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Original Article

Breast-conserving Surgery with Intra-operative Radiotherapy: The Right Approach for the 21st Century?

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ABSTRACT:
Wide local excision followed by external beam radiation therapy (EBRT) to the whole breast has become the standard of care for most patients with localised 'early' breast cancer in the UK, Europe, and the USA. Local relapse rates are low, and overall survival figures have improved during the past decade, with the advent of more effective systemic endocrine- and chemo-therapy.
A policy of EBRT for every patient undergoing breast conserving surgery (BCS) is however associated with a number of practical difficulties, acute radiation side effects and longer term toxicity, all of which detract from the obvious benefits of EBRT. In addition, with a disease as common as early breast cancer and a treatment programme typically requiring sophisticated radiation planning and many fractions of treatment, the policy of BCS plus EBRT has enormous resource implications within departments of oncology, greatly contributing to lengthy pre-treatment delays.
For all these reasons, we and others have developed an increasing interest in techniques of partial breast irradiation, with an emphasis in our own Department on the emerging technique of intra-operative radiotherapy (IORT), which we initially employed as a boost to the tumour bed for use in conjunction with EBRT to the whole breast. To test the possibility of replacing the whole of the EBRT 3–6 week programme by a single application of IORT at the time of surgery, we and others have commenced a large scale prospectively randomised clinical trail in selected patients. Nine international centres are currently participating, and 350 patients have now been randomised to receive either IORT as part of the initial surgical excision or conventional EBRT with a pragmatic dose policy according to the preference of the contributing centre. The majority of patients undergoing IORT receive this at the time of initial surgery but it is also permissible within the trial programme to randomise suitable patients after the excised specimen has been histologically examined, thus avoiding any unsuitable patients — for example, those with a lobular carcinoma. These patients will be stratified and assessed separately from the 'pre-pathology' group, whose surgery and IORT is completed within a single session; if the latter patients are found to have unfavourable histology we have the facility, within the trial, to add EBRT. The trial is ongoing and our early experience has been encouraging. We have also recently assessed the long term local failure rate in patients offered IORT as a tumour bed boost, in conjunction with conventional EBRT. This methodology will also be the subject of a future randomised clinical trial. Tobias, J. S. *et al*. (2006). *Clinical Oncology* 18, 220–228

Introduction

For most patients with localised breast cancer, the initial treatment recommendation includes wide excision of the primary tumour, the preferred form of breast-conserving surgery (BCS), followed as soon as practically possible by post-operative whole-breast external-beam radiation therapy (EBRT). This form of management, though generally successful in terms of local control [1], nonetheless carries a number of important disadvantages. In the first instance, it requires 4–6 weeks of daily treatment, a highly resource-consuming programme that is both inconvenient for patients and also contributes substantially to the unacceptable waiting lists experienced in many oncology departments worldwide. Furthermore, it is becoming clearer that treatment delay (often up to 18 weeks in the UK, for many patients scheduled for post-operative breast irradiation) may contribute significantly to a worse outcome [2]. In addition, although a radiation boost dose to the tumour bed is recognised as important, at least in younger patients [3], accurate placement of this treatment field is extremely difficult, particularly after many weeks of post-operative delay [4]. Finally, acute and long-term complications of whole-breast irradiation include erythema, fatigue,

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prolonged discomfort, radiation pneumonitis, rib fracture, cardiovascular effects and carcinogenesis in lung, oesophagus and contralateral breast [5 and Peto R, ECCO-13] — hazards which are sufficient to compromise the long-term benefit from post-operative radiotherapy [6,7].

The typical patient presenting with localised breast cancer nowadays has a small T1 or T2 tumour, is well into the post-menopausal years (at least in the UK, mainland Europe and the USA), has quite likely been initially recognised as a result of the national breast screening programme, and has a pathologically low or moderate grade, axillary node-negative, hormone-receptor-positive tumour. All these features confer a good prognosis, both for local control and overall survival [8]. In addition, recent data from randomised studies comparing tamoxifen with aromatase inhibitors confirm that for hormone-receptor-positive post-menopausal women, both the overall prognosis and also the probability of local control are significantly improved by current forms of adjuvant hormone therapy [9].

