

REVIEW ARTICLE

Techniques of tumour bed boost irradiation in breast conserving therapy: Current evidence and suggested guidelines

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Abstract

Breast conservation surgery followed by external beam radiotherapy to breast has become the standard of care in management of early carcinoma breast. A boost to the tumour bed after whole breast radiotherapy is employed in view of the pattern of tumour bed recurrences in the index quadrant and was particularly considered in patients with some adverse histopathological characteristics such as positive margins, extensive intraductal carcinoma (EIC), lymphovascular invasion (LVI), etc. There is however, now, a conclusive evidence of improvement in local control rates after a boost radiotherapy dose in patients even without such factors and for all age groups. The maximum absolute reduction of local recurrences by the addition of boost is especially seen in young premenopausal patients. At the same time, the addition of boost is associated with increased risk of worsening of cosmesis and no clear cut survival advantage. Radiological modalities such as fluoroscopy, ultrasound and CT scan have aided in accurate delineation of tumour bed with increasing efficacy. A widespread application of these techniques might ultimately translate into improved local control with minimal cosmetic deficit. The present article discusses the role of radiotherapy boost and the means to delineate and deliver the same, identify the high risk group, optimal technique and the doses and fractionations to be used. It also discusses the extent of adverse cosmetic outcome after boost delivery, means to minimise it and relevance of tumour bed in present day scenario of advanced radiotherapy delivery techniques like Intensity modulated radiation therapy (IMRT).

Breast conserving therapy (BCT) consisting of conserving surgery involving local excision of the lump with margin followed by whole breast external beam radiotherapy is the standard management for operable breast cancer. The success of this approach is based on level 1 evidence as per well conducted large randomised data comparing breast conserving surgery and local radiotherapy versus mastectomy [1–5]. Randomised trials have also conclusively proven the role of radiotherapy to the breast after conservative surgery, as the local recurrences were unacceptably high, when radiotherapy was omitted in patients undergoing surgery alone [2,4,6,7]. The conventional technique of radiotherapy after Breast conserving surgery (BCS) involves irradiation to the whole breast to a dose of 45 to 50 Gy followed by a tumour bed boost of 10–20 Gy. The concept of tumour bed boost originated from the observation that the vast majority of ipsilateral breast tumour recurrences arose in the vicinity of the original index lesion. At the same time, some authors argued that

the radiotherapy boost was not critical to achieve adequate local control, if the tumour resection margins were free of cancer [8]. The controversy regarding the role of tumour bed boost has now more or less been resolved by the European Organization for Research and Treatment for Cancer (EORTC) randomised trial, which demonstrated significantly improved local control with the addition of tumour bed boost irradiation in all age groups with greater absolute reduction of local recurrences in the younger cohort of patients [9–11]. Additional tumour bed boost however did result in worse cosmesis than patients who did not receive the boost [11,12]. Therefore, while a level I evidence favouring the administration of a boost does exist; this has to be tempered with the recognition of a possible worse cosmetic outcome [12], perhaps an equally important endpoint of the success of breast conserving therapy (BCT) programme. Other issues important from routine clinical practice point of view include the choice of optimal boost technique, target volume

delineation, total boost dose and the optimal methods of evaluation of cosmetic outcome. Other reviews in the literature have tended to focus on some of these aspects [13–15]. In this review, we present comprehensively the available evidence to address all of the above issues and suggest most optimal evidence based guidelines for the each of them.

Rationale for radiotherapy boost

Recurrence patterns

Role of radiotherapy after breast conserving surgery (BCS) has been well established following results of various randomised trials showing considerably higher local recurrence rates in patients who did not receive radiotherapy [2,4,6,7].

Ipsilateral breast tumour recurrence (IBTR) in the tumour bed and at margins has been found to be as high as 50–60% of all local recurrences in various studies [16–23]. The recurrence patterns in these studies clearly indicate high rates of local recurrences in the area close to primary tumour and index quadrant. In the NSABP-06 trial, at a follow-up of 25 years the cumulative incidence of IBTR was 39.3% in lumpectomy alone arm and 14.2% in patients who received postoperative radiotherapy [2]. Ninety five percent of these patients were found to develop IBTR at or close to the same quadrant as the index cancers [16]. In the EORTC boost vs. no boost trial [11], local recurrence was the first event in 5.9% of the patients in the standard-treatment group and 3.3% of those in the additional-radiation boost group. Forty seven percent of these local recurrences occurred in the primary tumour bed, 9% in the scar, and 29% outside the area of the original tumour, and 27% were diffuse throughout the breast at a median follow-up of 5.1 years.

The significantly higher number of patients developing recurrences within or close to index quadrant in National Surgical Adjuvant Breast Project (NSABP) trial can be suitably explained by the patient groups: total mastectomy, lumpectomy alone, and lumpectomy with post operative radiotherapy. While two thirds of the patient cohort did not receive any radiotherapy irrespective of nodal status, those receiving post lumpectomy radiotherapy did not receive any radiotherapy boost. In this trial, there was no significant difference among all three groups of patients in terms of overall survival, disease free survival and distant disease free survival. But the authors have reported a significant benefit in all these three parameters in node negative subgroup of patients, in total mastectomy and lumpectomy plus postoperative radiotherapy cohort of patients over patients who underwent lumpectomy alone [2]. A considerable

reduction in IBTR close to or within index quadrant in EORTC trial can be explained by postoperative radiotherapy in both the arms to a dose of 50 Gy to whole breast, which may be considered to be sufficient for most of microscopic subclinical disease not only in the index quadrant but also throughout the breast. This fact is clearly evident from the overall local recurrence rates in both the studies (27% in NSABP-06 and 5.4% in EORTC trial).

Another important conclusion made in NSABP-06 trial was that in 73% of patients who underwent lumpectomy alone developed adverse event within first 5 years, while in patients who received radiotherapy only one third of the patients had any event within first 5 years, i.e. radiotherapy not only decreases the incidence of events but also delays them.

Clinical basis

Irradiation of the breast forms an integral part of successful management in BCT protocols. Omission of radiotherapy after BCS resulted in significantly more incidence of locoregional relapse and a compromise in overall survival [1–4].

On the other hand, there were few studies which showed no difference in outcome when boost to the tumour bed was not employed [8]. This warranted testing in a randomized fashion and a few studies demonstrated an advantage of boost.

However, all these studies involved relatively small number of patients and though they elicited a statistically significant outcome, a large level I evidence was still needed to establish a clinical guideline. The landmark study, was the EORTC trial [9,11], which was initiated in 1989, closed accrual in 1996 and was powered to detect 5% improvement in 10 year survival with 90% probability in the two arms with endpoints being local control and time to event (disease free survival). A total of 5569 patients, with stage I and II cancers, after lumpectomy and axillary dissection, microscopically negative margins, received 50 Gy to the whole breast postoperatively. Patients were then randomly assigned to either receive no further local treatment (2657 patients) or an additional 16 Gy to the tumour bed (2661 patients). The boost was given to the tumour bed and a 1.5 cm margin, by either Co^{60} , 4–6 MV photons, electrons or interstitial brachytherapy. At 10 years, actuarial local recurrence rates for no boost arm were 10.2% and in the boost arm was 6.2% ($p < 0.0001$). This was the largest randomised study, which conclusively showed that an addition of radiotherapy boost to tumour bed does increase local control rates in all groups of patients though survival was not significantly affected. All randomised trials which have

shown benefit of role of radiotherapy boost are summarised in Table I.

Pathological basis

Although multicentricity has been regarded as hallmark of carcinoma breast, residual tumour foci have been shown in high density in 1–2 cm in around 20–25% of patients/histopathological specimens [30,31]. Still, multicentric foci (MCF) have been found in a large number of patients ranging from 43–79%, well beyond the reference tumour and index quadrant [30–32]. The results are summarised in Table II.

