Tumor bed boost radiotherapy in breast cancer

A review of current techniques

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ABSTRACT

يقوم هذا المقال بالمراجعة المنهجية للمؤلفات المتعلقة بتقنيات إعطاء الجرعة الإشعاعية المكثفة لموضع الورم بعد العلاج التحفظي للثدي ووضع المبادئ التوجيهية لكل منها بناءاً على الأدلة القائمة. تم أجراء البحث في قاعدة بيانات « مكتبة الطب الوطنية » (PubMed) للمواد المنشورة باللغة الإنجليزية من أول يناير 1990 حتى الآن. وتمت دراسة ومقارنة مختلف تقنيات إعطاء الجرعة الإشعاعية المكثفة لموضع الورم بعد العلاج التحفظي للثدي. لقد كانت التقنيات الأكثر استخداماً هي العلاج الإشعاعي الخارجي (EBRT) (الفوتونات أو الإلكترونات)، والعلاج الإشعاعي الداخلي بمعدل الجرعة العالية (HDR)، ولكن الدراسات التي أُجريت مؤخراً كشفت أيضاً عن استخدام تقنيات متقدمة للعلاج بالأشعة، مثل العلاج الإشعاعي متغير الشدة (IMRT)، والعلاج الإشعاعي أثناء العمليات الجراحية (IORT)، والعلاج الإشعاعي المقطعي (tomotherapy)، والبروتونات. تبين من هذا البحث أن تقنيات العلاج بالأشعة لسرطان الثدي قد شهدت تطوراً كبيراً خلال السنوات الماضية. ونحن نوصي بإجراء أبحاث لمقارنة تقنيات إعطاء الجرعة الإشعاعية المكثفة لموضع الورم بعد العلاج التحفظي للثدي من حيث النتائج طويلة الأجل، وموازنة التحكم الموضعي في الورم، والنتيجة الجمالية ضد الموارد اللوجستية بما في ذلك تحليل المنافع والتكاليف.

Various breast boost irradiation techniques were studied and compared. The most commonly used techniques are external beam radiation therapy (EBRT) (photons or electrons) and high dose rate (HDR) interstitial brachytherapy, but recent studies have also revealed the use of advanced radiotherapy techniques, such as intensity modulated radiation therapy (IMRT), intra-operative radiation therapy (IORT), tomotherapy, and protons. The purpose of this study is to systematically review the literature concerning breast boost radiotherapy techniques, and suggest evidence based guidelines for each. A search for literature was performed in the National Library of Medicine's (PubMed) database for English-language articles published from 1st January 1990 to 5th April 2011. The key words were "breast boost radiotherapy", "breast boost irradiation", and "breast boost irradiation AND techniques". Randomized trials comparing the long-term results of boost irradiation techniques, balancing the local control, and cosmesis against logistic resources, and including cost-benefit analysis are further needed.

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Breast conservative surgery is one of the standard options for treating breast cancer which requires local excision of the lump with adequate margin, followed by whole breast radiotherapy. The role of adjuvant radiotherapy to the breast after breast-conserving surgery (BCS) has been proven in large randomized trials comparing BCS and radiation therapy versus mastectomy.[1,2] A recent report of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) confirmed a 75% reduction in local recurrence risk after radiotherapy.[3]

Radiotherapy after BCS involves irradiation of the whole breast to a dose of 45-50 Gy, followed by a tumor bed boost of 10-20 Gy. The need for a tumor bed boost was based on the observation that the majority of ipsilateral breast tumor recurrences (IBTR) occurs in the vicinity of the initial lesion.[4] The benefit of tumor bed boost has been demonstrated by the European Organization for Research and Treatment of Cancer (EORTC) "boost versus no boost" randomized trial, which confirmed a significantly improved local control

among young patients (<50 years) who received a boost to the tumor bed of 16 Gy in 8 fractions.[5] Lately, this significant effect has also been shown in all age groups of patients, after longer follow-up.[6] However, the cosmetic results after a tumor bed boost proved to be worse, compared to the sole whole breast irradiation.[6,7] Therefore, while a level I evidence recommends the administration of a boost, a possible inferior cosmetic outcome needs to be considered, as an important endpoint of a successful BCT program.[7]

This study is a systematic review of literature, addressing treatment boost techniques, and suggesting evidence-based guidelines for each of them. The search for literature was performed using the National Library of Medicine's (PubMed) database for English-language articles published from 1st January 1990 to April 5th, 2011. The key words used were "breast boost radiotherapy", "breast boost irradiation", and "breast boost irradiation AND techniques". Further search was carried out by "related articles". Studies reported in the abstract form were not included in this review. The search results were 169 documents, of which 108 original articles, 48 reviews, 7 practice guidelines, and 6 editorials. Among all these documents, 42 were excluded, due to the lack of physics and/or technical details.

