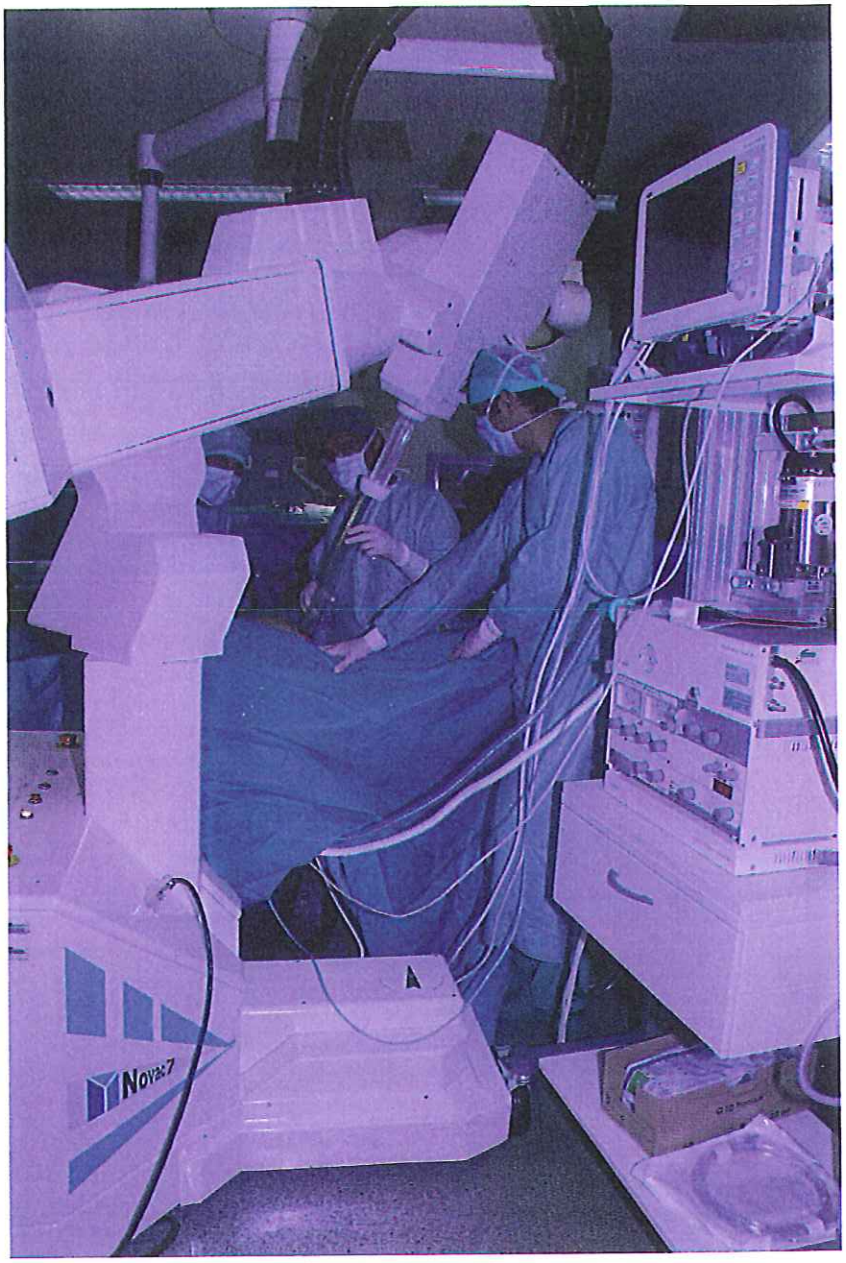

Figure 1. Mobile linear accelerator (Novac7®, Hitesys, Milan, Italy).

ELIOT as a boost

A 10-Gy boost to the tumor bed after WBI with 50 Gy (conventionally fractionated) was shown to reduce the incidence of local recurrences in a randomized trial against patients who received no boost; the reduction was most evident in women under 50 years of age [39]. However, it is not always easy to locate the tumor bed after breast conservation [31], particularly if the breast has been reconstructed or clips were not inserted. In such cases, the volume irradiated by the boost can be enlarged, but this can increase the likelihood of late tissue reactions compromising cosmetic outcome [32].