These pathological findings when correlated with clinical results of more than two-thirds of local recurrences being in the index quadrant indicate that probably, early local recurrences do not arise from microscopic MCF [32]. This hypotheses was further supported in various other studies too, which showed high rates of ipsilateral breast tumour recurrence, not only close to or in the index quadrant but also elsewhere [9,16–22]. Vicini et al [31] studied the pathology specimen which was microscopically examined and consisted of only the tumour bed and adjacent breast and at most index quadrant as it was conducted to find appropriate margins to tumour bed to define CTV for localised irradiation as practised in accelerated partial breast irradiation (APBI). So, it is possible that the MCF present in the remaining breast tissue might have been missed. Hence, very high percentage of microscopic foci within the index quadrant (55%) in this study might be misleading.

Pathological analyses in general indicate that microscopic MCF have been seen in the whole breast. Most pathologists believe that the local

recurrences are primarily due to the inherent biological property of carcinomas of breast rather than widespread multicentric microscopic deposits [14,30,32]. Hence an extra radiotherapy boost to the index quadrant has been suggested to achieve better local control and survival.

Delineation of tumour bed/boost volume

Accurate delineation of the target volume is of utmost importance while delivering tumour bed boost with external beam radiotherapy. Different institutions use different methods for delineation of the tumour bed. Clinical history and patients’ recollection of tumour position, clinical photographs, tattoos, surgical scar, mammography, surgical clips, ultrasonography, Computerized tomography (CT) scan and Magnetic resonance imaging (MRI) are the commonly utilized techniques. Many a times, a combination of one or more of these techniques is considered while delineating the tumour bed boost.

Amongst all the randomised trials assessing role of radiotherapy boost, surgical clips were used in all patients for assessing boost volume only in the Budapest trial. In other studies, the boost volumes were usually defined on clinical and surgical details. It was hypothesized that increasing differences between local failure rates in whole breast radiotherapy (WBRT) arm versus WBRT + boost arm in Lyon trial (4.5% vs. 3.6%) (24), EORTC trial (10.2% vs. 6.2%) [9,11] and Budapest trial (15.5% vs. 6.7%) [26,27] may well have been due to the different techniques of tumour bed delineation as the difference in boost doses between all these trials were not significantly different. Hence an accurate delineation of tumour bed is important as it may translate into improved local control rates.

Table I. Dose fractionations used in various prospective randomized studies of boost versus no boost.

Trial	Number of patients	EBRT (dose/ fraction)	Boost (dose/ fraction)	LR (%)	Median Follow-up (year)
Bartelink et al. [11]	2 657	46–50Gy/25 fr	–	10.2	10
	2 661	50 Gy/25 fr	16 Gy/8 fr	6.2	
Romestaing et al. [24]	503	47–50 Gy/20 fr	–	4.5	3.3
	521	50 Gy/20 fr	10 Gy/4 fr	3.6	
Teissier et al. [25]	327	48–50 Gy/25 fr	–	6.8	6.1
	337	50 Gy/25 fr	10 Gy/5 fr	4.3	
Polgar et al. [26,27]	103	49–50 Gy/25 fr	–	15.5	5.3
	104	50 Gy/25 fr	12–16Gy/3–8 fr	6.7	
Graham et al. [28]*	674	50 Gy/25 fr	–	NR	NR
	674	45 Gy/25 fr	–	NR	
Nagykalnai et al. [29]	55	50 Gy/25 fr	–	10.7	3.8
	56	50 Gy/25 fr	10 Gy HDR/20 Gy LDR	5.4	

*The results haven’t been reported as yet. Only early quality of life results have been reported.

EBRT: external beam radiation therapy; LR: local recurrence; fr: fractions; HDR: high dose rate; LDR: low dose rate; NR: not recorded.

Table II. Histopathological analysis for microscopic tumour foci.

Author	No. of pts/ Specimens	No MCF*	MCF in index quadrant/tumor bed	MCF elsewhere in ipsilateral breast
Holland et al. [29]	282	37%	20%	43%
Vicini et al. [30]	441	36%	55%	9%
Vaidya et al. [31]	30	37%	50%	13%

*MCF: Multicentric tumour foci; pts: patients; Tumor: tumour.

Clinically defined

In the institutions not having facilities to objectively define lumpectomy cavity, preoperative clinical description forms the basis of boost field definition. Patients' own recollection of tumour position, preoperative clinical photographs with tumour marked on skin, tattoos over tumour, mammographic findings and surgical notes have been put into use. These techniques are however subjective and sound to be quite vague in present scenario. While patients' own description can vary during the treatment itself, clinical photographs and tattoos may misguide the physician in post lumpectomy status, due to distortion of anatomy. Also, mammographic position of the tumour may not directly correlate with its position on skin, more so with deep seated tumours. Boost volumes defined by clinical description were found to be inadequate in almost 10–88% of cases [33] when compared with lumpectomy bed delineated by surgical clips.

Surgical scar

The surgical scar is most commonly used means to identify the tumour bed to determine the boost area. At many centres it is a policy to place the surgical scar at the epicentre of the tumour. This helps in delineation of the centre of the surgical cavity around which the margins are grown. The surgical scar could be of great help in centres where placement of scar is uniform and is based on institutional policy. Also at centres where other techniques like fluoroscopy or ultrasound guided tumour bed delineation is not feasible, surgical scar may play an important role. But, it has been observed that in most instances the lumpectomy scar is not necessarily directly related to the site of the tumour, mainly for cosmetic reasons. Tumour bed defined by surgical scar can not only lead to geographical miss leading to increased local failure rates but may also include tissues beyond the volume defined by clips causing poorer cosmesis [33,34].

Ultrasound (US) guided localisation

To further improve localisation of tumour bed, ultrasound has been used to delineate lumpectomy

cavity. On comparison, it was found that full extent of the lumpectomy cavity (dimensions as well as depth) was underestimated by clinical examination postoperatively in approximately 85–90% of patients [34]. Intraoperative clinical placement of needles for brachytherapy may also inadequately cover posterior extent of the lumpectomy cavity when visualized by intraoperative ultrasound [35]. The ultrasound images are highly compatible with radiotherapy planning systems; hence a proper dosimetric planning is also possible on these images [13].

On the other hand, it is thought that absorption of haematoma and seroma in the lumpectomy cavity postoperatively i.e. the natural healing process may obscure proper visualization of tumour bed. With present protocols advising chemotherapy postoperatively, in most of the patients, radiotherapy is delayed for significant duration. With increasing gap between surgery and radiotherapy planning and treatment, ultrasound may well underestimate the tumour bed and its margins [35,36].

Surgical clips

Since the advent of breast conserving surgery, the role of surgical clips, required number and accuracy for delineation of tumour bed for postoperative radiotherapy has been widely discussed. Surgical clips are usually placed at the time of wide excision lumpectomy and are generally placed at four corners and in the tumour bed. The placement of surgical clips and their number may vary according to institutional policy and experience. These clips are delineated by either fluoroscopy or CT scans to define the lumpectomy cavity for planning the volume for boost.

The clinically defined fields have shown inadequate coverage in 42–68% of patients when compared with position of clips [37,38]. The depth of lumpectomy cavity has been found to be most accurately assessed by surgical clips placed within tumour bed [38]. Also, increasing the margins to field in order to ensure coverage of lumpectomy cavity (3 cm) resulted in 25% breast tissues at low risk to be treated to an extra dose [38].

In a study comparing boost field defined by surgical clips and ultrasound, it was found that ultrasound significantly underestimates lumpectomy

cavity size and depth. After a median duration of 6–8 weeks, margins of lumpectomy were defined by ultrasound and compared with those defined by clips, fluoroscopically. The cavity defined by ultrasound varied significantly in all dimensions, transverse, longitudinal and depth. This variation was unpredictable and did not follow any fixed pattern [36].

With increasing gap between surgery and radiotherapy due to addition of chemotherapy issues like changes in the lumpectomy cavity and resultant clip displacement came into picture. To calculate the mean displacement of clips, Weed et al. compared images in CT scans done at an interval of 27 days. They found that there was a mean displacement of clips by 3 mm in all 3 co-ordinates which can be easily covered by a margin of 5 mm usually given for Clinical target volume (CTV) demarcation [39]. But by and large most studies have found that surgical clips and fluoroscopy are fairly accurate means of delineating tumour bed especially in centres where other advanced techniques are not feasible [34,36–38,40].