Rationale for tumor bed boost radiotherapy. Various randomized trials established the role of radiotherapy after breast-conserving surgery, showing significantly higher local control in patients receiving radiotherapy,[1,8] and recurrence in tumor bed or at its margins as high as 50-60% of all local recurrences.[9,10]

The National Surgical Adjuvant Breast Project (NSABP-06) trial, after a follow-up of 25 years, has demonstrated a cumulative incidence of IBTR of 39.3% in patients who underwent lumpectomy as sole treatment modality, and 14.2% in postoperative radiotherapy arm.[1] These results can be explained by the trial design: while two thirds of the patients did not receive any radiotherapy, those receiving post-lumpectomy radiotherapy did not receive any radiotherapy boost. This study has shown no significant difference regarding the overall survival, disease free survival, and distant disease free survival, but the authors have reported a significant benefit in all these 3 parameters in node negative subgroup of patients, in total mastectomy, and lumpectomy with postoperative radiotherapy subgroup of patients, compared to the patients who underwent lumpectomy alone.[1] The NSABP-06 trial also proved that 73% of patients who underwent sole lumpectomy developed adverse events within the first 5 years, while only 33% of patients who received radiotherapy had any adverse event within first 5 years, and concluded that radiotherapy not only decreased the incidence of events, but also delayed them.[4]

In the EORTC "boost versus no boost" trial, the first adverse event was IBTR, which occurred in 5.9% of the patients in the standard treatment arm and 3.3% of those in the additional radiation boost arm.[11] After a median follow-up of 5.1 years, among the local recurrences, 47% were in the primary tumor bed, 29% outside the area of initial tumor, 27% diffused throughout the breast, and 9% in the scar. Radiotherapy after BCS in both arms to a dose of 50 Gy to whole breast account for the significant decrease of IBTR within or close to the tumor bed; such dose is assumed to be adequate for subclinical disease control in the tumor bed and in the whole breast too, as noticed from the overall local recurrence rates in both NSABP-06 (27%) and EORTC (5.4%) trials.[4]

European Organization for Research and Treatment of Cancer trial,[11,12] included 5569 patients, with stage I and II, post-lumpectomy and axillary dissection, microscopically negative margins, who received postoperative radiotherapy to a dose of 50 Gy to the whole breast. Patients were then randomized to either receive no further radiotherapy (2657 patients), or an additional boost of 16 Gy to the tumor bed (2661 patients). The boost volume included the tumor bed and 1.5 cm additional margins, and the treatment was delivered using either Co-60, 4-6 MV photons, electrons or interstitial brachytherapy. At 10 years, actuarial local recurrence rate was 10.2% for the no boost arm and 6.2% for the boost arm (p<0.0001). This was the largest randomized trial, which definitely demonstrated that an additional radiotherapy boost to tumor bed increases local control rates in all groups of patients, although the survival was not significantly affected.[4] To date it is not the only randomized trial which have shown benefit of radiotherapy boost, as presented in **Table 1**.

It was commonly assumed that radiotherapy boost to tumor bed worsen breast cosmesis. In the EORTC trial, patients who received radiotherapy boost had significantly affected cosmesis at a median follow-up of 10 years,[11,13] while in the Budapest trial cosmesis was affected, but not significantly.[14,15] No significant difference in cosmetic outcome was observed for

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Table 1 - Prospective randomized trials of boost versus no boost.

Trial	Year	Number of patients	External beam radiation therapy dose	Boost dose	Boost modality	Median follow-up (year)	Local recurrence %
Nagykalnai et al[97]	1997	55	50 Gy/25 fr	-		3.8	10.7
		56	50 Gy/25 fr	10 - 20 Gy	HDR/LDR		5.4
Romestaing et al[98]	1997	503	47-50 Gy/20 fr	-		3.3	4.5
		521	50 Gy/20 fr	10 Gy/4 fr	EBRT		3.6
Teissier et al[99]	1998	327	48-50 Gy/25 fr	-		6.1	6.8
		337	50 Gy/25 fr	10 Gy/5 fr	EBRT		4.3
Bartelink et al[11]	2001	2657	46-50 Gy/25 fr	-		10	10.2
		2661	50 Gy/25 fr	16 Gy/8 fr	EBRT		6.2
Polgar et al[14,18]	2004	103	49-50 Gy/25 fr	-		5.3	15.5
		104	50 Gy/25 fr	12-16 Gy/3-8 fr	EBRT + HDR		6.7

EBRT - external beam radiation therapy, LR - local recurrence, fr - fractions, HDR - high dose rate, LDR - low dose rate

patients receiving brachytherapy boost compared to those receiving electrons beam boost; although overall cosmetic outcome was the same in both groups, telangiectasiae was more common in brachytherapy group, as shown in most of the comparative studies.[13,16] It was also reported that high dose gradients throughout the breast and boost volume affect cosmesis adversely; therefore, a homogenous dose distribution could potentially improve the cosmesis, especially in patients with large breasts, where cosmesis is known to be poor.[17] Axillary dissection and administration of chemotherapy are other factors known to unfavorably affect cosmesis.[16]

Various techniques of breast boost irradiation were studied and compared. The most commonly used techniques are external beam radiation therapy (EBRT) (photons or electrons) and high dose rate (HDR) interstitial brachytherapy, but recent studies have also revealed the use of advanced radiotherapy techniques, such as intensity modulated radiation therapy (IMRT), intra-operative radiation therapy (IORT), tomotherapy, and protons.

Definition of boost volume. If the modality to deliver breast boost radiotherapy is external beam or postoperative interstitial brachytherapy, the accurate delineation of the tumor bed volume is essential, as it may affect the local control. According to their resources and expertise, different institutions use different methods for delineation of the tumor bed. The routinely used modalities to define the boost volume are: clinical assessment, surgical clips, ultrasound, mammography, CT, and MRI.