The use of IORT to provide an intraoperative boost to the tumor bed, therefore, appears attractive as a way of reducing local recurrence rates, and some studies have addressed this. A prospective sequential intervention study on patients treated by conservative surgery plus postoperative radiation, who received either conventional postoperative external-beam electron boost (fractioned dose of 12 Gy) or intraoperative boost with electrons (single dose of 9 Gy) showed that the IORT boost yielded excellent local control and appeared to be superior in this respect to conventional postoperative boost. However, follow-up in the IORT boost group was shorter than in the conventional boost group [40]. An observational study of 50 women treated at the Montpellier Cancer Institute with IORT boost reported, after a median follow-up of 9.1 years (range: 5–15 years), two local recurrences in the tumor bed (after median follow-up of 30 months), and 45 patients alive with or without disease. Among the 42 disease-free patients, six had grade II late subcutaneous fibrosis in the boost area. Overall, scores indicated very good quality of life and good-to-excellent cosmesis in the evaluated patients [41].

These data, therefore, support the use of (intraoperative) ELIOT boost in the treatment of early breast cancer. Other advantages are that treatment time for conventional external-beam radiotherapy is reduced by 1–3 weeks, while the intraoperative boost requires only a modest (15–20 min) increase in surgery time. In addition, the tumor bed is directly exposed and the collimator is directly applied to the tumor bed, virtually eliminating the risk of topographic miss; the skin is spared completely, avoiding telangiectasia. The target volume is smaller for IORT boost than for conventional postoperative boost and the dose distribution is highly homogeneous, resulting in minimal fibrosis on long-term follow-up and good cosmesis, while permitting postoperative WBI to be reduced to 13–22 days. [33].

Full-dose ELIOT

We started our experience at the European Institute of Oncology with ELIOT in 1999. We first performed a dose-escalation study to identify the ELIOT dose suitable to substitute conventional external radiotherapy [32]. We then tested the tolerance of ELIOT in a group of 101 patients, and presented results after a mean follow-up of 48 months [35]. These studies suggested that ELIOT as the only irradiation treatment was acceptable in terms of local control and esthetic results.

Our more ample experience of 1822 patients treated with full-dose ELIOT (21 Gy) from January 2000 to December 2008 was published in 2010 [42]. Again, however, follow-up was limited (mean 36.1 months). The study found that local side effects were mainly liponecrosis (4.2%) and fibrosis (1.8%). First events were local recurrence (42 women, 2.3%), new primary ipsilateral tumor (24 women, 1.3%) and distant metastasis (26 women, 1.4%). Forty-six women (2.5%) had died, 28 from breast cancer and 18 from other causes. The 5- and 10-year actuarial survival were 97.4 and 89.7%, respectively. These encouraging findings provide indication that 21 Gy given in a single intraoperative session may substitute conventional fractionated WBI in selected patients with early breast cancer treated by breast-conserving surgery.

An important advantage of full-dose ELIOT is that it avoids the delay in administering (conventional) radiotherapy if anthracycline-based chemotherapy is to be given. Treatment with anthracyclines can begin 16–20 days after surgery plus ELIOT. Whether chemotherapy or radiotherapy should come first after surgery remains controversial. For patients receiving WBI without chemotherapy, there are theoretical reasons for believing that delaying radiotherapy increases the risk of local recurrence, particularly if the margins are positive. There is also clinical evidence that this is the case [43]. However, a large retrospective study found that the risk of local failure was not affected by increasing the surgery-to-radiotherapy interval by up to 4 months, regardless of margin status [44].

Full-dose ELIOT is now being evaluated in a randomized trial against WBI carried out by the European Institute of Oncology. The

trial started in November 2000 and closed in December 2007 after recruiting 1306 patients aged >48 years, with cancer up to 2.5 cm, treated by quadrantectomy. The WBI arm received 60 Gy of conventional radiotherapy; the ELIOT arm received 21 Gy intraoperatively. The study is in follow-up.