CT scan

CT scans alone or in combination with surgical clips have been found to be fairly accurate in determining the tumour bed. The chief advantages of CT scan include better visualization in early postoperative period and an obvious sparing of normal breast tissues at low risk seen as much as in 50% of cases [41,42].

The disadvantage of CT is its difficulty to distinguish glandular breast tissues from surrounding anatomy. Also, the images and cavity margins may vary with different window settings. For this purpose, CT scans have been aided with surgical clips.

Due to the hypothesized poorer images it was thought that ultrasound has a greater accuracy in defining boost fields as well as depth of prescription [35]. But, a random comparison of lumpectomy cavity delineated for electron boost planning by CT and US showed nearly identical dimensions and margins with both the techniques. The study showed that CT alone can be equally useful in defining lumpectomy cavity if the CT scans are done within 31–60 days post-operatively [43].

Surgical clips within the cavity, delineated by CT scans to define the tumour bed have increased the accuracy of field definition [13,44]. The role of surgical clips have been emphasized to an extent that in a retrospective analysis it was found that local control was significantly higher in patients in whom the boost field was defined by clips and CT simulator than when done clinically (97% vs. 88%) when total radiotherapy dose was similar in both the

groups. In these patients, 75% of the local recurrences were within clinically defined field margins indicating geographical miss in these patients [45].

MRI

While MRI provides excellent definition of breast and surrounding tissues along with accurate localisation of target volume and organs at risk, its widespread application is limited by limited resources, difficulty in scanning in treatment position as well as image distortion during co-registration with treatment planning systems [13]. MRI may be useful in delineating small cavities in dense breasts, or in large breasts and even in patients where a considerably long gap postoperatively has caused nearly complete absorption of lumpectomy cavity and seroma. This can be possible with MRI due to its capability to demarcate soft tissues in best possible manner.

In short, while CT based planning with surgical clips remains the most accurate method to delineate tumour bed, fluoroscopy with surgical clips is also a fairly acceptable method for delineating.

Various techniques of boost delineation have been summarised with their advantages and disadvantages (Table III).

Boost doses and fractionations

The earliest comment on the dose of radiotherapy boost dates back to 1985 when Arriagada et al. [46] published results of retrospective data of patients receiving radical breast radiotherapy (surgery contraindicated due to medical reasons or advanced stage). They commented that increasing cumulative doses to breast beyond a minimum of 15 Gy proportionately increases chances of local control. They have analysed that doses up to 80 Gy had been delivered with increasing response rates but, these high doses have to be tempered with possible late side effects and poorer cosmesis.

Radiotherapy doses to whole breast and boost doses have been discussed and investigated at length. Doses to a total of 60–65 Gy i.e. 45–50 Gy to whole breast and a boost of 15–20 Gy have shown significant improvements in local control rates with acceptable toxicities [7,14,26,28]. Though the evidences are weak from retrospective analyses, doses beyond 65 Gy have shown to further improve local control rates but these are to be tempered with higher incidence of complications. Hence, in the present era of 3-D conformal radiotherapy allowing sparing of normal tissues to their maximum, optimal doses to whole breast as well as tumour bed need to be investigated further.

Table III. Comparison of various techniques of boost delineation.

Technique	Advantages	Disadvantages
Surgical Scar	<ol style="list-style-type: none"> 1. Feasible. 2. No additional costs. 3. Non invasive. 	<ol style="list-style-type: none"> 1. Depends on placement of scar. 2. Highly subjective.
Clips & Fluoroscopy	<ol style="list-style-type: none"> 1. Feasible. 2. Inexpensive. 	<ol style="list-style-type: none"> 1. Mobility of clips in the lumpectomy cavity. 2. Variable position and numbers.
Ultrasonography	<ol style="list-style-type: none"> 1. Can be used intra as well as post-operatively. 2. Images are compatible with RT planning systems. 3. Is relatively inexpensive. 4. Non-invasive. 5. Reproducible images. 6. Tumour bed is directly visualised. 	<ol style="list-style-type: none"> 1. Ineffective for identifying tumour bed. 2. Definition hampered by healing process. 3. Poor definition 6–8 weeks post-operatively.
Clips & Computerised Tomography	<ol style="list-style-type: none"> 1. Accuracy same as that of clips and fluoroscopy. 2. Can be planned in treatment position. 3. Excellent definition of breast tissues. 	<ol style="list-style-type: none"> 1. Glandular tissues not well defined. 2. Clips necessary for definition. 3. Varies with window settings.
Magnetic resonance imaging	<ol style="list-style-type: none"> 1. Accurate localisation of target volume. 2. Accurate localisation of organs at risk. 	<ol style="list-style-type: none"> 1. Costly, limited resources. 2. Image distortion during co- registration with TPS. 3. Difficulty in scanning in treatment position.

Boost treatment has been delivered in various fractionation schedules ranging from 2–4 Gy/fraction (Table I). The dose fractionation most commonly used for electron boosts were 2–2.5 Gy per fraction with little difference in overall outcomes in terms of local control. Also, there is no evidence of difference in cosmetic outcome of patients receiving varying fractionations. A head to head comparison of boost fractionation schedules has not been done in a single study, hence an ideal fractionation schedule cannot be yet commented upon.

A few centres also practice concomitant boost to tumour bed with electrons along with external radiotherapy. The patients received WBRT for 5 days a week and electron boost on sixth day, usually on a Saturday. This schedule may well be potentially attractive in countries with limited resources to save time [47].

Hypofractionated regimens are also being investigated mainly for whole breast radiotherapy. Widespread application of these schedules is still not practiced in view of insufficient data addressing long-term complication rates [8,48,49].

Identification of patients with high risk for local recurrence

The effect of boost in preventing local recurrence and cosmesis has generated a discussion regarding the selection of the appropriate patient population who would benefit most by tumour bed boost. Also, in the EORTC trial, absolute risk reduction per age group at 10 years was 23.9% to 13.5% ($p = 0.0014$) in <40 year and from 7.3% to 3.8% in >60 year old ($p = 0.0008$) [11].

This emphasizes the fact that probably radiotherapy boost to tumour bed may turn out to be over treatment in some patients. Hence, demarcating the group of patients at a higher risk of local recurrence and appropriately advising radiotherapy boost may prove to be a practical approach. Most of the selection criteria are based on patient and tumour related factors which have shown consistent association with increased risk of local recurrence. While some of these factors are still investigational, many have been proved to have poor prognostic values by means of various retrospective and prospective study analyses.

Patient related factors

Younger patients i.e. age less than 40 years have been found to have higher incidence of recurrence than their older counterparts in various retrospective studies. Also, tumours in young age patients have been found to be associated with other negative prognostic factors that is negative receptor status causing further worsening of prognosis [20,50–59]. In the EORTC and Budapest trials, age was found to be a significant prognostic factor. They have also said that maximum benefit in terms of tumour regression is seen in younger patients probably due to inherent radiobiology of these tumours [9,26,27]. In some studies, after univariate analysis age was found to be significant factor affecting prognosis but in multivariate analysis it was not found to be significant factor [60,61]. Neuschatz et al. have prospectively studied margin directed dose escalation and have concluded that even an escalation of dose does not

fully overcome the influence of age thus signifying age as an independent prognostic factor [62].

In pooled results of two European randomised trials [63] comparing mastectomy and BCT, age was found to be a significant factor affecting local control in patients undergoing breast conservation but not in patients undergoing mastectomy. Similar results have been found in another randomised trial with a mean follow-up of more than 25 years [6]. Though many hypotheses have been laid to explain this event, exact mechanism for the same hasn't yet been found.

Menopausal status of the patient has been combined with age when documenting its importance in assessing prognosis of patients. Premenopausal patients have been shown to have poorer prognosis in terms of local control [50].

Pathological prognostic factors

Positive margin status. Positive margin status i.e. tumour emboli present at cut margins has been quoted to cause increased incidence of local recurrence in nearly all the studies. Various authors have coined terms like close, focally positive and gross positive margins and have shown consistent correlation with increased incidence of local recurrences [50,52–58,64,65]. Schnitt et al. [64] have shown that close (<1 mm), focally positive, and more than focally positive margins are not only associated with significantly increased risk of local recurrence but also nodal as well as distant metastases.