In the randomized trials evaluating the role of radiotherapy boost, the boost volumes were defined on clinical and surgical details, except the Budapest trial, where surgical clips have been used. Polgar et al[16] presumed that increased differences between local failure rates in whole breast radiotherapy (WBRT) arm versus WBRT + boost arm in Budapest trial (15.5% versus 6.7%),[14,18] compared to EORTC trial (10.2% versus 6.2%)[7,11] and Lyon trial (4.5% versus 3.6%),[14] could be due to the different techniques of tumor bed delineation, as the difference in boost doses between all these trials was not significant.[4]

1. Clinical assessment. Clinical assessment of the tumor bed was used in the past in those institutions without imaging facilities to reliably identify the tumor bed, and was employing pre-operative clinical marks of tumor position on the skin, mammographic data, surgical annotations, surgical scar, and so forth.[4] The surgical scar could play a role in the centers where placement of scar is uniform and is based on institutional policy, such as: if the surgical scar is placed over the tumor. However, it was revealed that the lumpectomy scar is not necessarily related precisely to the site of the tumor, usually for cosmetic reasons; therefore, defining the tumor bed by surgical scar can lead to geographical miss.[19,20] The clinical assessment of the tumor bed is highly subjective and several studies demonstrated that boost volumes defined by clinical description are inadequate in 10-88% of cases when compared with lumpectomy bed delineated by surgical clips.[19,20]

2. Surgical clips. Surgical clips are commonly placed at the time of surgery; their placement and number are variable, according to institutional policy and

experience. Surgical clips can be visualized by ultrasound, fluoroscopy or CT, and help in delineating the tumor bed for the purpose of computerized treatment planning of the boost.[4] The treatment fields defined on clinical assessment only have shown inadequate coverage in 42-68% of patients when compared with position of clips.[21,22] Because of the gap between surgery and radiotherapy, problems like changes in the lumpectomy cavity and consequent displacement of clips have raised concerns. Magnitude of clips displacement was investigated by Weed et al[23] comparing images in CT scans performed at a gap of 27 days and finding a mean displacement of clips by 3 mm in all 3 coordinates, which is covered by the usual margin of 5 mm applied for clinical target volume (CTV) delineation. Most studies have shown that surgical clips are good surrogates for tumor bed,[20-24] although not always consistent with the edge of the seroma,[25,26] and tending to underestimate the tumor bed extension.[27]

3. Ultrasound. Ultrasound is an imaging modality demonstrated to improve localization of tumor bed. Kovner et al[20] demonstrated that postoperative clinical examination underestimated the complete dimension of the lumpectomy cavity in approximately 85-90% of patients, compared to ultrasound imaging. Intraoperative placement of catheters for brachytherapy may also inadequately cover the distal extent of the lumpectomy cavity if intraoperative ultrasound is not used.[28] The ultrasound images have the advantage to be compatible with the most radiotherapy planning systems; therefore, allowing for a computerized dosimetric evaluation of the treatment plan.[29] The main drawback of ultrasound as a modality to define the tumor bed is that postoperatively absorption of seroma in the lumpectomy cavity may blur a proper visualization of tumor bed. Because of the interval between surgery and radiotherapy, as a result of current BCT protocols to administrate chemotherapy postoperatively, ultrasound can underestimate the tumor bed.[24,28] Ultrasound has the advantage of being a non-ionizing imaging modality; therefore, its frequent use does not bring up any concern or caution of radiation safety. Also, advanced technology, as 3D-ultrasound can be a feasible solution for the daily definition of the tumor bed position during breast boost radiotherapy.[30]

4. Computerized tomography. Computerized tomography has been proven to be an accurate imaging modality to define the tumor bed, especially in combination with surgical clips. The main advantages of CT include good visualization of patient anatomy, fair visualization of tumor bed in early postoperative period, the possibility to scan the patient in treatment position, and the compatibility of images to any treatment planning system.[31] Al Uwini et al[32] analyzed data of 1331 patients and concluded that the use of CT for delineation and treatment planning led to a significant increase of the irradiated boost volume by a factor of 1.5-1.8, compared to conventional simulator-based plans.[35]

The limitation of CT scanning is the difficulty in differentiating the tumor bed from surrounding breast tissues, especially if the gap between surgery and radiotherapy is long. Kader et al[33] evaluated the effect of the time from surgery on seroma volume and clarity, in an attempt to establish the optimal time to use the CT-based seroma for dosimetric planning purposes, and concluded that the optimal time of CT scanning is within 8 weeks after surgery; during 9-14 weeks, the seroma might remain adequately defined in some patients; however, after 14 weeks, alternate strategies are needed to identify the tumor bed; thus, the lack of correlation between the seroma volume and tumor size suggesting that the CT-based seroma should not be the sole guide for boost volume definition.[33]

The accuracy of treatment field definition can be significantly increased if CT images with surgical clips within lumpectomy cavity are used to define the tumor bed.[29] A retrospective report showed that local control was significantly higher in patients receiving the boost radiotherapy by irradiation fields defined by clips and CT images than when assessed clinically (97% versus 88%). In these patients, 75% of the local recurrences were outside clinically defined field borders, indicating a geographical miss.[34]

