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REVIEW

The Role of Boost Irradiation in the Conservative Treatment of Stage I-II Breast Cancer

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In this article, we review the current status, indication, technical aspects, controversies, and future prospects of boost irradiation after breast conserving surgery (BCS). BCS and radiotherapy (RT) of the conserved breast became widely accepted in the last decades for the treatment of early invasive breast cancer. The standard technique of RT after breast conservation is to treat the whole breast up to a total dose of 45 to 50 Gy. However, there is no consensus among radiation oncologists about the necessity of boost dose to the tumor bed. Generally accepted criteria for identification of high risk subgroups, in which boost is recommended, have not been established yet. Further controversy exists regarding the optimal boost technique (electron vs. brachytherapy), and their impact on local tumor control and cosmesis. Based on the results of numerous retrospective and recently published prospective trials, the European brachytherapy society (GEC-ESTRO), as well as the American Brachytherapy Society has issued their guidelines in these topics. These guidelines will help clinicians in their medical decisions. Some aspects of boost irradiation still remain somewhat controversial. The final results of prospective boost trials with longer follow-up, involving analyses based on pathologically defined subgroups, will clarify these controversies. Preliminary results with recently developed boost techniques (intraoperative RT, CT-image based 3D conformal brachytherapy, and 3D virtual brachytherapy) are promising. However, more experience and longer follow-up are required to define whether these methods might improve local tumor control for breast cancer patients treated with conservative surgery and RT. (Pathology Oncology Research Vol 7, No 4, 241–250, 2001)

Keywords: breast cancer, radiotherapy, boost, brachytherapy, electron, local control

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Abbreviations

ABS: American Brachytherapy Society; BCS: breast conserving surgery; BT: brachytherapy; CT: computer tomograph; DBCG: Danish Breast Cancer Group; EIC: extensive intraductal component; EORTC: European Organization for Research and Treatment of Cancer; GEC-ESTRO: Groupe Europeen de Curietherapie – European Society for Therapeutic Radiology and Oncology; HDR: high dose rate; HG: histological grade; IGR: Institut Gustav-Roussy; ILC: infiltrating lobular carcinoma; IORT: intraoperative radiation therapy; LDR: low dose rate; LTC: local tumor control; L: lumpectomy; LVI: lympho-vascular invasion; MRI: magnetic resonance imaging; NCI: National Cancer Institute; NSABP: National Surgical Adjuvant Breast and Bowel Project; Q: quadrantectomy; RFS: relapse-free survival; RR: relative risk; RT: radiotherapy; TE: tumorectomy; 3D: three dimensional.

Introduction

Breast conserving surgery (BCS) and radiotherapy (RT) of the conserved breast became widely accepted in the last decades for the treatment of early invasive breast cancer.[1-6] The standard technique of RT after BCS is to treat the whole breast via tangential fields up to a total dose of 45 to 50 Gy.[7] However, there is no consensus among radiation oncologists about the neccessity of boost dose to the tumor bed.[8] In earlier prospective and retrospective trials, a 10-30 Gy boost was routinely used, based on the observation that the vast majority of ipsilateral breast tumor recurrences originated from the vicinity of the original index lesion.[1-2,4-6,9] Others suggested that boost was not neccessary to maintain adequate local control, if tumor resection margins were free of cancer.[3,10-12] To date, only the preliminary results of five randomized studies have been published on this issue.[13-17] All these studies proved

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that boost dose reduced the incidence of ipsilateral breast tumor recurrence indeed. However, generally accepted criteria for identification of high risk subgroups, where boost is recommended, have not been established yet. Further controversy exists regarding the optimal boost technique (electron vs. brachytherapy), and their impact on local tumor control (LTC) and cosmesis.[8,18-30] Based on the evolving retrospective data and recently published results of randomized trials, the European brachytherapy society (GEC-ESTRO) organized a consensus meeting on breast cancer in June 2001 to answer the question "To boost or not to boost and how to do it".[31] The American Brachytherapy Society (ABS) has also published their guidelines specifically for the use of brachytherapy in breast carcinoma.[24] These guidelines will help clinicians in their medical decisions. However, some aspects of boost irradiation still remain controversial. In this article we review the current status, indication, technical aspects, and controversies of boost irradiation after BCS.