To overcome the adverse effects of positive margins on overall outcome of the patients many radiation oncologists have escalated the boost dose to increase total dose to tumour bed [14,56,58,60]. Although in all these studies, patients with positive margins underwent re-excision or revision surgery, the boost doses to tumour bed were escalated to 20 Gy. All these studies showed comparable local control rates in all patient subgroups i.e. patients with positive, focally positive and negative margins. Neuschatz et al. have found that in patients with positive margin status though the control rates in first 5 years were comparable with escalated boost doses; there were increased incidences of local recurrences later in these patients [62].

Extensive intraductal component. Extensive intraductal component (EIC) is considered to be present when at least 25% of the tumour mass comprises intraductal carcinoma, and in situ cancer is also present in the surrounding tissue. Various studies have demonstrated EIC to be associated with a higher rate of positive margins, a greater frequency of residual cancer on re-excision specimens, and more extensive residual intraductal disease in mastectomy

specimens [14,27,50,52,62]. It was not found to be significant independent factor for local recurrence in few studies [60].

Polgar et al. [26,27], have also shown EIC to be associated with increased risk of recurrence and have correlated this with higher residual tumour outside reference tumour in these patients.

Lymphovascular invasion (LVI). Lymphovascular invasion in histopathological specimens has shown to have increased local failures [26,50,52,53,59,61,62,64]. But, at the same time it was not seen to be related with significantly increased risk of LR in few studies [48,53]. *Poorly differentiated tumours* with high histological grade, *lobular carcinomas* and proportion of *in situ component* have been correlated with poor local control rates. [11,58,60,64,65,67].

Estrogen receptor positivity. Estrogen receptor positivity has been well established as a good prognostic factor as these patients respond well to hormonal therapy [50,60].

While, most of the studies and reviews have quoted tumour size as an insignificant independent prognostic factor [29,35,37,42,44]; involvement of lymph nodes has been associated with increased local failures as well as earlier distant metastases [60,64,65].

In a retrospective analysis assessing risk factors in early breast cancer patients over a period of 25 years [6], it was found that four factors that strongly correlated with risk of death were tumour size, histologic grade, the number of involved axillary lymph nodes, and age at diagnosis. But, after 10–15 years of follow-up only age at diagnosis affected survival.

Treatment related factors

Total radiation dose to affected breast and tumour bed is proportionately related to relapse free survival [40,41,56,61]. Other factors which significantly influence disease free survival are administration of chemotherapy and hormonal therapy.

To summarise, age at diagnosis remains the most important prognostic factor determining long-term local control and survival. Other factors determining prognosis are margin status, EIC, LVI, histological grade, receptor status, number of involved axillary lymph nodes and total dose of radiotherapy delivered.

Radiotherapy boost in ductal carcinoma in situ (DCIS)

This has been a controversial issue, but recent retrospective analyses have shown that post excision radiotherapy with an electron boost definitely

improves relapse free survival [66–68]. It has been suggested that patients not having any negative prognostic factors viz. young age and positive margin status can be exempted from radiotherapy boost. However, to generate a hypotheses regarding management of these tumours, it is essential to conduct randomised trial to study the recurrence patterns.

Techniques of radiotherapy boost delivery

Various techniques of tumour bed boost delivery have been extensively studied and their efficacy has been compared retrospectively as well as prospectively. The techniques most commonly used are electrons, photons (less commonly used) and interstitial brachytherapy (High dose rate-HDR and low dose rate-LDR).

Electrons

With most of the centres now having linear accelerators, coronal en face electron beams have now become standard practice in most institutions. Minimal dose to underlying normal structures, i.e. lung and breast to the maximum, varying energy of electrons, feasibility of defining field on skin, an outpatient procedure with minimal patient discomfort make it a favourable option for both the patient as well as treating radiation oncologist. Most commonly used energies are 9–12 MeV, but as discussed earlier the boost fields defined on the basis of clinical details have been found to be erroneous in several studies. Hence, the dimensions as well as depth for tumour bed boost should be determined either by fluoroscopy or CT combined with surgical clips, or an ultrasound [33–35,41,42,69,70].

The most common prescription isodose for electron boost delivery is 90–95% isodose. But, in an organ such as breast with multiple edges and curvatures in different axes, the prescription isodose may not cover the whole target volume uniformly. This problem is commonly seen when tumours are located at areas where there is a sudden change in the depths like inframammary and axillary folds. The depths of soft tissue vary greatly in these areas and uniform energy electron beam may either underdose the tumour bed, or deliver higher dose to underlying normal structures. The electrons have limited role in patients with large breasts, tumours situated at a depth i.e. closer to heart (on left) and lungs and in folds. CT based planning in three dimensions may help to determine the dose distributions accurately and help in choosing the optimal energy.

The margins to be given to tumour bed for defining boost field have also been discussed. Harrington et al. [38], have shown that a boost field marked on the basis of clinical data and background with a margin of 2 cm all around covers radiological field with same margin in only 1/3rd (33%) of patients. Although Vicini et al. showed that a margin of 1 cm around the tumour covers microscopic disease adequately, in EORTC trial margins of 1.5 cm were given for microscopically completely excised tumours. Overall, a margin of 1.5–2 cm to the tumour bed has been reported to cover all subclinical disease in patients with clear microscopic margins [9,27,38].

Brachytherapy

Radiotherapy boost to tumour bed can also be delivered by interstitial brachytherapy i.e. interstitial placement of needles into tumour bed either intraoperatively or postoperatively. Intraoperative placement of needles is usually done under direct visualization of lumpectomy cavity, but ultrasound placement of needles has also been studied and has been found beneficial [9,13,69,70].

It was discussed in subset analysis of EORTC trial that the target volume for boost irradiation for electrons and photons was approximately 2–3 times that for brachytherapy boost. Although total duration of treatment was slightly longer for patients planned for brachytherapy boost, probably because of gap after completion of radiotherapy lent for healing of skin reactions etc local control rates was marginally better in the latter group of patients with nearly similar cosmesis [9].

Brachytherapy till recent times had a major limitation of hospitalization during the treatment, but with the advent of newer flexible plastic tubes, this limitation also seems to be overcome in near future.

Local control rates and disease free survival achieved by electrons and brachytherapy used for delivering tumour bed boost have been compared in many studies (Table IV). As is evident from the table the relapse rates for both the techniques are comparable with no significant differences amongst them.

Photons

Some of the institutions have reported tumour bed boost by 4–6 MV photons. The practice of delivering boost by photons has declined after widespread availability of electrons due to higher penetration and increased doses to underlying critical structures. Photons can be used in patients with small tumour bed as late term sequelae of electrons such as telangiectasia may not be acceptable to some patients treated with electrons.

Table IV. Comparison of electron beam and interstitial brachytherapy boost.

Author	Electron Beam			Brachytherapy		
	No. of pts.	10 yr DFS	IBTR	No. of pts.	10 yr DFS	LR*
Mansfield et al. [23]	416	78%	18%	654	76%	12%
Perez et al. [71]	490	79%	6%	129	80%	7%
Touboul et al. [72]	160	85%	15%	169	86%	8%
Bartelink et al. [9]	1 653	–	4.7%*	225	–	2.5%#
Polgar et al. [27]	52	94%#	–	52	91.4%*	–

*LR: local (ipsilateral breast) recurrence; #5 year survival.

DFS: Disease free survival; IBTR: Ipsilateral breast tumour recurrence.

Newer techniques

Modern radiotherapeutic techniques such as intensity modulated radiotherapy (IMRT) are being explored as a means to deliver whole breast irradiation, including boost. While IMRT as a means for delivering whole breast irradiation including the boost is not a standard treatment as yet, it is nevertheless being considered in some situations such as patients with large breast and delivering cardiac safe irradiation, particularly in left sided breast cancers. For tumour bed boost only, IMRT may not hold a great deal of advantage over conventional techniques as has been demonstrated in planning dosimetric studies [73]. However, IMRT due to its unique ability to deliver a simultaneous integrated boost (SIB) may be considered for whole breast and tumour bed boost [74].