5. Magnetic resonance imaging. Due to its capability to discriminate soft tissues, MRI provides an outstanding definition of breast and surrounding tissues and accurate localization of tumor bed.[4] However, its broad application is restricted by institutional limited resources, difficulty in scanning the patient in treatment position, as well as image distortion during co-registration with treatment planning systems.[29] Magnetic resonance imaging can be useful in defining small tumor beds in large or dense breasts, or in patients where the postoperative gap between surgery and radiotherapy has induced almost complete absorption of seroma within lumpectomy cavity.[4]

A note of caution should be added: the inter-physician variability in delineating the tumor bed seems to be much higher on MR images, compared to CT images, showing an overestimated extension of the tumor bed into the cranio-lateral and cranio-medial directions.[35] Thus, while the MR imaging provide superior soft tissue contrast, physicians may require

specialized training and experience in breast MR image interpretation prior to introduce this modality into the target volume delineation process.[36,37]

Techniques of breast boost irradiation. *1. Electrons.* Direct electron beams is currently the routine practice in many institutions, due to the advantages of this technique, such as: rapid fall-off of the dose, wide range of electrons energies, and feasibility of defining the treatment field on the skin. Most commonly used energies are in the range of 9-15 MeV. Defining the boost field on the basis of clinical assessment has been found to be erroneous, as demonstrated in several studies.[19,20,31,38] Therefore, the treatment field size and the depth of boost volume should be optimally determined by imaging modalities, as ultrasound, fluoroscopy, CT, or MRI.[28,39,40]

Usually, the dose for electron boost delivery is prescribed on 90-95% isodose, but given the deformable nature of the breast tissue, the prescription isodose may not cover the whole boost volume uniformly. This problem is regularly seen when tumors are located in infra-mammary and axillary folds; the depth of breast soft tissue varies significantly in these areas and an electron beam may either deliver low dose to the tumor bed, or overdose the underlying normal tissues. The role of electrons is also limited in patients with large breasts and deep tumors. Computerized tomography-based treatment planning helps in choosing the optimal electron energy and accurately determining the dose distribution.

2. Brachytherapy. Interstitial brachytherapy is also a common technique to deliver breast radiation boost, by interstitial placement of needles or flexible catheters into tumor bed either intraoperatively, under direct visualization of lumpectomy cavity, or postoperatively, under ultrasound.[12,29,39,40] Since the EORTC "boost versus no boost" trial initiated, electrons and interstitial brachytherapy were the modalities of choice to deliver the boost irradiation, and their clinical outcomes were compared in many studies. As presented in **Table 2**, the relapse rates for both techniques are comparable. A very recent report of Hill-Kayser et al[42] presenting long-term follow-up clinical data, confirms that after 20 years there is no difference in rates of local recurrence, freedom from distant metastases, overall survival, or patterns of failure between groups treated with these 2 radiotherapy boost techniques. The authors observed better cosmesis in the electron boost group at one year after radiotherapy, with a trend continuing for 10 years and a similar incidence of complications, with a trend toward increased fibrosis in interstitial brachytherapy boost group.[41] Recently, Kirk et al[41] presented dosimetric data comparing breast boost radiotherapy using electrons to MammoSite applicator brachytherapy,[42] but clinical data regarding the use of MammoSite applicator for breast tumor bed boost are currently lacking.

3. Three-dimensional conformal radiation therapy (3D-CRT). Three-dimensional conformal radiation therapy technique is a relatively new modality of delivering radiation boost,[43-45] to tumor bed, using either photon beams or a combination of photon and electron beams.[45] In order to optimally implement a 3D-CRT technique into the clinical practice of breast boost radiotherapy, concepts of ICRU reports 50 and 62, as: gross target volume (GTV), clinical target volume (CTV), planning target volume (PTV) have to be considered, and their related margins to be determined.[46] The necessary margins to be given to tumor bed for defining the CTV of the boost have been investigated. Previous study[18] determined that a margin of 1 cm around the tumor bed adequately covers microscopic disease,[18] in EORTC trial margins of 1.5 cm were used for clear microscopic margins.[12] Regardless the treatment delivery technique used, breast boost irradiation requires additional consideration to: delineation uncertainties (namely, identifying the tumor bed after surgery, inter-observer variability in contouring the boost volume on CT images),[47,48] changes of tumor bed volume during radiotherapy,[38,49] and position verification of the excision cavity.[21,50]

In the conventional tangential breast irradiation, where the target volume includes the whole breast, the set-up error has been so far underestimated. In the case of a boost however, the target volume of the boost is significantly smaller, and the probability of a geographical miss is consequently higher. As radiotherapy treatments become more conformal, image-guidance role becomes more important, in order to reduce the set-up errors. The set-up errors determine the size of PTV margins; therefore, playing an important role in achieving dose objectives in the treatment planning process.[51] The CTV to PTV margins depend on the patient immobilization devices and protocol, as well as on imaging modalities and technologies. The size of these margins can vary from 5 mm, if Cone Beam CT (CBCT) and surgical clips are used[48,51-53] to 15 mm, for a patient set-up protocol based on skin marks.[54]

The margins used to account for patient set-up uncertainties should be derived from institutional studies, corresponding to the actual inaccuracies found in daily practice. Particularly in the application of highly conformal techniques such as 3D-CRT and IMRT, it is essential to accurately define tumor bed volumes

Table 2 - Comparison of clinical outcome for various breast boost irradiation techniques.