Pathological basis for tumor bed boost

In the classical pathological studies of Holland et al,[32-33] mastectomy specimens of patients with T1-2 breast cancers were evaluated to assess where residual tumor was located after simulated tumor excision. If tumors were removed with a margin of 2, 3, and 4 cm, about 42%, 17%, and 10% of the patients would have had residual tumor foci in the remaining breast, respectively. These foci could theoretically be the sources of local recurrence. These results prove that prominent residual carcinoma is usually confined to the same quadrant as the reference tumor, so more aggressive RT of the tumor bearing quadrant might be able to eliminate multicentric residual tumor foci after BCS.

Clinical basis for tumor bed boost

The main rational for boosting the tumor bed after 45-50 Gy whole breast RT was based on the clinical observation that 67-100% of ipsilateral breast tumor recurrences originated from the vicinity of the original index lesion.[10,16,30,34-36] These data are in accordance with the pathological findings of Holland et al.[32]

Results from retrospective studies

At least 3 retrospective series proved a dose-local control relationship above 50 Gy (***Table 1***).[37-39] Based on the analysis of dose-response curves, Van Limbergen et al[40] reported that above 50 Gy, an increase of 15 Gy would reduce the local recurrence rate by a factor of 2. Jacobs et al[22] published a series of 336 patients with a minimum follow-up of 3 years. The crude rate of local recurrence with or without boost was 7.2% and 11.6%, respectively.

Results from earlier prospective breast conservation trials

In the majority of earlier prospective studies, evaluating the value of BCS with or without RT, boost irradiation was routinely used in RT arms.[1-2,4-6,9,41-42] In the NSABP-B-06 and Uppsala-Örebro studies, however, boost was not given.[3,34] Nevertheless, excellent and similar LTC has been reported from these trials after BCS and RT, resulting an annual local recurrence rate between 0.46 and 2.50% (***Table 2***). The primary goal of these studies was to justify the adequacy of breast conserving treatment, so direct conclusions regarding dose-response realtionships can not be drawn from these results. Inclusion criteria (eg. tumor size, stage) and extent of surgery were also different in each trial. However, the results of the NSABP-B-06 trial suggested that boost was not neccessary to maintain adequate local control, if tumor resection margins were free of cancer.[3] Findings of the Milan group showed that quadrantectomy yielded better local control than tumorectomy.[6,41] The larger extent of surgery would decrease the relative gain expected from boost irradiation. On the other hand, more radical surgery would increase the cosmetic failure rate, as well. Thus, surgery and RT should be viewed as complimentary therapies. As the radicality of surgery increases, the aggressiveness of RT may be decreased.

Results of prospective boost trials

To date, five prospective studies evaluated the impact of boost dose on LTC (***Table 3***).[13-17] In an earlier Hungarian study from the Uzsoki Hospital, 10 Gy high dose rate (HDR) or 20 Gy low dose rate (LDR) brachytherapy (BT) boost reduced the incidence of local recurrence by a factor of 2.[16] However, the number of patients per treatment arm was low, and statistical analysis was not performed. In the Teissier et al[17] trial, 664 patients with free surgical margins

Table 1. **Dose-response relationship for local control after BCS and RT**

Author	*Tumor bed dose (Gy)*	*5-year LR rate (%)*	*p-value*
Clarke[37]	< 65	6.6	0.003
	> 65	2.3	
Recht[38]	< 60	7	0.06
	60-70	4	
	> 70	1	
Van Limbergen[39-40]	40-49	28*	0.01
	50-59	15*	
	60-69	10*	
	70-79	6*	
	80-89	2.5*	

BCS: breast conserving surgery; RT: radiotherapy; LR: local recurrence; * 10-year rates

Table 2. **Annual local recurrence rate after BCS and RT – results from prospective breast conservation trials**