Some of the fundamental issues pertaining to IMRT of the breast in general and boost in particular include patient positioning, accurate target volume delineation, interfraction and intrafraction motion, dose constraints to critical structures such as heart and lung, dose calculation at the interfaces etc.

Positioning and day to day reproducibility is one of the major issues in breast irradiation and is especially true for women with large breast. In general, there has not been much gain with immobilization devices for breast irradiation and could especially pose a problem for techniques like IMRT with a relatively rapid fall off of the doses [75,76].

One of the ways to decrease the movement of the chest wall with respiration, exclude the heart and lung, reduce the chest wall volume and reduce the desquamation in the inframammary fold in women with large breasts is treatment in the prone position [77]. Tumour bed irradiation as a part of APBI has been also shown to be feasible in prone position by the same group [75,78–80].

Intrafraction and interfraction motion is another much studied topic in these type of techniques [81,82]. Although a lot of emphasis is being given on the intrafraction motion as can be seen from the development on the gating, it is the interfractional

motion that is responsible for a majority of the errors [83] Use of gated CT scan for radiation planning and use of respiratory gating for the treatment could reduce the intrafractional errors associated with the treatment [84].

Most of the planning systems currently still use pencil beam algorithm, which has its limitations in the accuracy especially at interfaces like lung where small changes can lead to very large variations. Kernel based convolution superposition algorithm is more accurate in areas like tangents for the breast where there is lung as well as air interface. However such algorithm is relatively slow and not incorporated in many planning systems. While Monte Carlo calculations may be considered in such situations, their use is wrought with complexities and time constraints for practical use and therefore very seldom used in clinical practice.

One of the concerns with IMRT is also higher leakage radiation and higher monitor units which could possibly increase the risk of second cancers. In breast cancer particularly, beams directing on the isocenter from all sides could well significantly increase the whole body dose and possibly increase the chances of second neoplasm including cancers in the contralateral breast. The Early breast cancer trialist cooperative group (EBCTCG) meta-analysis comprising of 42 000 women from 78 randomised trials showed increased in the contralateral breast cancer by 1.18 (p=0.002), increase in the lung cancer by 1.61 (p=0.0007) and overall there was significant increase in the risk of second primary cancer [85]. Almost all patients in these trials have received radiation with bitangential portals. However if the beams are placed from all the sides during IMRT (even if for the boost volume) this could possibly increase the risk of all these cancers. In addition it may also lead to higher circulatory disorders. Therefore inverse planned IMRT though has shown good dosimetric outcome is not advisable and should be considered only for complex cases where internal mammary chain irradiation is indicated or in patients with complex thoracic contours

[86]. In such a scenario, a relatively simpler technique of forward planned IMRT, where multiple small segments of bitangential portals are used to compensate for the high dose region resulting in homogenous dose distribution. These multiple bitangential fields can be fused together to form a continuous MLC motion and is increasingly becoming popular for whole breast IMRT [87].

The long-term results of these techniques in terms of local control and cosmesis along with logistics including cost benefit analysis are needed to put these techniques into routine clinical practice [88].

One of the important trials in this regard would be IMPORT high trial which is one of the proposed randomized trials comparing standard tangential portals vs. IMRT for women with breast cancer treated with IMRT. The study arm in the trial involves delivery of radiation with forward planned IMRT portals in which the entire breast will be delineated into three groups: low dose breast volume, standard dose breast volume and tumour bed. The low dose breast volume would receive 36 Gy in 15 fractions, standard risk breast volume would receive 40 Gy in 15 fractions and the tumour bed would receive 48 Gy or 53 Gy with simultaneous integrated boost technique [74].

The primary end point in this trial is palpable induration while the secondary end point is late effect on normal tissue, local, regional and distant control.

Effect of tumour bed boost on cosmesis

External beam radiotherapy boost to tumour bed has conventionally been thought to worsen the cosmesis. In the EORTC trial cosmesis was found to be significantly affected at a median follow-up of 10 years in patients who received radiotherapy boost [10,11], whereas in the Budapest trial cosmesis was affected but the difference in two arms was not significant [14,27]. Some studies have shown that a larger dose per fraction or a concomitant electron boost causes worsening of cosmesis [30] but at the same time few others have denied the same [11,26,27].

It has also been shown that increasing inhomogeneities throughout the breast as well as boost volume also affects cosmesis adversely. Thus achieving a good homogenous distribution with newer techniques viz. IMRT may marginally improve the cosmesis [89]. Larger breasts, where cosmesis is known to be poorer, these techniques might help in avoiding hot as well as cold spots in the target volume. No significant difference in cosmetic outcome of patients receiving brachytherapy by various techniques such as electrons and tumour bed boost has been established. Though overall cosmesis rating

was same in both the groups in most of the comparative studies telangiectasiae were more common in brachytherapy group [10,90,91].

Although Touboul et al. have found significantly poorer cosmesis in patients who received a brachytherapy boost; they have suggested it to be due to a combination of several factors. The patients in the brachytherapy group were mostly treated with Co⁶⁰ (others were treated with 4–6 MV photons) and a higher percentage of these patients underwent axillary dissection [72].

The other factors which affect cosmesis adversely are administration of chemotherapy and axillary dissection [91].

Discussion and suggested guidelines

Radiotherapy boost to tumour bed along with WBRT after BCS has been shown to have improved local control rates in various randomised studies, EORTC trial being the largest and most important of them [9,11,24–28]. The patient population who would benefit most and should be compulsorily advised boost is yet to be defined. Yet, younger patients [9,26,27,48–57] with close or positive margins [49,53–56,58], extensive intraductal components (EIC) [27,48,50,52], lymphovascular invasion [27,51–54,60,63,64], axillary node positivity [59] and negative hormonal receptors [51,61] are definitely the candidates who should receive the boost.

Still, radiotherapy schedules and doses in treatment of carcinoma breast are in evolution. The recent evidences discussing role of hypofractionation in breast radiotherapy have further added to the spectrum of our knowledge [8,48,49]. The randomised trial by Whelan et al. [8], have shown similar local control rates in patients who received post-operative radiotherapy with conventional fractionation (50 Gy in 25 fractions), and those who received hypofractionated radiotherapy (42.5 Gy in 16 fractions). The local recurrence rates at 5 years were 3.2% and 2.8% respectively in both the arms. The recurrence rate in conventional fractionation arm in this study was quite lower when compared to similar treatment group in EORTC trial (7.3%). Although head on comparisons may not be possible, this difference can be suitably explained by patient selection. While Whelan et al. included only node negative patients, Bartelink et al. included patients with negative (78%), positive (21%) and unknown (1%) axillary nodal status. The cosmetic results of both the arms were similar, though it was lower when compared to results of EORTC trial in similar treatment groups (86% vs. 76.8%). Another randomised study by Owen et al. with a median follow-up of 9.7 years, compared various fractionation

schedules (50 Gy in 25 fractions, 39 Gy in 13 fractions and 42.9 Gy in 13 fractions) with similar local control rates even though the effect on cosmesis was adverse [48,49]. Approximately 75% of the patients in this trial received boost to tumour bed with conventional fractionation. Still, the long-term effects of larger doses per fraction on breast tissue in large breasts, brachial plexus (neural tissue), heart and lung have to be further investigated and only then these schedules can be incorporated into routine clinical practice.

Accurate delineation of boost field is important not only to cover the subclinical disease effectively, but also to treat the minimal possible volume thus avoiding adverse cosmetic events. While ultrasound seems to be the best option for both intra and post operative brachytherapy boost [13,34,35], surgical clips in the tumour bed (4–5: at corners and depth) guided by CT scans have proved to be best for electron boost field delineation [12,49]. The placement of clips, their position and number should be standardised to further help in setting up guidelines for adding margins to the clips. Newer modalities such as ultrasound and CT scan have an advantage in terms of proper coverage of cavity with direct visualization and sparing of normal breast tissues with easy and cheap availability of resources. MRI, though can have better delineation of tissues, its use is limited in daily practice due to costly resources and time consuming procedures.