Indications for full-dose ELIOT

Evidence is insufficient to recommend ELIOT as standard treatment. The consensus statement of the ASTRO on APBI [13] considered that patients suitable for APBI were age 60 years or above, with pathologically negative nodes, T1 disease, positive estrogen receptors, absence of lymphovascular space invasion, negative margins (>2 mm), no multicentricity and no pure DCIS. These are the characteristics of most patients treated in Phase I/II studies. ASTRO also identified a 'cautionary' group characterized by age 50–59 years, up to T2, pure DCIS up to 3 cm, close margins (<2 mm), extensive intraductal component up to 3 cm, microscopic multifocality in the presence of a clinically unifocal lesion, invasive lobular carcinoma and estrogen receptor negativity.

The European GEC-ESTRO group identified three categories of patients for APBI. The low-risk group was considered suitable for APBI outside the trial setting. Their characteristics were ≥50 years with unicentric, unifocal, pT1–2 (≤30 mm), pN0, nonlobular breast cancer with negative surgical margins (≤2 mm), without an extensive intraductal component or lymphovascular invasion. In the high-risk group (age ≤40 years, positive margins, multicentric or large tumor, extensive intraductal component or lymphovascular space invasion, four or more positive nodes, and unknown axillary status) APBI was contraindicated. Patients intermediate between high and low risk were considered suitable for APBI only in the trial setting [45].

Since, according to the above guidelines, most of the characteristics of patients suitable for APBI are determined by pathological examination, they are not applicable to ELIOT, unless Mammotome® is performed preoperatively or the tumor is assessed intraoperatively.

We would suggest that candidates for ELIOT should be 48 years or above with no mammographic evidence of multifocality. To reduce the problem of positive margins, the conservative surgical technique should not be lumpectomy but something more extensive such as quadrantectomy, or the resection margins should be examined intraoperatively. Neither previous irradiation for lymphoma [46], pregnancy [47,48] nor a previously irradiated breast [49] appear to contraindicate ELIOT.

ELIOT & nipple-sparing mastectomy

For advanced resectable breast cancer, and for a number of other indications such as intraepithelial neoplasia not amenable to breast-conserving surgery, or local recurrence after breast conserving surgery, mastectomy is the treatment of choice. Skin-sparing mastectomies are increasingly performed in selected patients as they facilitate breast reconstruction. There is also increasing interest in preserving the nipple–areolar complex along with the skin since the patient's sense of mutilation is reduced [50]. However, nipple-sparing mastectomy remains controversial in view of the high risk of local recurrence behind the nipple reported in some studies [51]. The advent of this operation has also resulted in new complications such as nipple–areolar necrosis that do not occur with conventional mastectomy [48].

At the European Institute of Oncology, we have carried out several studies giving ELIOT to the nipple–areolar complex to reduce the incidence of subareolar recurrence and, hence, improve the success rate of the nipple-sparing operation. The most recent study assessed experience with 1001 nipple-sparing mastectomies performed from March 2002 to November 2007 [48]. Outcomes in 800 mastectomies treated by ELIOT (16 Gy to the nipple region) were compared with 201 mastectomies treated by delayed one-shot radiotherapy (given in the days following the operation). The main reason for the delayed radiotherapy was poor vascularization of the nipple. During surgery, a thin specimen of tissue was removed from the retroareolar area for frozen-tissue examination. If positive, a further layer of tissue was removed, and if that was positive the nipple–areolar complex was removed. All patients underwent immediate breast reconstruction. After a median follow-up of 20 months (83% of patients remained in follow-up), the nipple–areolar complex had necrosed totally in 35 cases (3.5%), partially in 55 (5.5%) and had to be removed in 50 (5%). Forty-three prostheses (4.3%) were removed. Median patient rating of cosmetic outcome was 8 on a 0–10 (very poor to excellent) scale, but only 414 patients were assessed. There were 14 (1.4%) local recurrences, ten close to the tumor site and four distant from the mastectomy scar. There were no recurrences in the nipple region.

The fact that no local recurrences occurred in the nipple region is encouraging, even though follow-up is short and 17% of patients were lost to follow-up. (A considerable proportion of European Institute of Oncology patients come from distant parts of Italy and, unfortunately, many never return for check-ups.) Longer follow-up is necessary to enable conclusions regarding the utility of ELIOT in reducing subareolar recurrences in patients undergoing nipple-sparing mastectomy.