Study (treatment period)	*Patient no.*	*Stage*	*Tumor size (cm)*	*Margin status*	*Surgery*	*Boost dose (Gy)*	*Annual LR rate %*
IGR (1972-1980)[1]	88	I-II	≤ 2	NS	TE	15	0.83
Milano I-II-III (1973-89)[6]	1006	I-II	≤ 2.5	free/pos.	Q	10	0.46
NSABP-B-06 (1976-84)[3]	731	I-II	≤ 4	free	L	0	0.83
NCI (1979-87)[4]	121	I-II	≤ 5	free*	L	15-20	2.50
EORTC-10801 (1980-86)[5]	452	I-II	≤ 5	NS	L	25	1.62
Uppsala-Örebro (1981-88)[34]	184	I	≤ 2	free	Q	0	0.85
DBCG (1983-89)[2]	430	I-III	NL**	free/pos.	L/Q	10-25	0.84
Ontario (1984-89)[9]	416	I-II	≤ 4	free	L	12.5	1.49
Milano II (1985-87)[6]	345	I-II	≤ 2.5	free/pos.	TE	15	2.45

BCS: breast conserving surgery; RT: radiotherapy; LR: local recurrence; IGR: Institut Gustav-Roussy; NSABP: National Surgical Adjuvant Breast and Bowel Project; NCI: National Cancer Institute; EORTC: European Organization for Research and Treatment of Cancer; DBCG: Danish Breast Cancer Group; NS: not stated; TE: tumor excision; Q: quadrantectomy; L: lumpectomy; * all patients with incomplete resection were re-excised; ** NL: not limited – some patients with tumors > 5 cm were also included.

Table 3. **Results of prospective breast boost trials**

Trial	*Patient no. n*	*Median FUP years*	*Boost dose Gy (technique)*	*Crude LR % (p-value*) boost vs. no boost*	*5-y actual LR % (p-value**) boost vs. no boost*	*5-y RFS % (p-value**) boost vs. no boost*
Uzsoki Hosp[16]	111	3.8	10-20 (BT)	5.4 vs 10.7 (0.2537)	NR	NR
Nice[17]	664	6	10 (E)	4.3 vs 6.8 (0.1036)	NR (0.13)	NR
Lyon[15]	1024	3.3	10 (E)	1.9 vs. 4.0 (0.0381)	3.6 vs. 4.5 (0.044)	86.0 vs. 82.2 (0.011)
EORTC[13]	5318	5.1	15-16 (E/BT)	4.1 vs. 6.8 (0.0001)	4.3 vs. 6.8 (< 0.0001)	NR
Budapest[14]	207	4.8	12-16 (E/BT)	6.7 vs. 14.6 (0.0537)	8.0 vs. 15.7 (0.0790)	79.5 vs. 67.3 (0.0438)
All	7324	–	–	3.9 vs 6.7 (< 0.0001)	–	–

FUP: follow-up period; LR: local recurrence; RFS: relapse-free survival; E: electron; BT: brachytherapy; NR: not reported; EORTC: European Organization for Research and Treatment of Cancer; *Fisher-exact p; **log-rank p.

were included: 6.8% had suffered a recurrence in the no boost group versus 4.3% in the boost group. The difference was not statistically significant, however, their results showed a trend in favour of the boost group. The interim results of a randomized clinical trial in Lyon showed that a 10 Gy electron boost to the tumor bed significantly reduced the risk of ipsilateral breast tumor recurrence.[15] The difference in the 5-year LTC between the two treatment arms was only 0.9%. However, it is to be noted that only patients with tumors up to 3 cm and free "inked" surgical margins were entered onto this trial. The relapse-free survival (RFS) was also significantly better in the boost arm, but the effect of boost on overall survival was modest. The first results of the EORTC "boost versus no boost" study were reported very recently.[13,43] A boost dose of 16 Gy decreased the 5-year actuarial local recurrence rate with 2.5% in the 5318 patients with complete excision ($p < 0.0001$). Metastasis rates and overall survival were similar for both arms.

The results of the Budapest boost trial have also shown that 16 Gy electron or 12-14.25 Gy HDR BT boost decreased the crude rate of local relapse from 14.6% to 6.7%.[14] The difference in the 5-year LTC between the two arms was 7.7%, resulting in a strong, non-significant trend for better local relapse-free survival in the boost arm ($p = 0.0790$). The 5-year RFS was significantly better in the boosted group (79.5%) than in the control arm (67.3%; $p = 0.0438$). The trial also showed a non-significant difference in cancer-specific survival in favour of the boosted group.