For all these reasons, we feel that the current standard of care, a blanket recommendation of a lengthy (typically 3—6 weeks) programme of daily radiation therapy given post-operatively after wide local excision, may be more than sufficient for the majority of patients. In the past it has been regarded as mere flight of fancy to imagine that we can identify patients at sufficiently low risk of recurrence so accurately that less intensive treatment than BCS plus whole-breast EBRT could properly be regarded as 'adequate'. In this sense, this general policy has remained little different — at least in principle — from the equally compelling policy (in its day) of radical mastectomy, though admittedly, using BCS with post-operative whole-breast irradiation is generally regarded — rightly — as more 'humane' even though attempts at demonstrating an improved quality of life have been largely elusive [10].

We believe that the time has come to move on further. For many patients, especially those in the post-menopausal age group with small, low grade, hormone-receptor-positive, sentinel-node-negative tumours, it is surely right to question the necessity of a lengthy and sometimes damaging course of radiation therapy. Radiation oncologists who are totally satisfied with their often excellent cosmetic results and low relapse rates following standard treatment should recall the work of the Oxford-based EBCTCG, namely that despite a lower breast cancer cause-specific death rate in irradiated patients, the increased mortality from other non-cancer causes diminishes this advantage [7]. The assumption that the excess non-cancer related deaths in this large meta-analysis was due essentially to reliance on older outmoded radiation techniques may be correct, but it remains an assumption only, and considerable additional data attest to the cardiac and pulmonary dangers of whole-breast irradiation.

The use of single fraction intra-operative irradiation (IORT), at the time of initial surgical excision, is attracting considerable interest. For example, the Instituto Europeo di Oncologia in Milan has recognised it (since 1999) as an important potential step forward, reducing the otherwise inevitable treatment delay between surgery and radiation therapy that patients (and staff in Departments of Clinical Oncology) find so unsettling. In Milan, the use of ELIOT (electron beam intra-operative radiation therapy) requires a substantial electron generating linear accelerator brought in a dedicated fashion to the operating room [11,12], but other techniques have also been employed. Our own approach (since 1998) has been to use the Intrabeam device (manufactured by Carl Zeiss AG, Oberkochen, Germany) — essentially a miniaturised low-energy photon generator, taken to the operating theatre at the time of surgery. The technique has been fully described in a previous communication from our group [13], and we employ this method both in conjunction with surgery or occasionally, definitively — with no surgical procedure — for frail patients whose general medical condition precludes a general anaesthetic or surgical operation [14].

The Paradox of Local Recurrence

As part of the rationale for treating low risk patients with IORT (without added EBRT) it is important to recall that most in-breast local recurrences following breast-conserving surgery occur within the index quadrant, despite the fact that many breasts are known to harbour other foci of malignancy (often DCIS) at additional sites. This interesting distribution of the location of in-breast recurrences remains only partially understood; with respect to site of the primary tumour, over 91% occur in the same quadrant [15]. Although Bartelink and colleagues reported that in their series, only 56% of local recurrences occurred in the original tumour bed [3], an additional 27% of their patients recurred diffusely throughout the breast, (including the tumour bed). Thus, although apparently 29% of recurrences appeared *outside* the index quadrant, we would argue that this is probably artefactual because of the intensive mammographic follow-up that might have unearthed sub-clinical occult tumours in the other quadrants, of unproven clinical significance — in other words, an example of ascertainment bias. These observations are in contrast to the findings of earlier three-dimensional whole-organ analysis of mastectomy specimens, which revealed that 63% of breasts harboured occult cancer foci, with 80% situated remotely from the index quadrant [16]. We therefore believe that these widespread, occult, often unrecognised multi-focal/multi-centric cancers in other quadrants of the breast remain dormant, often for many years, and have a low risk of developing into clinically detectable tumours. This is supported by the observation that autopsy studies have shown a far higher frequency of tumours in histologically examined breasts (20% even in young women, with a median age of 39 years, and 33% in women between ages 50 and 55) than the frequency of clinical breast cancer in the general population [17].