Advantages & disadvantages of ELIOT

The main reason for developing IORT is that radiotherapy facilities are often distant from patients' homes, and costs of travel and accommodation are prohibitive [4]. Many patients are given mastectomies because of these difficulties, despite the fact that they are candidates for conservative surgery [52]. In many countries there is a significant shortage of breast irradiation facilities [15]. Wider availability of ELIOT and other IORT modalities may permit more women to have conservative surgery, and may also increase rates of irradiation use as a standard component of breast-conserving treatment, since data suggest that up to 20% of women undergoing conservative surgery do not receive radiotherapy [15]. Furthermore, completing both the radiation and surgical treatments in a single session is likely to appeal to many breast cancer patients, and not simply for logistical reasons.

The second major advantage of ELIOT is that it obviates the requirement to delay administration of irradiation in patients scheduled for adjuvant anthracyclines [53]. Another advantage is that the skin is not irradiated, thereby facilitating plastic reconstruction [33].

A further major advantage is that, because a lead–aluminum disc is inserted between the gland and pectoralis muscle, irradiation to the lungs and heart is practically eliminated [33]. The contralateral mammary gland is spared as well due to the limited penetrating power of electrons.

Conclusion

IORT in general and ELIOT in particular emerge as promising irradiation modalities in early breast cancer. ELIOT boost markedly reduces the duration of the conventional radiotherapy course and full-dose ELIOT appears promising as a substitute for postoperative WBI in selected patients. Esthetic outcomes are good in general and the radiation dose to healthy tissues (particularly skin, heart, lungs and contralateral breast) is greatly reduced compared with conventional external-beam radiotherapy. While modern external-beam techniques also markedly reduce radiation to surrounding organs and are successfully used to deliver radiation to only part of the breast, unlike IORT, they cannot deliver the radiation in a single session.

The main unanswered question regarding IORT is its long-term oncological safety; it is also important to assess long-term side effects. To this end, several randomized controlled trails are comparing IORT to the current gold standard of WBI. These studies should also make it possible to refine indications for IORT. In the meantime, WBI remains the standard irradiation modality for breast cancer: those given IORT should be carefully selected and the experimental nature of the treatment always explicitly stated.

Future perspective

APBI techniques can be expected to begin replacing traditional WBI in the near future. The most interesting of these techniques, in our opinion, are those that deliver irradiation intraoperatively.

Techniques of partial breast irradiation

- Accelerated partial breast irradiation (APBI) includes brachytherapy, high dose conformal external radiotherapy, and intraoperative radiotherapy.
- These techniques irradiate part of the breast, sparing healthy tissues to a greater extent and requiring less time, than traditional whole breast irradiation.

ELIOT in early breast cancer

- Intraoperative radiotherapy, with electrons (ELIOT) or soft x-rays, appears the most attractive APBI technique since treatment can be completed in a single intraoperative session, the irradiation is directed by the surgeon who removed the tumor, the dose to healthy tissues is greatly reduced, and dose homogeneity is high.

Conclusion

- The safety of all APBI techniques has been demonstrated.
- We await the long-term results of the ongoing trials to determine whether recurrence and survival rates after the various forms of APBI are equivalent to those of traditional whole breast irradiation.

First, because the collimator or applicator is applied to the tumor bed by the surgeon who removed the tumor, the risk of topographic miss is eliminated and dose homogeneity is excellent. Second, the entire irradiation course can be delivered in a single intraoperative session, reducing patient stress and the inconvenience associated with the 5–7 weeks of traditional WBI. The safety of these techniques has been demonstrated and, although early results of one randomized trail against traditional WBI have been published, we await long-term outcomes to learn whether recurrence and survival rates are equivalent to those of WBI. The capital cost of intraoperative accelerators is high; nevertheless, they may contribute to reducing the overall cost of breast cancer treatment.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing assistance was utilized in the production of this manuscript. The authors are grateful to Don Ward for help with the English. He was paid for his services by the European Institute of Oncology.