The results of the randomized boost trials are summarized in ***Table 3.*** The apparently higher local recurrence rate in the Budapest series is explained by the worse prognostic characteristics of patients, compared to the Lyon and EORTC trial.[13-15] In both studies, only patients with pathologically free surgical margins were analyzed. Patients with involved resection margins (18 patients; 8.7%) were also enrolled onto the Budapest trial. A sub-

stantially higher proportion of patients had T2 (39.1%), poorly differentiated (29.5%) and EIC positive (27.5%) tumors, as well.

Identification of a high risk subset of patients who may benefit from boost irradiation

The evidence obtained from retrospective and prospective studies proved that boost irradiation reduced the incidence of ipsilateral breast tumor recurrence indeed.[8,13-17,22,37-40,43] However, generally accepted criteria for identification of high risk subgroups, in which boost is recommended, have not been established yet. Young age, positive or close surgical margins, and EIC have been reported as the most important prognostic factors for higher risk of breast relapse.[16,23,44-57] The effect of other possible prognostic factors (tumor size, lympho-vascular invasion, high grade, high mitotic activity, lobular carcinoma) on LTC are also well documented, but partially controversial data exist in the literature about their value.[16,56-62]

Patient age

Young age, as a prognostic factor for local breast recurrence, has been widely disputed in the literature.[30,43-48] Most series reported an increased breast failure rate using a variety of different age cutoffs. The EORTC boost trial demonstrated that young age was the most important prognostic factor for local recurrence.[13,43] The largest clinical benefit from boost was seen in patients younger than 40 years: at 5 years their local recurrence rate was reduced from 19.5% to 10.2%. In the age groups 41-50, 51-60, and above 60 years boost therapy reduced 5-year local recurrence rate from 9.5% to 5.8%, from 4.2% to 3.4%, and from 4.0% to 2.5%, respectively. The authors concluded that boost therapy should be recommended, at least for patients less than 50 years of age.

In the Budapest boost trial, age less than 40 years was also found to be an independent prognostic factor for local recurrence.[14] The actuarial 5-year local failure rate was 31.4% for younger women, and 10.0% for patients above 40 years ($p = 0.0009$; RR: 4.92).

These results suggest that there is a distinct biological difference in breast carcinoma presenting in young women that predisposes them to local recurrence.

Margin status

Positive margin status have been accepted as a major risk factor for local recurrence after BCS and RT (***Table 4***).[23, 49-52, 63] Furthermore, the number of positive margins, as well as the width of clear surgical margin have influence on LTC.[52-53,63] However, the pathologists' examination of margins is far from uniform, and many clinical series report the status of the margins, without describing how the margins were determined.[64] There is a consensus among pathologists that the use of the "India ink method" is essential to adequately assess margin status.[64-65] The specimen should be oriented with sutures, and delivered unfixed and intact to the pathologist. Previously, Carter[66] proposed to peel the specimen like an orange for the examination of the entire specimen surface in an en face fashion. However, to section the margins in this fashion would require up to 54 sections in each case, which is clearly not feasible in routine practice.[64] Based on the guidelines of the EORTC Breast Cancer Cooperative Group, it seems to be a reasonable compromise to assess specimen margins in 6-8 blocks.[65] A complete cross-section through the largest diameter of the tumor should be sampled, including periphery and closest surgical edges, if necessary in more than one block. At least 3 additional blocks including nearest margins and tumor should be also sampled.[65]

In the Schnitt et al[53] study, the 5-year breast failure rate was 0%, 4%, 6% and 21% with clear, close, focally positive, and diffusely positive surgical margins, respectively. In the Budapest boost trial the respective rate with clear, close (≤ 2 mm), and positive margins was 8.2%, 30.0%, and 34.7%.[63] In case of positive or close margins boost dose decreased the incidence of breast relapse from 46.7% to 8.3% ($p = 0.0385$).[63] On the contrary, in the EORTC "boost versus no boost" trial margin status had no significant impact on LTC (unpublished data).