Study	Year	N of patients	Median follow-up (year)	EBTR dose	Boost technique	Boost dose	IBTR (%)	DFS (%)	Cosmesis
Mansfield et al[101]	1995	1070	10	45 Gy/25 fr	416 electrons	20 Gy	19.0*	78*	
					654 HDR interstitial BT		12.0*	76*	
Touboul et al[102]	1995	329	10	40-45 Gy/25 fr	160 electrons	15 Gy	15.0	85	
					169 HDR interstitial BT		8.0	86	
Perez et al[103]	1996	619	5.6	48-50 Gy/25 fr	490 9-12 MeV electrons	10-20 Gy	6.0	79	84% good or excellent
					129 HDR interstitial BT		7.0	80	81% good or excellent
Bartelink et al[11]	2001	1878	5.1	50 Gy/25 fr	1653 electrons	16 Gy	4.7**		
					225 LDR/HDR interstitial BT	10 Gy	2.5**		
Polgar et al[18,98]	2001	104	5.3	50 Gy/25 fr	52 electrons	16 Gy		94.2	82.7% good or excellent
					52 HDR interstitial BT	12-14 Gy		91.4	88.5% good or excellent
Guix et al[104]	2001	294	10	50 Gy/25 fr	LDR interstitial BT	20-25 Gy	5.0	75.0	82% good or excellent 2% breast fibrosis
Resch et al[105]	2002	410	10	50 Gy/25 fr	LDR/HDR interstitial BT	20-28 Gy LDR 10-15 Gy HDR	3.9	79.0	
Poortmans et al[43]	2004	2661	5	50 Gy/25 fr	1635 electrons	16 Gy	4.8		9.1% moderate breast fibrosis 0.9% severe breast fibrosis
					753 photons		4.0		12.9% moderate breast fibrosis 2.1% severe breast fibrosis
					225 LDR interstitial BT		2.5		6.2% moderate breast fibrosis 0.9% severe breast fibrosis
Lemanski et al[84]	2006	50	9.1		IORT 9 MeV electrons	10 Gy	4.0	84.0	12% breast fibrosis
Wenz et al[79]	2010	154	2.8	46-50 Gy/25 fr	IORT 50 kV X-rays	20 Gy		98.5	5% grade 3 breast fibrosis 6% teleangiectasia and hyper-pigmentation
Vaidya et al[78]	2010	299	5	45-50 Gy/25 fr	IORT 50 kV X-rays	20 Gy	1.73		
Murphy et al[106]	2010	2567	6.5	46-50 Gy/25 fr	72 6 MV photons	10-16 Gy			19% breast fibrosis
					2495 6-21 MeV electrons				16% breast fibrosis
McDonald et al[76]	2010	354	2.7	45 Gy/25 fr	SIB IMRT 6 MV photons	15 Gy	2.8 for invasive breast cancer 1.4 for DCIS		96.5% good or excellent 3.5% fair
Polgar et al[107]	2010	100	7.8	50 Gy/25 fr	HDR interstitial BT	8-14 Gy	7.0	76.1	56% good or excellent 33% fair 11% poor 6.6% grade 3 breast fibrosis 2.2% teleangiectasia
Hill-Kayser et al[42]	2011	282	16.7	44-50 Gy /25 fr	141 HDR interstitial BT	13-26 Gy	26.1*		83%* excellent /good
			12.6	46-50 Gy /25 fr	141 electrons	10-20 Gy	17.3*		96%* excellent /good

*Kaplan-Meier estimates at 10-year actuarial rate, †Kaplan-Meier estimates at 5-year actuarial rate, EBRT - external beam radiation therapy, fr - fractions, BT - brachytherapy, LDR - low dose rate, HDR - high dose rate, IORT - intra-operative radiation therapy, IMRT - intensity modulated radiation therapy, SIB - simultaneously integrated boost, IBTR - ipsilateral breast tumor recurrence, DFS - disease free survival, DCIS - ductal carcinoma in situ

and to use valid margins, as this will ultimately impact treatment outcome. Furthermore, it has been shown that the shape and size of the tumor bed may change during the course of radiotherapy.[49] As a result, adaptive radiotherapy techniques may become more important in the near future.

4. Intensity modulated radiation therapy (IMRT). Although IMRT is not widely used for breast radiotherapy, it has been considered in some particular situations, as patients with large breast and delivering cardiac safe irradiation in the case of left sided breast cancers. For sole tumor bed boost, IMRT does not offer considerable advantage compared to conventional techniques, as shown in planning dosimetric studies.[55,56] However, due to its unique ability to deliver a simultaneous integrated boost (SIB), IMRT has been considered as a technique of choice.[57] In a recent study, van der Laan[56] demonstrated the limited benefit of IMRT in breast-conserving therapy with simultaneously integrated boost and concluded that the results obtained with 3D-CRT-SIB and IMRT-SIB are generally comparable and the small improvement seen in dose uniformity does not support the need for such a costly technique as IMRT. Some of the challenges related to IMRT of the breast boost include: patient positioning, accurate target volume delineation, inter-fraction and intra-fraction motion, dose constraints to critical structures such as heart and lung.