References

Papers of special note have been highlighted as:
- • of interest
- •• of considerable interest

1. NIH Consensus Development Conference on the Treatment of Early-Stage Breast Cancer. Bethesda, Maryland, June 18–21, 1990. *J. Natl Cancer Inst. Monogr.* 11, 1–187 (1992).
2. Veronesi U, Cascinelli N, Mariani L *et al.* Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N. Engl. J. Med.* 347, 1227–1232 (2002).
3. Malmstrom P, Holmberg L, Anderson H *et al.* Breast conservation surgery, with and without radiotherapy, in women with lymph node negative breast cancer: a randomized clinical trial in a population with access to public mammography screening. *Eur. J. Cancer* 39, 1690–1697 (2003).
4. Morrow M, Strom EA, Bassett LW *et al.* Standard for breast conservation therapy in the management of invasive breast carcinoma. *CA Cancer J. Clin.* 52, 277–300 (2002).
5. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol.* 6, 557–565 (2005).
6. Veronesi U, Luini A, Galimberti V, Zurrida S. Conservation approaches for the management of stage I/II carcinoma of the breast: Milan Cancer Institute trials. *World J. Surg.* 18(1), 70–75 (1994).
7. Fisher ER, Anderson S, Redmond C, Fisher B. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation. pathological findings from NSABP protocol B-06. *Semin. Surg. Oncol.* 8(3), 161–166 (1992).
8. Bernier J, Viale G, Orecchia R *et al.* Partial irradiation of the breast: old challenges, new solutions. *Breast* 15(4), 466–475 (2006).
9. Sauer R, Sautter-Bihl ML, Budach W *et al.* Accelerated partial breast irradiation: consensus statement of 3 German Oncology societies. *Cancer* 110(6), 1187–1194 (2007).
10. Arthur DW, Koo D, Zwicker RD *et al.* Partial breast brachytherapy after lumpectomy: low-dose-rate and high-dose-rate experience. *Int. J. Radiat. Oncol. Biol. Phys.* 6, 681–689 (2003).
11. Bartelink H, Horiot JC, Poortmans P *et al.* Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N. Engl. J. Med.* 345, 1378–1387 (2001).
12. Vaidya JS, Vyas JJ, Chinoy RF *et al.* Multicentricity of breast cancer: whole-organ analysis and clinical implications. *Br. J. Cancer* 74, 820–824 (1996).
13. Smith D, Arthur D, Buchholz T *et al.* Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int. J. Radiation Oncology Biol. Phys.* 74(4), 987–1001 (2009).
14. Beitsch PD, Shaitelman SF, Vicini FA. Accelerated partial breast irradiation. *J. Surg. Oncol.* 103(4), 362–368 (2011).
15. Ross G. Accelerated partial breast irradiation: technically feasible but who will benefit? *Breast Cancer Res.* 7(3), 110–112 (2005).
16. Nag S, Kuske RR, Vicini FA *et al.* Brachytherapy in the treatment of breast cancer. *Oncology* 15(2), 195–202, discussion 205–207 (2001).
17. Pierquin B, Dutreix A, Paine CH *et al.* The Paris system in interstitial radiation therapy *Acta Radiol. Oncol.* 17, 33–48 (1978)
18. Strnad V, Hildebrandt G, Pötter R *et al.* Accelerated partial breast irradiation: 5-year results of the German–Austrian multicenter Phase II trial using interstitial multicatheter brachytherapy alone after breast-conserving surgery. *Int. J. Radiat. Oncol. Biol. Phys.* 80(1), 17–24 (2011).
19. Guedea F, Venselaar J, Hoskin P *et al.* Patterns of care for brachytherapy in Europe: updated results. *Radiother. Oncol.* 97(3), 514–520 (2010).
20. Patel R, Becker S, Das R, Mackie T. A dosimetric comparison of accelerated partial breast irradiation techniques: multicatheter interstitial brachytherapy, three-dimension conformal radiotherapy and supine versus prone helical tomotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 68(3), 935–942 (2007).
21. Zannis V, Beitsch P, Vicini F *et al.* Descriptions and outcomes of insertion techniques of a breast brachytherapy balloon catheter in 1403 patients enrolled in the American Society of Breast Surgeons MammoSite breast brachytherapy registry trial. *Am. J. Surg.* 190(4), 530–538 (2005).
22. Polgár C, Major T, Fodor J, Sulyok *et al.* Accelerated partial-breast irradiation using high-dose-rate interstitial brachytherapy: 12-year update of a prospective clinical study. *Radiother. Oncol.* 94(3), 274–279 (2010).
23. Chen PY, Vicini FA, Benitez P *et al.* Long-term cosmetic results and toxicity after accelerated partial-breast irradiation: a method of radiation delivery by interstitial brachytherapy for the treatment of early-stage breast carcinoma. *Cancer* 106(5), 991–999 (2006).
24. Polgár C, Major T. Current status and perspectives of brachytherapy for breast cancer. *Int. J. Clin. Oncol.* 14(1), 7–24 (2009).
25. Dzhugashvili M, Tournay E, Pichenot C *et al.* 3D-conformal accelerated partial breast irradiation treatment planning: the value of surgical clips in the delineation of the lumpectomy cavity. *Radiat. Oncol.* 4, 70 (2009)