We have suggested that local recurrence may well be the result of a dynamic interaction between the intra-mammary milieu, the systemic hormonal environment, background

genetic instability in the normal breast tissue surrounding the tumour, and specific features of the tumour [15,18 — and also see www.targit.org.uk]. We have also proposed that the effect of radiotherapy on the breast parenchyma might be more important than previously supposed, based on the finding that local recurrence generally occurs in the index quadrant, whether or not radiotherapy is given and irrespective of marginal status [19—21]. Of the trials that have tested the effect of radiotherapy after BCS, the NSABP-B06 [22], Ontario [23], Swedish [24], and Scottish [25] trials had less extensive surgery compared with the Milan III trial [26]. The recurrence rate in the control arm of the Milan III trial was lower (15%) than in the other studies (24—39%), albeit at the cost of worse cosmetic outcome. Nevertheless, patients treated with radiotherapy in the Milan trial had an even smaller risk of local recurrence (3%), with radiotherapy having roughly the same proportional effect in reducing local failure as it did in the other trials. If local recurrence were caused by residual disease only, then radiotherapy should have resulted in a substantially much larger proportionate reduction in patients undergoing less extensive surgery; so this observation suggests that radiotherapy may have more of an effect on the 'soil', rather than the 'seed'. If local irradiation does indeed have such dual benefits (inhibiting the growth of genetically unstable cells around the primary tumour and making the whole-breast tissue less conducive to growth), then its action would presumably overlap with that of systemic therapies that reduce oestrogen concentration in the breast (such as aromatase inhibitors or ovarian suppression). This then could imply that radiotherapy to the tissues surrounding the primary tumour might be all that is necessary in patients receiving the appropriate systemic therapy. Such an approach might solve many of the problems associated with conventional post-operative radiotherapy already mentioned, both reducing waiting times and increasing the opportunity for BCS in patients currently considered unsuitable.

The Manchester Trial: For or Against the Concept of Partial Breast Irradiation?

Irradiation of the index quadrant alone (without whole-breast irradiation) has been tested before. The results of the Christie Hospital trial (performed in Manchester, UK) are often regarded as confirming the superiority of wide-field radiotherapy [27], but in our view the outcome of this study, perhaps surprisingly, is in fact encouraging. Seven hundred and eight patients were randomised to receive either standard wide-field radiotherapy or limited-field irradiation (an 8×8 cm electron field directed to the index quadrant). Overall, there was a higher recurrence rate in the limited-field arm. However, a single field-size was used for all patients in this arm, irrespective of the tumour dimensions or other characteristics, which could well have resulted in several instances of 'geographical miss'. When the results were analysed according to the *type* of the primary tumour, it was found that limited-field radiotherapy was inadequate only for patients with *infiltrating lobular cancers* or cancers with an *extensive intra-ductal component*. For the majority of patients, i.e. the 504 with infiltrating duct carcinoma, there was no significant difference in the rates of local recurrence rates between the two arms.

Case Selection with Modern Imaging and Surgical Staging

The confident selection of suitable cases for BCS has been greatly assisted by recent developments in diagnostic radiology and surgery. Both MRI and sentinel-node biopsy are now in routine use at many centres (including our own) and have made a substantial impact in clinical practice.

Breast MRI provides far greater anatomical definition than any other imaging modality and is increasingly regarded as a potentially useful tool for patient selection for BCS [28].

In the future, indications for primary medical therapy are likely to increase and will include a larger proportion of patients. We are likely to see novel endocrine, anti-angiogenic and anti-endothelial treatments assessed within clinical trials. The primary aim of surgical resection has changed in recent years from improving overall survival to ensuring local disease control (wherever possible, by BCS and post-operative radiotherapy) and, by nipple preservation and reconstructive surgery, to improving patient quality of life. Consequently, minimally invasive adjuvant therapeutic (e.g. intra-operative radiotherapy) and ablative techniques (e.g. radiofrequency or laser ablation) for the treatment of small breast cancers are under active development in many centres worldwide. The welcome shift towards breast conservation and effective adjuvant systemic therapy relies to a considerable degree upon the availability of imaging modalities suitable for surveillance of the remaining breast tissue.