Similar to the 3D-CRT techniques, patient positioning and its daily reproducibility is one of the major issues in IMRT breast irradiation, especially for women with large breast. In general, immobilization devices for breast radiotherapy proved to not be too efficient in the case of IMRT technique, with relatively high dose gradients.[58] Intra-fraction and inter-fraction motion has been extensively studied.[59,60] Although a lot of emphasis has been given to the intra-fraction motion as can be seen from the development on the respiratory gating technology,[61-65] the analyzed studies have shown that during normal breathing, the dosimetric impact of respiratory motion is clinically insignificant, and it is the inter-fractional variation that is responsible for the majority of the set-up errors.[61,64,65]

A practical way to decrease the movement of the chest wall due to respiration, spare the heart and lung, and reduce the desquamation in the infra-mammary fold especially for women with large pendulous breasts is the treatment in the prone position.[64,66,67] Intensity modulated radiation therapy raises also serious concerns regarding radiation safety: its inherent high radiation leakage and high monitor units could possibly increase the risk of secondary cancers. In breast cancer particularly, beams targeting the breast from all directions may significantly increase the whole body dose and possibly increase the probability of a second cancer, including a cancer in the contralateral breast. A meta-analysis of The Early Breast Cancer Trialist Cooperative Group (EBCTCG), including 42000 women from 78 randomized trials, showed an increase in the contralateral breast cancer by 1.18 (p=0.002), increase in the lung cancer by 1.61 (p=0.0007), and an overall significant increase in the risk of second primary cancer.[68] Almost all patients in these trials have received radiotherapy with tangential fields. However, in the case of IMRT, where the beams are directing on the isocenter from all directions, and taking into account that more MUs are needed to deliver the desired dose, thus leading to leakage radiation and a higher total-body dose, the carcinogenic risk after IMRT is estimated to be almost doubled compared to 3D-CRT (1.75% versus 1% for 10 years survival); this is especially relevant for breast-conserving patients, as they have a long life-expectancy.[69] Therefore, although IMRT has shown good planning dosimetric results, should be considered only for complex cases, such as the indication for internal mammary chain irradiation, or in patients with complex thoracic contours.[70] Instead, a relatively simple technique of forward planning can be employed, where multiple small segments of tangential fields are used to generate a homogenous dose distribution.[71,72] A large phase III randomized trial, in which patients with all breast sizes were eligible, confirmed that breast dosimetry can be significantly improved with a simple method of forward-planned IMRT and has little impact on radiotherapy resources, especially for patients with large breasts.[73] Recent planning studies analyzed the dosimetric outcome of IMRT, especially in the particular case of SIB.[56,74] However, clinical data are still limited: Freedman et al[75] reported the acute toxicity of 75 patients treated with hypofractionated SIB IMRT, after a follow-up of 9 months, while McDonald et al[76] recently presented their clinical experience with breast IMRT with SIB and data of 3 years follow-up of 354 patients.

5. Intraoperative radiation therapy (IORT). Intraoperative irradiation of breast tumor bed is an innovative technique aiming to address some of the problems of conventional external beam radiotherapy. As shown above, the accurate targeting of tumor bed can be difficult because of deformation and positional change of the postoperative breast, which is further complicated in cases undergoing plastic surgery, when the position of the tumor bed is virtually impossible to predict. The delay between surgery and radiotherapy planning can

also contribute to a geographical miss that the modern image-guided radiotherapy may be able to reduce, but cannot eliminate.[77,78] Intraoperative irradiation of breast can be performed using either low x-rays or electrons. With this technique, the tumor bed tissue is wrapped around or conformed to the radiotherapy source during surgery procedure. In 1998, the randomized controlled TARGIT trial was launched, aiming to establish whether targeted intraoperative radiotherapy with low x-rays of 50 kV can replace conventional whole breast external beam radiotherapy in selected patients. Some of the centers participating in this trial treated a series of pilot cases to test the feasibility and safety of using the intraoperative technique as a substitute for the usual tumor bed boost in a series of 299 unselected patients undergoing BCT.[78-80]

Intraoperative radiotherapy with low x-rays followed by external beam radiotherapy results in a low-local recurrence rate (1.73% at a median follow-up of 5 years) in a standard risk patient population,[81] which seems superior to the results of external beam boost in the EORTC trial (4.3%) and the UK Standardization of breast radiotherapy (START B) trial (2.8%).[82] Accurate localization of the tumor bed and the timing of treatment have a favorable effect on tumor micro-environment leading to this outstanding local control.

Intraoperative irradiation of breast tumor bed using electrons is a procedure derived from the electron intraoperative radiotherapy (ELIOT) trial, initiated in 1999 by the European Institute of Oncology, designed as a procedure of partial breast radiotherapy and consisting of a single high dose of 21 Gy delivered during the surgical session by an electron beam of a mobile linear accelerator.[83] Lemanski et al[84] designed a pilot study of IORT to a tumor bed dose of 10 Gy, delivered intraoperatively with a 9 MeV electron beam, followed by external beam therapy to the whole breast with a dose of 50 Gy in 25 fractions. After a median follow-up of 9.1 years of 50 patients, they concluded that IORT given as a boost after breast-conserving surgery is a reliable alternative to conventional postoperative fractionated boost radiation. Hypo-fractionated external beam radiotherapy of the whole breast after electron intraoperative boost to the tumor bed has been also investigated, showing that this treatment is feasible, compliance is high, and the rate of acute toxicity and the preliminary data on chronic toxicity seem acceptable.[85] However, the number of patients in these studies is small to be conclusive and further randomized trials are needed to test the benefit of intraoperative boost radiation to the tumor bed.