Various dose fractionation schedules have been utilized for boost treatment and 2–2.5 Gy per fraction seems to be most acceptable fractionation schedule in terms of local control as well as late effects on cosmesis [25–27,91]. The role of concomitant boost is still investigational and its wide-spread applicability can be advocated only after its effects on cosmesis are defined [47].

Boost dose can be delivered by photons, electrons or brachytherapy. All these techniques have been

found to be equally beneficial in terms of local control. The use of photons has now decreased due to higher doses to underlying structures. Both electrons and brachytherapy not only deliver desired dose to tumour bed, they have similar effects on cosmesis. The role of IMRT with conformal boost are still under investigation, though initial results have shown little benefit over other techniques [44,73,89].

It has been proved that an additional radiotherapy dose in form of boost does cause worsening of cosmesis. But a statistically significant difference in cosmesis has been found only in few studies [11], while others have shown trend towards worsening [26,27]. Hence, not only the patients who ought to receive boost should be selected carefully, boost volumes should also be delineated with caution. A larger volume than needed is bound to cause poorer cosmesis. Though electrons and brachytherapy cause similar changes in cosmesis, telangiectasiae have been reported to be more common in patients who received brachytherapy [11,12]. With newer techniques like 3-D brachytherapy planning to remove these side effects will decrease due to better definition of dose to skin and subcutaneous tissues.

The guidelines for various aspects of boost treatment and levels of evidence to justify them are summarised in Table V.

Conclusions

From the above discussion, it can be concluded that an additional radiotherapy boost to tumour bed after BCS is effective in improving local control rates and subsequently disease free survival. Identification of group of patients who would benefit most by radiotherapy is also important so as to avoid unnecessary extra radiotherapy dose to patients with low risk of local recurrence. The localisation of tumour bed is an important issue, and while surgical clips delineated by fluoroscopy are fairly good and cost

Table V. Controversies and suggested guidelines in tumour bed boost in breast cancer.

Controversy	Suggested Guidelines	Level of Evidence
To boost or not to boost	To give boost to all patients; maximum absolute risk in younger patients	I
Boost dose	15–20 Gy	I
Positive margins	Boost dose escalation.	III
Boost fractionation	Electrons: 2–2.5 Gy per fraction HDR: 3–4 Gy per fraction	III
Concomitant/Simultaneous integrated boost	Investigational	III
Technique of Boost delivery	Electrons or brachytherapy	I
Boost delineation	Electrons – CT with surgical clips Brachytherapy – Ultrasound	III
Margins to tumour bed	Electrons – 1–2 cm High dose rate brachytherapy – 1 cm	III

effective means to delineate lumpectomy cavity, surgical clips combined with CT scan should prove to be an ideal method based on various quantitative and qualitative analyses. The technique used for delivery of radiotherapy boost whether it is by means of photons, electrons and brachytherapy have similar local control rates as well as similar effects on cosmesis. Hence an accurate delivery of radiotherapy boost to tumour bed to ideal candidates can ensure better local control with acceptable toxicities.

References

- [1] Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A metaanalysis. *J Clin Oncol* 2000;18:1220–9.
- [2] Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty five years of follow-up of a randomized trial comparing Total Mastectomy, lumpectomy and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Eng J Med* 2002;347:1233–41.
- [3] Liljegren G, Holmberg L, Bergh J, Lindgren A, Tabar L, Nordgren H, et al. 10-year results after sector resection with or without postoperative radiotherapy for Stage I breast cancer: A randomized trial. *J Clin Oncol* 1999;17:2326–33.
- [4] Forrest AP, Stewart HJ, Everington D, Prescott RJ, McArdle CS, Hammett AN, et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish Trial. *Lancet* 1996;348:708–13.
- [5] Early Breast Cancer Trialists' Collaborative Group. Radiotherapy for early breast cancer. *Cochrane Database Syst Rev* 2002;2:CD003647.
- [6] Arriagada R, Le MG, Dunant A, Tubiana M, Contesso G. Twenty-five years of follow-up in patients with operable breast carcinoma. Correlation between clinicopathologic factors and the risk of death in each 5 year period. *Cancer* 2006;106:743–9.
- [7] Arriagada R, Le MG, Guinebretiere JM, Dunant A, Rochard F, Tursz T. Late local recurrences in a randomized trial comparing conservative treatment with total mastectomy in early breast cancer patients. *Ann Oncol* 2003;14:1617–22.
- [8] Whelan T, MacKenzie R, Julian J, Levine M, Shelley W, Grimard L, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002;94:1143–50.
- [9] Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, Barillot I, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Eng J Med* 2001;345:1378–87.
- [10] Collette L, Fourquet A, Horiot JC, et al. Impact of boost dose of 16 Gy on local control in patients with early breast cancer: The EORTC "Boost versus no boost" trial. *Radiother Oncol* 2000;56(Suppl. 1):46 (Abstract).
- [11] Bartelink H, Horiot JC, Poortmans P, Struikmans H, Bogaert WV, Barillot I, et al. Impact of radiation dose on local control, fibrosis and survival after breast conserving treatment: 10 years results of the EORTC Trial 22881–10882. San Antonio Conference, 2006 (Abstract).
- [12] Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JC, Jager JJ, et al. The influence of the boost in breast-conserving therapy on cosmetic outcome in the EORTC "boost versus no boost" trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. European Organization for Research and Treatment of Cancer. *Int J Radiat Oncol Biol Phys* 1999;45:677–85.
- [13] Coles CE, Moody AM, Wilson CB, Burnet NG. Reduction of radiotherapy-induced late complications in early breast cancer: The role of intensity-modulated radiation therapy and partial breast irradiation. *Clin Oncol* 2005;17:98–110.
- [14] Polgar C, Fodor J, Major T, Orosz Z, Nemeth G. The role of boost irradiation in the conservative treatment of Stage I–II breast cancer. *Pathol Oncol Res* 2001;7:241–50.
- [15] Graham P, Fourquet A. Placing the boost in breast-conservation radiotherapy: A review of the role, indications and techniques for breast-boost radiotherapy. *Clin Oncol (R Coll Radiol)* 2006;18:210–9.
- [16] Fisher ER, Fisher ER, Anderson S, et al. Ipsilateral breast tumour recurrence and survival following lumpectomy and irradiation: Pathological findings from NSABP protocol B-06. *Semin Surg Oncol* 1992;8:161–6.
- [17] Schmidt-Ullrich R, Wazer DE, Tercilla O, Safaii H, Merchant DJ, Smith TJ, et al. Tumor margin assessment as a guide to optimal conservation surgery and irradiation in early stage breast carcinoma. *Int J Radiat Oncol Biol Phys* 1989;17:733–8.
- [18] Kim KJ, Huh SJ, Yang JH, Park W, Nam SJ, Kim JH, et al. Treatment results and prognostic factors of early breast cancer treated with a breast conserving operation and radiotherapy. *Jpn J Clin Oncol* 2005;35:126–33.
- [19] Pass H, Vicini FA, Kestin LL, Goldstein NS, Decker D, Pettinga J, et al. Changes in management techniques and patterns of disease recurrence over time in patients with breast carcinoma treated with breast-conserving therapy at a single institution. *Cancer* 2004;101:713–20.
- [20] Fodor J, Mozsa E, Zaka Z, Polgar C, Major T. Local relapse in young (< or =40 years) women with breast cancer after mastectomy or breast conserving surgery: 15-year results. *Magy Onkol* 2005;49:203:205–8.
- [21] Touboul E, Buffat L, Belkac Y, Lefranc JP, Uzan S, Lhuillier P, et al. Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer. *Int J Radiat Oncol Biol Phys* 1999;43:25–38.
- [22] Truong PT, Bernstein V, Lesperance M, Speers CH, Olivetto IA. Radiotherapy omission after breast-conserving surgery is associated with reduced breast cancer-specific survival in elderly women with breast cancer. *Am J Surg* 2006;191:749–55.
- [23] Mansfield CM, Komarnicky LT, Schwartz GF, Rosenberg AL, Krishnan L, Jewell WR, et al. Ten-year results in 1070 patients with stages I and II breast cancer treated by conservative surgery and radiation therapy. *Cancer* 1995;75:2328–36.
- [24] Romestaing P, Lehingue Y, Carrie C, Coquard R, Monbarbon X, Ardiet JM, 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* 1997;15:963–8.
- [25] Teissier E, Henry M, Ramaoli A, et al. Boost in conservative treatment: 6 year results of randomized trial. *Breast Cancer Res Treat* 1998;50:345.
- [26] Polgar C, Major T, Fodor J, Nemeth G, Orosz Z, Sulyok Z, et al. High-dose-rate brachytherapy alone versus whole breast radiotherapy with or without tumor bed boost after breast-conserving surgery: Seven-year results of a comparative study. *Int J Radiat Oncol Biol Phys* 2004;60:1173–81.
- [27] Polgar C, Orosz Z, Fodor J, Major T, Mangel L, Takacsi-Nagy Z, et al. The effect of tumour bed boost on local control after breast conserving surgery. First results of the randomized boost trial of the National Institute of Oncology. *Magy Onkol* 2001;45:385–91.