Since MRI has both a very high sensitivity for breast cancer detection and a high spatial resolution, we have previously suggested that MRI could be used to investigate prospectively the clinical significance of unresected cancer foci, in order to convincingly determine their natural history in the context of BCS and post-operative radiotherapy [28]. Further advances in imaging — and therefore case selection — include the use of newer contrast agents both for breast MRI and also colour Doppler ultrasound [29,30]. These newer techniques may also prove useful in monitoring response to primary medical treatment by measuring changes in tumour vascularity rather than merely changes in tumour size. This tumour vascularity information might have important implications in 'tailoring' the most effective surgical and adjuvant treatment for the individual patient.

As far as axillary staging is concerned, routine axillary lymph node dissection (ALND) has up till now been the standard of care. However, the development of sentinel lymph node (SLN) biopsy is now challenging our clinical practice. The SLN is defined as 'any lymph node which

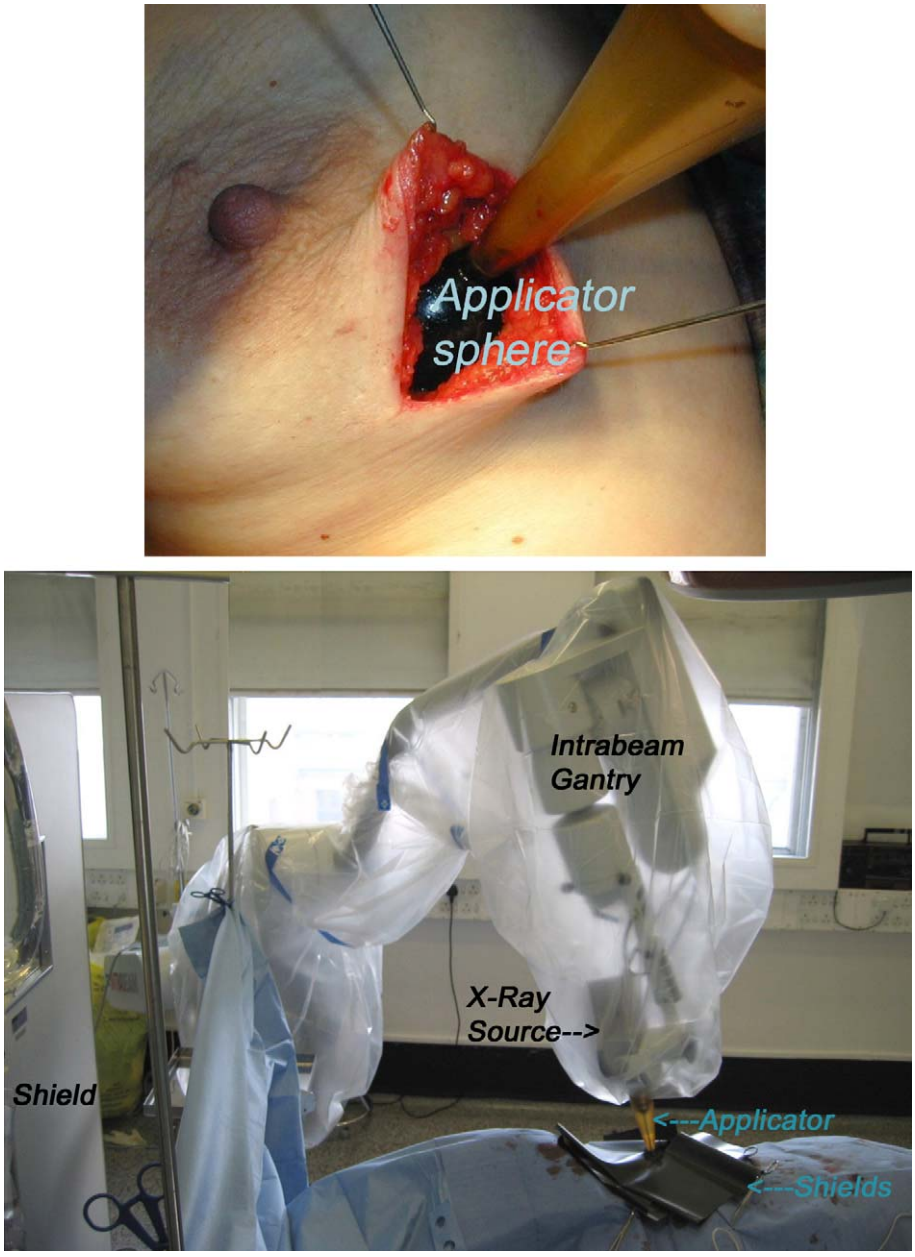

Fig. 1 — Intrabeam device for delivering intra-operative radiotherapy. The applicator is inserted in the tumour bed which wraps around it (above). The whole X-ray source is held by an easily manoeuvrable arm on a mobile base.