6. Advanced radiotherapy techniques. Helical tomotherapy (HT) and protons were investigated as modalities to deliver breast boost radiotherapy, focusing in the particular case of simultaneously integrated boost. Few dosimetric studies have been recently published, comparing the HT to 3D-CRT and showing that both HT and 3D-CRT provided adequate target volume coverage and low heart doses; HT avoided unnecessary breast overdosage and improved ipsilateral lung sparing, but tumor bed coverage was slightly lower and the dose to the contralateral breast was significantly higher with HT.[86,87] Toscas et al[88] have performed a planning study comparing electron, photon and proton beams for breast boost irradiation and concluded that boosting the tumor bed with optimized photon or proton beams should be preferred to electron, especially for deep-seated targets, due to the marked dose-sparing of ipsilateral breast, lung, heart, and skin.

Table 3 summarizes the dosimetric properties, and **Figure 1** shows the axial dose distribution of the breast boost irradiation techniques. **Table 3** shows the comparison of breast boost irradiation techniques. **Figure 1** shows the dose distribution of breast boost irradiation techniques.

As shown by our review, there is a wide variety of radiotherapy techniques for breast boost irradiation, and each institution should establish its own practice according to the logistics resources and level of expertise. In 2010, the European Organization for Research and Treatment of Cancer-Radiation Oncology Group (EORTC-ROG) published a survey on 68 institutions members of EORTC from 16 European countries, in an attempt to evaluate the current technological clinical practice of breast radiotherapy.[89] The survey revealed that the main boost modality was electrons in 55%, photons in 47%, and brachytherapy in 3% of the institutions. All institutions used CT-based treatment planning, with wide variations in the definition of the breast and boost target volumes, with margins around the resection cavity, ranging from 0 to 3 cm. The fact that the use of photon and electron irradiation was rather balanced could be explained by the unclear effects of boost irradiation with respect to the boost modality. The long-term results of boost irradiation techniques, balancing the local control and cosmesis against logistic resources, and including cost-benefit analysis are needed.[90] **Table 2** presents and compares the clinical outcomes of different breast boost radiotherapy techniques, as revealed by the reviewed published studies.

Doses and fractionation schedules. Doses of 45-50 Gy to whole breast and an additional boost of 15-20

Table 3 - Comparison of breast boost irradiation techniques.

Criteria	Electrons	Interstitial brachytherapy	3D-CRT	IMRT	IORT x-rays	IORT electrons
Planning target volume and dose prescription	Dose prescribed to 90-95% isodose line 90% isodose at 25 mm (9 MeV), 45 mm (15 MeV)	1-2 cm	PTV = tumor bed + 20–25 mm	PTV = tumor bed + 10–15 mm	Dose prescribed to the surface of applicator	Dose prescribed to 90% isodose line 90% isodose at 25 mm (9 MeV)
Coverage of target	Variable	Good	Best	Best	Good	Good
Dose homogeneity	Fair	Fair	Best	Best	Fair	Fair
Sparing of normal tissue	Good	Good	Good	Best	Best	Varies with location
Sparing of skin	Variable	Variable	Good	Best	Best	Best
Technical feasibility	Not suitable if inadequate tissue	Not suitable if inadequate tissue or near axilla	Suitable for all cases	Suitable for all cases	Not suitable for large or irregular cavities, or at the periphery of the breast	Not suitable for tumors near brachial plexus, axilla or skin
Expertise required	Average	High	Average	High	Very high	Very high
Drawbacks	Sensitive to breast surface irregularities	Invasive	Sensitive to inter-fraction variations	Sensitive to inter-fraction variations	Sensitive to cavity shape and size	Sensitive to cavity shape and size
	Sensitive to tumor bed depth	Extensive planning required	Sensitive to breathing motion	Sensitive to breathing motion	Histology not available	Histology not available
	Skin dose can be high	Extensive QA required		Extensive QA required		

Modified from Offersen et al,[100] 3D-CRT - 3-dimensional conformal radiation therapy, IMRT - intensity modulated radiation therapy IORT - intra-operative radiation therapy, QA - quality assurance