- [28] Graham P, Capp A, Fox C, Nasser E, Delaney G, Ahem V, et al. Why a breast boost should remain a controversial aspect of routine breast conservation management in Australia and New Zealand in 2002. *Australas Radiol* 2003;47:44–9.
- [29] Nagykalnai T, Nemeskeri CS, Mayer A, et al. Effectivity of boost radiotherapy on the local recurrence rate following breast conserving surgery plus whole breast irradiation. *Proceedings of the 2nd European Congress on Senology*: 1994. p 591–596.
- [30] Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer* 1985;56:979–90.
- [31] Vicini FA, Kestin LL, Goldstein NS. Defining the clinical target volume for patients with early-stage breast cancer treated with lumpectomy and accelerated partial breast irradiation: A pathologic analysis. *Int J Radiat Oncol Biol Phys* 2004;60:722–30.
- [32] Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mitra I. Multicentricity of breast cancer: Whole-organ analysis and clinical implications. *Br J Cancer* 1996;74:820–4.
- [33] Machtay M, Lanciano R, Hoffman J, Hanks GE. Inaccuracies in using the lumpectomy scar for planning electron boosts in primary breast carcinoma. *Int J Radiat Oncol Biol Phys* 1994;30:43–8.
- [34] Kovner F, Agay R, Merimsky O, Stadler J, Klausner J, Inbar M. Clips and scar as the guidelines for breast radiation boost after lumpectomy. *Eur J Surg Oncol* 1999;25:483–6.
- [35] Deboise DA, Horwitz EM, Martinez AA, Edmundson GK, Chen PY, Gustafson GS, et al. The use of ultrasonography in the localisation of lumpectomy cavity for interstitial brachytherapy of breast. *Int J Radiat Oncol Biol Phys* 1997;38:755–9.
- [36] Rabinovitch R, Finlayson C, Pan Z, Lewin J, Humphries S, Biffi W, et al. Radiographic evaluation of surgical clips is better than ultrasound for defining the lumpectomy cavity in breast boost treatment planning: A prospective clinical study. *Int J Radiat Oncol Biol Phys* 2000;47:313–7.
- [37] Denham JW, Hamilton CS, Cross P. Boost dosage to the excision site following conservative surgery for breast cancer: It's easy to miss! *Clin Oncol (R Coll Radiol)* 1991;3:257–61.
- [38] Harrington KJ, Harrison M, Bayle P, Evans K, Dunn PA, Lambert HE, et al. Surgical clips in planning the electron boost in breast cancer: A qualitative and quantitative evaluation. *Int J Radiat Oncol Biol Phys* 1996;34:579–84.
- [39] Weed DW, Yan D, Martinez AA, Vicini FA, Wilkinson TJ, Wong J, et al. The validity of surgical clips as a radiographic surrogate for lumpectomy cavity in image guided Accelerated Partial Breast Irradiation. *Int J Radiat Oncol Biol Phys* 2004;60:484–92.
- [40] Bedwinek J. Breast conserving surgery and irradiation: The importance of demarcating the excision cavity with surgical clips. *Int J Radiat Oncol Biol Phys* 1993;26:675–9.
- [41] Goldberg H, Prosnitz RG, Olson JA, Marks LB. Definition of postlumpectomy tumor bed for radiotherapy for radiotherapy boost field planning: CT versus surgical clips. *Int J Radiat Oncol Biol Phys* 2005;63:209–13.
- [42] Regine WF, Ayyangar KM, Komarnicky LT, Bhandare N, Mansfield CM. Computer-CT planning of the electron boost in definitive breast irradiation. *Int J Radiat Oncol Biol Phys* 1991;20:121–5.
- [43] Smitt MC, Birdwell RL, Goffinet DR. Breast electron boost planning: Comparison of CT and US. *Radiology* 2001;219:203–6.
- [44] Fein DA, Fowble BL, Hanlon AL, Hoffman JP, Sigurdson ER, Eisenberg BL. Does the placement of surgical clips within the excision cavity influence local control for patients treated with breast-conserving surgery and irradiation? *Int J Radiat Oncol Biol Phys* 1996;34:100–17.
- [45] Kokubo M, Mitsumori M, Yamamoto C, Fujishiro S, Mise K, Kodama H, et al. Impact of boost irradiation with surgically placed radiopaque clips on local control in breast-conserving therapy. *Breast Cancer* 2001;8:222–8.
- [46] Arriagada R, Mouriesse H, Sarrazin D, Clark RM, Deboer G. Radiotherapy alone in breast cancer. I. Analysis of tumor parameters, tumor dose and local control: The experience of the Gustave-Roussy Institute and the Princess Margaret Hospital. *Int J Radiat Oncol Biol Phys* 1985;11:1751–7.
- [47] Jalali R, Malde R, Sarin R, Budrukkar A, Badwe RA, Dinshaw KA. Concomitant weekly tumour bed boost with whole breast irradiation in patients with locally advanced breast cancer undergoing breast conservation therapy: A prospective study. *Eur J Cancer Suppl* 2005;3:112.
- [48] Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: Long-term results of a randomised trial. *Lancet Oncol* 2006;7:467–71.
- [49] Yarnold J, Ashton A, Bliss J, Homewood J, Harper C, Hanson J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: Long-term results of a randomised trial. *Radiother Oncol* 2005;75:9–17.
- [50] Fourquet A, Campana F, Zafrani B, Mosseri V, Vielh P, Durand JC, et al. Prognostic factors of breast recurrence in the conservative management of early breast cancer: A 25-year follow-up. *Int J Radiat Oncol Biol Phys* 1989;17:719–25.
- [51] Nixon AJ, Neuberger D, Hayes DF, Gelman R, Connolly JL, Schnitt S, et al. Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. *J Clin Oncol* 1994;12:888–94.
- [52] Kurtz JM. Which patients don't need a tumor-bed boost after whole-breast radiotherapy? *Strahlenther Onkol* 2001;177:33–6.
- [53] Kurtz JM. Recurrence in the conserved breast: Why all this fuss about risk factors? *Eur J Cancer* 1999;35:1752–4.
- [54] Kurtz JM. How to predict the risk of local relapse in the preserved breast: Recent results. *Cancer Res* 1996;140:263–72.
- [55] Rapiti E, Fioretta G, Verkooijen HM, Vlastos G, Schafer P, Sappino AP, et al. Survival of young and older breast cancer patients in Geneva from 1990 to 2001. *Eur J Cancer* 2005;41:1446–52.
- [56] Ryoo MC, Kagan AR, Wollin M, Tome MA, Rao AR, Hintz BL, et al. Prognostic factors for recurrence and cosmesis in 393 patients after radiation therapy for early mammary carcinoma. *Radiology* 1989;172:555–9.
- [57] Zafrani B, Vielh P, Fourquet A, Mosseri V, Durand JC, Salmon RJ, et al. Conservative treatment of early breast cancer: Prognostic value of the ductal in situ component and other pathological variables on local control and survival. Long-term results. *Eur J Cancer Clin Oncol* 1989;25:1645–50.
- [58] Cabioglu N, Hunt KK, Buchholz TA, Mirza N, Singletary SE, Kuerer HM, et al. Improving local control with breast-conserving therapy: A 27-year single-institution experience. *Cancer* 2005;104:20–9.
- [59] Dinshaw KA, Sarin R, Budrukkar AN, Shrivastava SK, Deshpande DD, Chinoy RF, et al. Safety and feasibility of breast conserving therapy in Indian women: Two