receives direct drainage from the primary tumour', and the concept relies on the general observation that lymphatic flow is orderly and predictable, and that tumour cells disseminate sequentially. The histological status of the SLN would reflect the status of the distant lymph node basin so this technique introduces a new concept of selective lymphadenectomy [31].

Since 1994 several studies have reported their results with SLN biopsy and validated both the logic and also the technique. In the randomised trial from the Milan group, 516 patients with T1 cancers were randomly assigned to either sentinel-node biopsy or total axillary dissection, or to sentinel-node biopsy followed by axillary dissection only if the sentinel-node-contained metastases [32]. Morbidity including post-operative pain, numbness and arm swelling was significantly less in the SLN biopsy group. Similar results were echoed in the UK ALMANAC trial which randomised 1031 patients [33]. The ALMANAC trial also found that hospital stay, operative time, drain usage and time to return to normal activities were all significantly reduced in the SLN biopsy group. Another series of 953 patients from Milan who underwent SLN biopsy only, without any further axillary surgery suffered only three (0.3%) axillary relapses at a median follow-up of 38 months

Table 1 — Some characteristics of intra-operative radiotherapy systems

Device	Radiation type	Dose	Weight of treatment device (kg)
Intrabeam	X-rays at 50 kVp	Typical physical dose of 20 Gy next to the applicator over 25—30 min. Set-up time 10—12 min.	1.8
Mobetron	Electrons at 4—12 MeV	20 Gy physical dose in 3—5 min. Set-up time ~20 min	1275
Novac 7	Electrons at 4—12 MeV	20 Gy physical dose in 3—5 min. Set-up time ~20 min	650

[34]. Of course there exists a small definite false negative rate (5—10%) and its effects [35] need to be included in the consent discussions.

Thus, when used along with MRI for better case selection, intra-operative radiotherapy and sentinel-node biopsy have the potential to reduce the overall morbidity of local treatment of early breast cancer.

Intra-operative Radiotherapy

Several attempts have been made to irradiate the breast in a single session intra-operatively. Older IORT devices were technically cumbersome or required custom-built specially shielded operating rooms. Some institutions performed IORT by transporting the patient from the operating room to the radiotherapy unit during surgery, limitations which have hampered widespread adoption of IORT. The technology of miniaturisation that has permeated the modern world today has more recently enabled the development of mobile IORT devices.

The first device to be used for IORT was the Intrabeam, developed by the Photoelectron Corporation (Lexington, MA), and currently manufactured by Carl Zeiss AG (Oberkochen, Germany) (Fig. 1). Two mobile linear accelerators have also been developed: the Mobetron System (Oncology Care Systems Group of Siemens Medical Systems, Intraop Medical Inc, Santa Clara, CA) and the Novac 7 System (Hitesys SPA, Aprilia, Italy [36,37]). Some of the characteristics of these machines are described in Table 1. For the remainder of this article, we will concentrate on the intra-operative radiotherapy approach and the Intrabeam system.

Large single radiotherapy doses, such as those given by the Intrabeam device (e.g. a dose of 20 Gy at the applicator surface and 5—6 Gy at 1 cm from the applicator in tissue, our standard dose prescription following BCS), should always be used with caution. This is especially important when treating late-reacting tissues such as breast, brain, or liver. Cell survival curves of such tissues after single-dose irradiation typically show an increased cell kill at higher doses, compared with acutely reacting tissues, which typically have a shallower cell survival curve. There is now abundant clinical information regarding the effects and side effects of high single doses. For example, radiosurgery doses of 20—25 Gy are sufficient to sterilise macroscopic brain metastases with a very low risk of causing brain necrosis or functional damage when the dose is given to a small volume [38—40]. In the pelvis, long-term follow-up of large Dutch [41] and Swedish [42] rectal cancer trials (in which 25 Gy in 5 fractions was the routinely prescribed dose) has not resulted in unacceptable toxicity. Thus, severe long-term side effects should not routinely be expected after administration of the dose delivered with Intrabeam tissue surrounding an excision cavity, although caution should perhaps be exercised when giving high single doses to skin and ribs. Assessing the radiobiological implications of the Intrabeam system requires consideration of the increased relative biologic efficiency (RBE) of the low-energy X-rays, the steep dose-dependency of RBE, and the rate of damage repair during radiotherapy delivery (30—50 min) [43].