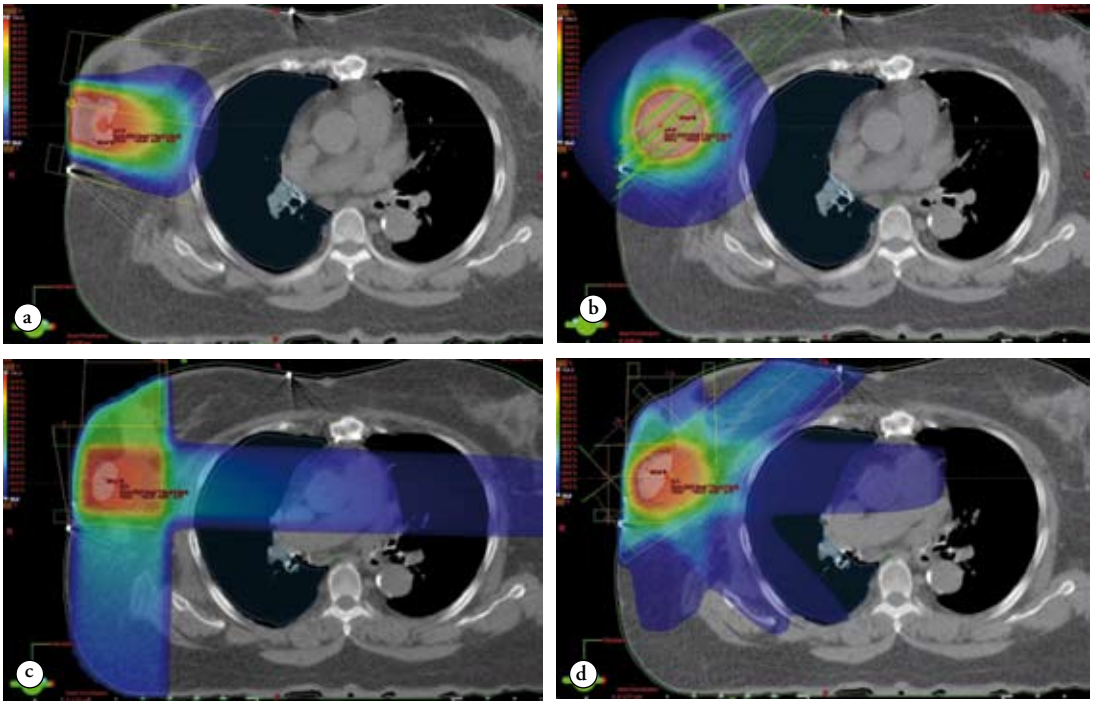

Figure 1 - Dose distribution of breast boost irradiation techniques. **a)** Electrons, **b)** high dose rate brachytherapy, **c)** 3-dimensional conformal radiation therapy, and **d)** intensity modulated radiation therapy.

Gy have shown significant improvement in local control rates, with acceptable toxicities.[15,18,91] Breast boost radiotherapy has been delivered in various fractionation schedules, as presented in **Table 2**. In the case of sequential breast boost with external beam radiotherapy, the dose per fraction most commonly used was 2-2.5 Gy for electron and 2 Gy for photon, with little difference in overall outcome in terms of local control. Retrospective studies showed no difference in cosmetic outcome among patients treated with different fractionation schedules. A parallel comparison of boost fractionation schedules has not been yet presented in any published study, therefore an ideal fractionation schedule cannot be recommended. The practice of simultaneous integrated boost has been presented by several authors,[91] sometimes with hypofractionated schedules.[91-92] The doses delivered in these studies were determined on the basis of the biological equivalence to the conventional fractionation and aiming to 45-50 Gy to whole breast and 60 Gy to tumor bed. The biologically effective doses of conventional sequential boost used in current practice were converted, using the linear-quadratic model, to their corresponding equivalent doses of SIB.[56,74,75] However, the widespread clinical application of these schedules is still not practiced, due to insufficient data addressing long-term results. The recent evidence-based guidelines of American Society for Radiation Oncology (ASTRO) regarding the fractionation schedules for breast radiotherapy reported the lack of consensus among the members of the task force regarding the appropriateness of a hypofractionated schedule when a tumor bed boost is indicated, and could not determine either the optimal hypofractionated whole breast regimen to be used when a boost is given, nor the optimal tumor bed boost dose-fractionation to use in conjunction with a hypofractionated whole breast regimen.[94]

Important clinical data in this regard are expected from the Intensity Modulated and Partial Organ Radiation Therapy (IMPORT-high) randomized trial, which compares standard tangential fields versus forward planning IMRT, using hypofractionated schedules.[95] Intensity Modulated and Partial Organ Radiation Therapy-high trial opened in January 2009 and entered the first patient in March 2009. The total accrual is aimed to be 840 patients achieved by February 2012. The trial tests dose escalated radiotherapy delivered using IMRT in a group of women with early breast cancer at higher than average risk of local tumor recurrence. The trial compares the standard radiotherapy for this group (RT treatment to the whole breast, 15 fractions over 3 weeks followed by a sequential boost dose to the tumor bed for a further 8 fractions over 1.6 weeks, a total of 23 fractions over 4.6 weeks) with 2 different test arms delivering varying doses across the breast: low risk breast volume receiving 36 Gy in 15 fractions, standard risk breast volume receiving 40 Gy in 15 fractions, and tumor bed receiving 48 or 53 Gy in 15 fractions with simultaneous integrated boost technique. The varying doses across the breast in the test arms reflect the fact that the risk of true local recurrence is highest in the area of the breast close to the site of the original tumor.[57,95,96]

In conclusion, radiotherapy techniques for breast cancer treatment have significantly progressed during the last years. Computed tomography had a major impact on radiotherapy, allowing the transition from conventional treatment simulation of electron beams to photons 3D-CRT dose planning and implementation of advanced radiotherapy techniques as IMRT, tomotherapy and protons. Recent advances of radiotherapy technology, such as intraoperative equipment, led to new approaches of breast tumor bed irradiation, demonstrating feasible treatment with good outcome.

Further randomized trials comparing the long-term results of boost irradiation techniques, balancing the local control and cosmesis against logistic resources, and including cost-benefit analysis are needed.

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