- decades of experience at Tata Memorial Hospital. *J Surg Oncol* 2006;94:105–13.
- [60] Sinn HP, Anton HW, Magener A, von Fournier D, Bastert G, Otto HF. Extensive and predominant in situ component in breast carcinoma: Their influence on treatment results after breast-conserving therapy. *Eur J Cancer* 1998;34:646–53.
- [61] Chu AM, Cope O, Russo R, Lew R. Patterns of local-regional recurrence and results in Stages I and II breast cancer treated by irradiation following limited surgery: An update. *Am J Clin Oncol* 1984;7:221–9.
- [62] Neuschatz CA, DiPetrillo T, Safaai H, Price LL, Schmidt-Ullrich, Wazer DE. Long-term follow-up of a prospective policy of margin-directed radiation dose escalation in breast-conserving therapy. *Cancer* 2003;97:30–9.
- [63] Voogd AC, Neilsen M, Peterse JL, Blichert-Toft M, Bartelink H, Overgaard M, et al. Differences in risk factors for local and distant recurrence after breast conserving therapy or mastectomy for Stage I and II breast cancer: Pooled results of two large European trials. *J Clin Oncol* 2001;19:1688–97.
- [64] Schnitt SJ, Abner A, Gelman R, Connolly JL, Recht A, Duda RB, 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* 1994;74:1660–1.
- [65] Solin LJ, Fowble BL, Schultz DJ, Goodman RL. The significance of the pathology margins of the tumor excision on the outcome of patients treated with definitive irradiation for early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1991;21:279–87.
- [66] Omlin A, Amichetti M, Azria D, Cole BF, Fournier P, Poortmans P, et al. Boost radiotherapy in young women with ductal carcinoma in situ: A multicentre, retrospective study of the Rare Cancer Network. *Lancet Oncol* 2006;7:652–6.
- [67] Yau TK, Chan K, Chan M, Lau HW, Soong IS, Cheung P, et al. Wide local excision and radiotherapy for the treatment of ductal carcinoma in situ of the breast: The Hong Kong experience. *Clin Oncol* 2006;18:447–52.
- [68] Vicini FA, Kestin LL, Goldstein S, Chen PY, Pettinga J, Frazier RC, et al. Impact of young age on outcome in patients with ductal carcinoma in situ treated with breast conserving therapy. *J Clin Oncol* 2000;18:296–306.
- [69] Haba Y, Britton P, Sinnatamby R, Sycamore CM, Wilson C. Can ultrasound improve the accuracy of delivery of electron boost treatment following breast conserving surgery? *Eur J Cancer* 2001;37:38 (Abstract).
- [70] Leonard C, Harlow CL, Coffin C, Drose J, Norton L, Kinzie J. Use of ultrasound to guide radiation boost planning following lumpectomy for carcinoma of the breast. *Int J Radiat Oncol Biol Phys* 1993;27:1193–7.
- [71] Perez CA, Taylor ME, Halverson K, Garcia D, Kuske RR, Lockett MA. Brachytherapy or electron beam boost in conservation therapy of carcinoma of the breast: A non-randomized comparison. *Int J Radiat Oncol Biol Phys* 1996;34:995–1007.
- [72] Touboul E, Belkacemi Y, Lefranc JP, Uzan S, Ozsahin M, Korbas D, et al. Early breast cancer: Influence of type of boost (electrons vs. iridium-192 implant) on local control and cosmesis after conservative surgery and radiation therapy. *Radiother Oncol* 1995;34:105–13.
- [73] Horton JK, Halle JS, Chang SX, Sartor CI. Comparison of three concomitant boost techniques for early stage breast cancer. *Int J Radiat Oncol Biol Phys* 2006;64:168–75.
- [74] Conway L, Tsang Y. A forward-planning solution for the IMPORT HIGH Breast IMRT Trial. *Clin Oncol* 2007;19:15.
- [75] Formenti SC, Truong MT, Goldberg JD, Mukhi V, Rosenstein B, Roses D, et al. Prone accelerated partial breast conserving surgery: preliminary clinical results and dose volume histogram analysis. *Int J Radiat Oncol Biol Phys* 2004;60:493–504.
- [76] Pradier O, Schmidberger H, Weiss E, Bouscayrol H, Daban A, Hess CF. Accuracy of alignment in breast irradiation: A retrospective analysis of clinical practice. *Br J Radiol* 1999;72:685–90.
- [77] Formenti SC. External beam partial breast irradiation. *Semin Radiat Oncol* 2005;15:92–9.
- [78] van Tienhoven G, Lanson JH, Crabeels D, Heukelom S, Mijnheer BJ. Accuracy in tangential breast treatment set-up: A portal imaging study. *Radiother Oncol* 1991;22:317–22.
- [79] Dobbs JH. Radiation therapy for breast cancer at the millennium. *Radiother Oncol* 2000;54:191–200.
- [80] Algan O, Fowble B, Mcneelay S, Fein D. Use of the prone position in radiation treatment for women with early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1998;40(5):1137–40.
- [81] Letts N, Remouchamps V, Martinez A, Vicini F, Wong J. Set-up inaccuracies in breast irradiation: A comparison of free breathing and Active Breathing Control (ABC) treatment using Electronic Portal Images (EPI). *Int J Radiat Oncol Biol Phys* 2003;57:S309.
- [82] Sarrut D, Boldea V, Ayadi M, Badel JN, Ginestet C, Clippe S, et al. Nonrigid registration method to assess reproducibility of breath-holding with ABC in lung cancer. *Int J Radiat Oncol Biol Phys* 2005;61:594–607.
- [83] Smith RP, Bloch P, Harris EE, McDonough J, Sarkar A, Kassae A, et al. Analysis of interfraction and intrafraction variation during tangential breast irradiation with an electronic portal imaging device. *Int J Radiat Oncol Biol Phys* 2005;62:373–8.
- [84] Berson AM, Emery R, Rodriguez L, Richards GM, Ng T, Sanghavi S, et al. Clinical experience using respiratory gated radiation therapy: Comparison of free-breathing and breath-hold techniques. *Int J Radiat Oncol Biol Phys* 2004;60:419–26.
- [85] Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15 years survival: An overview of the randomised trials. *Lancet* 2005;366(9503):2087–106.
- [86] Thilmanl C, Zabel A, Nill S, Rhein B, Hoess A, Haering P, et al. Intensity-modulated radiotherapy of the female breast. *Med Dosim* 2002;27:79–90.
- [87] Vicini FA, Sharpe M, Kestin L, Martinez A, Mitchell CK, Wallace MF, et al. Optimizing breast cancer treatment efficacy with intensity modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;54:1336–44.
- [88] Probst H, Griffiths S. Moving to a high-tech approach to the irradiation of early breast cancer: Is it possible to balance efficacy, morbidity and resource use? *Clin Oncol* 2006;18:268–75.
- [89] Ma CM, Ding M, Li JS. A comparative dosimetric study on tangential photon beams, intensity-modulated radiation therapy (IMRT) and modulated electron radiotherapy (MERT) for breast cancer treatment. *Phys Med Biol* 2003;48:909–24.
- [90] Vass S, Bairati I. A cosmetic evaluation of breast cancer treatment: A randomized study of radiotherapy boost technique. *Int J Radiat Oncol Biol Phys* 2005;62:1274–82.
- [91] Sarin R, Dinshaw KA, Shrivastava SK, Sharma V, Deore SM. Therapeutic factors influencing the cosmetic outcome and late complications in the conservative management of early breast cancer. *Int J Radiat Oncol Biol Phys* 1993;27:285–92.