As the treatment volume is small for IORT, we believe that the risk of side effects will probably be lower than that calculated from this model. Because the TD50/5 for pneumonitis is about 9—10 Gy, the thickness of the chest wall should generally ensure that there is virtually no risk of pneumonitis. The same is true for radiation effects on the heart. Because the dose to the heart lungs, oesophagus and contralateral breast during IORT is almost negligible, the mortality from cardiac ischaemia or carcinogenesis that has been observed in some trials using conventional radiation therapy with or without chemotherapy [6,45] will probably not be encountered. The TD50/5 for subcutaneous fibrosis is in the range of 13 Gy, showing a steep decrease with increasing distance from the applicator, and reaching almost zero at about 5-mm tissue depth. The calculated low risk of toxicity is in close agreement with the available pilot clinical data in 13 patients with a maximum follow-up of 4 years [46].

Radiobiological features of the Intrabeam system are more fully described in published articles from our international collaborators [43,44] and ourselves [47,48].

Local Excision Surgery with Immediate Intra-operative Irradiation Using Intrabeam (Fig. 1)

The Intrabeam machine contains a miniature electron gun and accelerator contained in a radiograph tube, powered by a 12-V power supply. 'Soft' X-rays (50 kVp) are emitted from the point source. The irradiated tissue is kept at a distance from the source by spherical applicators to give a more uniform dose, and depending on the size of the surgical cavity, various sizes of applicator spheres are available. The dose rate depends on the diameter of the applicator and the energy of the beam, both of which may be varied to optimise the radiation treatment.

For example, a dose of 5 Gy can be delivered in about 20 min at 1 cm from the margins of a 3.5-cm cavity. The steep attenuation of the radiation (inverse-square law) minimises the need for radiation protection to the operating personnel. Usually the operating team leaves the room, but the anaesthetist and any observer sit behind a mobile lead shield. The technique has been previously described in detail [13,49,50], and an operative video is available from the authors via the Internet (www.targit.org.uk).

In the operating theatre, wide local excision of the primary tumour is performed in the usual manner, with a margin of normal breast tissue. After the lumpectomy, it is important to achieve complete haemostasis, because even a small amount of bleeding in the 20—25 min during which radiotherapy is being delivered can distort the cavity enough to considerably alter the dosimetry. Different sized applicators are available to ensure a close fitting within the cavity. A purse-string suture needs to be skilfully placed; it must pass through the breast parenchyma and oppose it to the applicator surface.

Local Excision Surgery followed by Intra-operative Irradiation Using Intrabeam as a Second Procedure

In some patients giving radiotherapy at the same time as the primary procedure may not be either possible or desirable for logistic or clinical reasons. Such patients are considered for eligibility after primary surgery is completed so that complete histopathology is available. Delivery of Intrabeam as a second procedure is relatively simple and can be done as a day case procedure.

Our Current International Randomised Trial

Based on the hypothesis that for many of our patients, irradiation of the index quadrant should be sufficient, in July 1998 we introduced the technique of targeted intra-operative radiotherapy (Targit) using the Intrabeam device [49,50]. In the initial pilot studies in the UK, USA, Australia, Germany, and Italy testing the feasibility and safety of the technique, over 300 patients underwent Targit as a 'boost' dose and also received whole-breast EBRT. The morbidity of this procedure is no different from standard therapy and the local recurrence rate is very low. The details of this series were presented at SABCS in December 2005 and the manuscript is under preparation. In a sub-group of our patients, the cosmetic outcome was assessed formally by an independent surgeon and a nurse not involved in the trial, with a median follow-up of 42 months [46]. On a scale of 1 to 5 (5, best), the mean scores for appearance, texture, and comfort of the breast given by these observers were 3.5, 2.7, and 3.7, respectively. The corresponding scores given by the patient herself were 4, 3.1, and 3.5.