26. Niehoff P, Polgar C, Ostertag H *et al.* Clinical experience with the MammoSite radiation therapy system for brachytherapy of breast cancer: results from an international Phase II trial. *Radiother. Oncol.* 79, 316–320 (2006).

27. Chao KK ,Vicini F, Wallace M, Mitchell C, Chen P, Ghilezan M. Analysis of treatment efficacy, cosmesis, and toxicity using the MammoSite breast brachytherapy catheter to deliver accelerated partial-breast irradiation: the William Beaumont Hospital experience. *Int. J. Radiat. Oncol. Biol. Phys.* 69, 32–40 (2007).

28. Dragun AE, Harper JL, Jenrette JM, Sinha D, Cole DJ. Predictors of cosmetic outcome following MammoSite breast brachytherapy: a single institution experience of 100 patients with two years of follow-up. *Int. J. Radiat. Oncol. Biol. Phys.* 68, 354–358 (2007).

29. Njeh CF, Saunders MW, Langton CM. Accelerated partial breast irradiation using external beam conformal radiation therapy: a review. *Crit. Rev. Oncol. Hematol.* doi:10.1016/j.critrevonc.2011.01.011 (2011) (Epub ahead of print).

30. Vicini F, Winter K, Straube W *et al.* A Phase I/II trial to evaluate three-dimensional conformal radiation therapy confined to the region of the lumpectomy cavity for stage I/II breast carcinoma: initial report of feasibility and reproducibility of Radiation Therapy Oncology Group (RTOG) Study 0319. *Int. J. Radiat. Oncol. Biol. Phys.* 63, 1531–1537 (2005).

31. Landis DM, Luo W, Song J, Bellon J, Punglia R, Wong J. Variability among breast radiation oncologists in delineation of the post surgical lumpectomy cavity. *Int. J. Radiat. Oncol. Biol. Phys.* 67, 1299–1308 (2007).

32. Vaidya JS, Joseph DJ, Tobias JS *et al.* Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomized, non-inferiority Phase 3 trial. *Lancet* 376(9735), 91–102 (2010).

• **A potentially important trial marred by short follow-up.**

33. Veronesi U, Orecchia R, Luini A *et al.* A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated. *Eur. J. Cancer* 37, 2178–2183 (2001).

•• **A pioneering study presenting the rationale and describing the method of intraoperative radiotherapy with electrons (ELIOT), opening the way to a new irradiation treatment that is much more convenient for the patient.**

34. Herskind C, Griebel J, Kraus-Tiefenbacher U, Wenz F. Sphere of equivalence – a novel target volume concept for intraoperative radiotherapy using low-energy x-rays. *Int. J. Radiat. Oncol. Biol. Phys.* 72(5), 1575–1581 (2008).

35. Orecchia R, Luini A, Ciocca C *et al.* Electron intraoperative treatment in patients with early-stage breast cancer: data update. *Expert Rev. Anticancer Ther.* 6, 605–611 (2006).

36. Veronesi U, Gatti G, Luini A *et al.* Intraoperative radiotherapy for breast cancer: technical notes. *Breast J.* 9, 106–112 (2003).

37. Brenner DJ. The linear-quadratic model is an appropriate methodology for determining isoeffective doses at large doses per fraction. *Semin. Radiat. Oncol.* 18(4), 234–239 (2008).