Table 4. **Local recurrence rate according to margin status after BCS and RT**

Author	*Local recurrence (%)*		*Tumor bed dose*	*Follow-up*
	MS+	*MS–*	*Gy*	*years*
Mansfield[23]	16	8	60–65	10
Smitt[49]	18	2	44–79	10
Spivack[50]	18.2	3.7	45–66,4	4
Anscher[51]	10	2	42–71	5
Dibase[52]	14	6	60–65	5
Polgár[63]	34.7	9.5	50–66	5

BCS: breast conserving surgery; RT: radiotherapy; MS: margin status

Table 5. **Local recurrence rate according to EIC after BCS and RT**

Author	*Local recurrence (%)*		*Tumor bed dose*	*Follow-up*
	EIC+	*EIC–*	*Gy*	*years*
Wazer[29]	12	3	50–70.4	7
Fowble[54]	22	4	60–70	10
Eberlein[55]	27	7	> 60	10
Krishnan[56]	9.1	5.2	60–70	10
Nagykálnai[16]	25	6	50–70	3.8
Fodor[44]	27.2	7.2	50	10
Polgár[63]	16.2	9.8	50–66	5

EIC: extensive intraductal component; BCS: breast conserving surgery; RT: radiotherapy

Extensive intraductal component (EIC)

EIC is usually reported when 25% or more of an invasive ductal cancer consist of intraductal carcinoma, and ductal carcinoma in situ is also present in adjacent breast tissue. Holland et al[32-33] reported that patients with EIC were more likely to have residual tumor outside the reference tumor than without EIC (74% versus 42%).The amount of residual tumor was also correlated with the presence of EIC. These findings explain why EIC positive patients were more likely to fail locally after BCS and RT (*Table 5*).[16, 29, 44, 54-56, 63]

Tumor size

In most series tumor size did not affect significantly LTC.[16,39,44,55-59,63] However, in the NSABP-B-06 trial, patients with T2 tumors were more likely to develop local recurrence following BCS without RT.[3]

Lympho-vascular invasion (LVI)

Peritumoral LVI has also been reported by numerous authors as a risk factor for local recurrence after breast conservation.[16,45,58,61] In the Uzsoki Hospital series endolymphatic spread caused a 2.5-fold higher risk for intrabreast relapse.[16] On the contrary, in the Budapest boost trial the actual 5-year local failure rate was similar with or without LVI (13.4% versus 11.0%).[63]

Histological grade (HG)

The value of HG as a prognostic factor for local recurrence is controversial, too. It is difficult to compare the results of different series, because of the variety of grading systems and the difficulty in grading of breast carcinomas.[67] Clarke[37] found that high grade was a strong predictor for both local-regional relapse and for breast alone relapse. Van Limbergen et al[39] noted 5-year control rates of 95% for grade I, 90% for grade II, and 84% for grade III tumors, but this did not reach statistical significance (p=0.12).

In the Budapest series, HG did not have significant impact either on LTC.[63] However, the average time to local recurrence was shorter for grade III tumors (20 months; range: 10-34), than for grade I-II carcinomas (38 months; range: 28-50).

Mitotic activity index (MAI)

Only a few authors examined the relationship between MAI and LTC. In the Schnitt et al[60] study high mitotic activity was associated with significantly higher local recurrence rate (MAI ≥ 20: 16% versus MAI < 20: 3%). Polgár[63] also found that MAI above 10 was an independent risk factor for breast failure (RR: 5.75; p = 0.0186).

Infiltrating lobular carcinoma (ILC)

ILC was thought to be a relative contraindication for breast conservation for decades, due to its multifocality and diffuse pattern of spreading. However, long-term results from the nineties proved that adequate surgery and RT for ILC maintained similar LTC as seen for ductal cancers.[44, 58-59, 62]

Which boost technique should be preferred – brachytherapy or electrons?

Only a few reports have compared outcome in patients treated with BT or electron boost.[14,18,20-23,25,27-28,63] Most of these authors used LDR Iridium-192 implants.[18,21,23,25,27-28] Mansfield et al[23] found that 20 Gy perioperative LDR BT boost yielded a significantly better LTC for stage II patients. Others reported similar local control and cosmesis for women boosted with either LDR BT or electrons.[20-21,25,27-28] In the Berberich et al[18] study the cosmetic results were worse in the BT group. However, the two patient groups were treated with different biological total dose, radiation quality and dose per fraction.