Our international TARGIT study has moved an important step further with the decision (approved by MREC in the UK and NHMRC in Australia) to test IORT alone, vs conventional EBRT, in suitable patients with localised breast cancer (www.targit.org.uk). This multi-centre randomised trial 'TARGIT' using the Intrabeam system is now recruiting patients in the UK, Germany, Italy, USA, and Australia [51,52]. Patients are enrolled before tumour excision to receive either IORT or conventional whole-breast radiotherapy. This means, for example, at our own centre that patients randomised to IORT generally undergo their surgical excision, axillary sentinel-node biopsy or clearance and definitive IORT at a single procedure. We believe this to be the most efficient and 'elegant' solution for the immediate management of the primary tumour and axillary nodes. Each centre may decide that patients randomised to IORT who are found to have certain pathologic findings (e.g. lobular carcinoma or an extensive intra-ductal component) may subsequently receive additional whole-breast irradiation.

An alternative approach that is entirely acceptable within the trial is to randomise patients only after initial surgery. An advantage of this approach is that all pathological features of the tumour including the margins are known before randomisation; secondly, it can allow patients from centres that do not have the Intrabeam machine to enter into the trial, if they are randomised to receive IORT then they need to travel once to the centre with the facility for a day case procedure and if not receive their routine radiotherapy in their own centre.

Delivering IORT with the Intrabeam prolongs the primary operation by 5 to 45 min (the shorter extra time when it is performed in conjunction with immediate analysis of the sentinel lymph node). In addition, approximately 1 h of a radiotherapy physicist's time is needed to prepare the device. On the other hand, EBRT requires about 9 man-hours of planning, approximately 6 h of radiotherapy-room time, and 30—60 h of the patient's time and in pathological review, in order to exclude the small group with lobular carcinoma or an extensive intra-ductal component who if randomised pre-operatively to IORT alone would in addition require treatment by EBRT — in our experience, approximately 10—15% of our patients. This pragmatic centre-by-centre approach is perfectly permissible within the TARGIT protocol, but it does of course involve a second anaesthetic and surgical procedure.

Is Margin Assessment Available Before Randomisation?

Yes, especially in those centres randomising after primary surgery and delivering Targit as a second procedure.

Can We Exclude Multi-centricity before Randomisation?

Yes, even though we are uncertain about the significance of multi-centric foci detected by MRI, some centres may prefer to exclude patients who are found to have multiple foci of cancer on MRI.

In a Patient who Has already Received TARGIT, Can We Add External-beam Radiotherapy (without a Boost) if Final Pathology Reveals Adverse Prognostic Factors?

The pragmatism of the Targit trial [51] allows the clinician to add external-beam radiotherapy if it is felt that tumour biology is aggressive and that there is a higher risk of local recurrence especially in other quadrants. This approach of delivering only the boost in the operation theatre followed by the usual external-beam radiotherapy for all patients (without the boost) has now been used in many centres [46,53] and appears to have a very low rate of local recurrence and good cosmetic result. We believe that this approach may actually be superior to conventional radiotherapy and a randomised trial is planned to test this.