38. Rosenstein B, Lymberis S, Formenti S. Biologic comparison of partial breast irradiation protocols. *Int. J. Radiat. Oncol. Biol. Phys.* 60, 1393–1404 (2004).

39. Romestaing P, Lehingue Y, Carrie C *et al.* Role of a 10-Gy boost in the conservative treatment of early breast cancer. results of a randomized clinical trial in Lyon, France. *J. Clin. Oncol.* 15(3), 963–968 (1997).

40. Ivaldi GB, Leonardi MC, Orecchia R *et al.* Preliminary results of electron intraoperative therapy boost and hypofractionated external beam radiotherapy after breast-conserving surgery in premenopausal women. *Int. J. Radiat. Oncol.* 72, 485–493 (2008).

41. Lemanski C, Azria D, Gourgon-Bourgade S *et al.* Intraoperative radiotherapy in early-stage breast cancer. results of the Montpellier Phase II trial. *Int. J. Radiat. Oncol. Biol. Phys.* 76(3), 698–703 (2010).

42. Veronesi U, Orecchia R, Luini A *et al.* Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons. *Breast Cancer Res Treat.* 124(1), 141–151 (2010).

43. Schnitt SJ, Abner A, Gelman R *et al.* The relationship between microscopic margins of resection and the risk of local recurrence in patients with breast cancer treated with breast-conserving surgery and radiation therapy. *Cancer* 74, 1746–1751 (1994).

44. Froud PJ, Mates D, Jackson JS *et al.* Effect of time interval between breast-conserving surgery and radiation therapy on ipsilateral breast recurrence. *Int. J. Radiat. Oncol. Biol. Phys.* 46, 363–372 (2000).

45. Polgár C, Van Limbergen E, Pötter R *et al.* Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) Breast Cancer Working Group based on clinical evidence. *Radiother. Oncol.* 94(3), 264–273 (2010).

46. Intra M, Gentilini O, Veronesi P *et al.* A new option for early breast cancer patients previously irradiated for Hodgkin's disease: intraoperative radiotherapy with electrons (ELIOT). *Breast Cancer Res. Treat.* 7, R828–R832 (2005).

47. Galimberti V, Ciocca M, Leonardi MC *et al.* Is electron beam intraoperative radiotherapy (ELIOT) safe in pregnant women with early breast cancer? *In vivo* dosimetry to assess fetal dose. *Ann. Surg. Oncol.* 16(1), 100–105 (2009).

48. Petit JY, Veronesi U, Orecchia R *et al.* Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five years experience at the European Institute of Oncology of Milan (EIO). *Breast Cancer Res. Treat.* 117(2), 333–338 (2009).

•• **Reports extensive experience with nipple-sparing mastectomy inspired by the desire to preserve the woman's appearance and quality of life, even though mastectomy is necessary.**

49. Veronesi U, Luini A, Del Vecchio M *et al.* Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N. Engl. J. Med.* 328(22), 1587–1591 (1993).

50. Slavin SA, Schnitt SJ, Duda RB *et al.* Skin-sparing mastectomy and immediate reconstruction: oncologic risks and aesthetic results in patients with early stage breast cancer. *Plast. Reconstr. Surg.* 102(1), 49–62 (1998).

51. Carlson GW, Styblo TM, Lyles RH *et al.* Local recurrence after skin-sparing mastectomy: tumor biology or surgical conservatism? *Ann. Surg. Oncol.* 10(2), 108–112 (2003).

52. Legorreta AP, Liu X, Parker RG. Examining the use of breast-conserving treatment for women with breast cancer in a managed care environment. *Am. J. Clin. Oncol.* 23, 438–441 (2000).

53. Bellon JR Come SE, Gelman RS *et al.* Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: updated results of a prospective randomized trial. *J. Clin. Oncol.* 23(9), 1934–1940 (2005).

Website

101. Ontario Clinical Oncology Group, Canadian Institutes of Health Research, Canadian Breast Cancer Research Alliance. RAPID. Randomized trial of accelerated partial breast irradiation (2008). www.clinicaltrials.gov/ct2/ show/ NCT00282035