Discussion

In many parts of the world, a proportion of patients with breast cancer (and their surgeons) still prefer mastectomy to breast-conserving treatment even if BCS is clearly a realistic approach. It even happens in the UK at the present time. Local culture, distance from radiotherapy facilities, delay in the availability of post-operative radiotherapy, the surgeon's choice and patient preference, not necessarily in that order, all dictate which operation is chosen. For several reasons the perceived need for undergoing a prolonged course of post-operative radiotherapy can be a major barrier to the wider acceptance of breast-conserving therapy. It adds yet another tiresome — even exhausting — period of treatment for patients who in addition may already be facing a 6- to 9-month course of chemotherapy. Many women are reluctantly obliged to choose mastectomy because they live too far away from a radiotherapy department or have difficulty travelling to one. Even patients treated by BCS may not receive optimal treatment because of living too far from a radiotherapy centre. For example, one study from USA [54] demonstrated that if the travel distance was less than 10 miles, 82% of patients received radiotherapy after BCS; when it was 50—75 miles, 69% received it; and when it was more than 100 miles, only 42%! The estimated proportions of patients in these three groups treated by BCS plus full EBRT were 39%, 22%, and 14%, respectively. Furthermore, in countries with scarce radiotherapy resources, which include countries not normally regarded as 'third-world', patients treated with BCS may wait for a prolonged time before starting radiotherapy. A large-scale recent study of 7800 patients suggested that delay in initiating conventional EBRT for 20—26 weeks after surgery was associated with decreased *survival* [2]. The delay imposed by giving chemotherapy before radiotherapy might conceivably also increase the risk of local recurrence. Finally, if giving a 'boost' dose to the tumour bed is important (and there is plenty of evidence to support this, at least in younger patients), then inaccurate localisation of the tumour bed boost carries a significant hazard. This frequently occurs of course, as a result of non-image-guided treatment planning that is still the norm in many centres, such that a portion of the target volume is missed in 24—88% of cases [4,55,56]. As a tumour bed boost is an important component of treatment, such a 'geographical miss' almost certainly contributes to a substantial proportion of local recurrences.

Using the Intrabeam device to deliver single-treatment IORT has many advantages compared with other forms of radiation therapy. The target, i.e. the pliable breast tissue around the cavity of the surgical excision, is moulded or 'conformed' to the radiation source [13] — in fact we regard this method of treatment as a form of conformal intra-operative brachytherapy [57]. This avoids the need for prohibitively time-consuming or tedious techniques of interstitial radioisotope implantation, or expensive technology for complex computed tomography — guided planning of conformal EBRT using linear accelerators. With respect to the radiation boost of the tumour bed, it unequivocally eliminates the possibility of irradiating the wrong site and of course delivers radiotherapy at the earliest possible time — at surgery. The steep attenuation of the radiation dose protects normal tissues and unlike the ELIOT technique, for example, allows the treatment to be performed in unmodified operating rooms. We believe that by using this approach both the biological effect, adverse toxicities to normal tissues (including long-term breast discomfort, often under-recognised) as well as the cosmetic outcome of breast-conserving therapy could be improved.

For a variety of reasons, many hospitals in the UK and elsewhere are experiencing lengthening delays for patients who require radiotherapy. It is far from unusual for them to be told that treatment cannot begin for 3 months or even longer. For younger women, either with positive axillary nodes or other features indicative of high risk of recurrence, initial treatment is likely to be with chemotherapy — in which case, the patient can be booked for radiotherapy at the outset of such treatment, undergoing radiation at the appropriate time, after the chemotherapy had been completed. They can have the option of taking part in our trial of intra-operative boost. The majority of patients however, fall into the lower risk category, or for other reasons cannot justifiably be recommended to undergo chemotherapy. This will include the majority of post-menopausal patients who, after all, still comprise 75% of the women we see. For this large group, a delay in treatment is not only psychologically disturbing but also potentially dangerous [2]. The use of 'single shot' intra-operative radiation therapy, if proven in the Targit trial, carries the potential advantages of immediacy, precision and freeing up of precious resources within hard-pressed departments of clinical oncology.

Whilst the initial outlay for an intra-operative radiation advice may be high, the overall economics strongly favour its use in terms of both manpower and equipment. It has been calculated that many millions of pounds could be saved annually for the NHS, quite apart from the substantial saving of expensive staff time and inconvenience for patients [15,50].

As we have previously argued, we must not be attracted by mere novelty and the convenience of the new technology. Innovation does not necessarily mean progress. Although various approaches to partial breast irradiation have already been widely adopted, particularly in the USA (Harris J, personal communication), we feel that this uncritical enthusiasm is premature. However, there are already some encouraging data [58].

Randomised clinical trials are essential to test what is still an unconventional approach. However, we believe that the future for local treatment of breast cancer is bright. The patient, the surgeon, and the radiation oncologist will be able to choose from several well-tested options. This may mean not just a wider availability of breast-conserving therapy for more patients with breast cancer but also that small incremental benefits from targeted and tailored treatment could further reduce morbidity, even enabling in the longer term a real reduction in mortality from this common disorder which in the UK accounts for about 30% of all female cancer.

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