The largest HDR series have been reported by Hammer et al.[68-69] The 5-year local relapse rate of 3.5% with encouraging cosmetic results proved the safety of the use of HDR BT as a boost of 10 Gy in one fraction.[69] Jacobs et al[22] found that a 12 to 15 Gy boost with HDR BT given in a single treatment session resulted a better LTC than with electrons. To date, only three groups reported early experience with fractionated HDR BT boost.[14, 63, 70-71] In the Hennequin et al[70] study, 106 patients were treated with a boost of 10 Gy in two fractions. They found a 5.1% local recurrence rate at 5 years and excellent/good cosmetic outcomes in 63.2%. In another series from Virginia, a total HDR boost dose of 15 Gy was delivered in 6 fractions of 2.5 Gy over 3 days in 18 women with close or focally positive surgical margins.[71] There have been no in-breast failures observed at a median follow-up of 50 months. Sixty-seven percent of patients were considered to have experienced excellent good cosmesis. Results from Budapest showed that local control and cosmetic outcome were excellent and similar to women boosted with either 12-14.25 Gy HDR BT in 3 daily fractions or 16 Gy electrons.[14,63] Moderate/severe fibrosis occured more frequently after BT, but fibrotic mass was always confined to the tumor bed and it did not affect cosmetic appearance.

Based on these results, it seems that interstitial BT boost can be used in the conservative therapy of breast cancer with low incidence of late side effects and with at least similar LTC as with percutaneous boost techniques. Furthermore, BT is preferable in some anatomical situations, especially in cases of deep-seated tumor bed in large volume breasts. Van Limbergen[72] compared dose distribu-

tions of 4.5 to 15 MeV electron beam boosts to different settings of interstitial implants. He found that for target depths reaching beyond 28 mm under the skin, interstitial implants delivered significantly lower skin doses than electron beams.

What should be the target volume for boost? – Requirements for target volume definition

Whatever boost method is used, a crucial point is to define the target volume adequately. The target volume for boost is usually defined as the tumor bed with 1 to 2 cm safety margin. So, accurate tumor bed delineation should be an important goal of treatment planning. In the past, only palpation, mammograms, surgical reports, and scars were available landmarks to localize the excision cavity. Nowadays, several techniques exist to maintain better coverage of the target volume.[8,63,73-79]

Ultrasound (US) examination

Some authors used US for localization of the excision cavity.[73-74] DeBiose et al[73] emphasized that US was an appropriate method for boost target definition only in the first 6-8 weeks after surgery. Rabinovitch et al[74] prospectively compared the precision of different methods in target volume delineation. He found that radiographic evaluation of surgical clips was better than US for defining the lumpectomy cavity, since US significantly underestimated all three dimensions of the excision cavity.

Titanium tumor bed clips

The majority of authors suggested that the best orientation was given by titanium marker clips implanted by the surgeon intraoperatively.[8,73-78] The ideal approach is to place 6 clips into the walls of the excision cavity according to its latero-medial, antero-posterior, inferior, and superior dimensions. It should be emphasized that small titanium clips do not alter the dose distribution during RT, and the quality of diagnostic MR images, afterwards.[63]

Cross-sectional imaging – CT and MRI

The irregular 3 dimensional (3D) shape of the excision cavity and the normal tissue structures can only be localized correctly on the visual information obtained from cross-sectional imaging.[8,63,76,78-79] The use of surgical clips and CT or MRI together seems to be the best method to determine the target volume, since both titanium clips and borders of the excision cavity can be visualized exactly from slice to slice. Recently Vicini et al[79] and Polgár et al[63,78] implemented 3D virtual BT of breast cancer based on two sets (pre- and postimplant) of CT scans (***Figure 1***). They found that 3D virtual BT showed excellent agreement in target volume coverage between the preplanned virtual implant geometry and the actual position of the final afterloading needles.[63,79]

Intraoperative implantation – perioperative brachytherapy

Electron boost treatments are given continously following whole breast RT. Interstitial boost implantations are usually performed 2-3 weeks after the completion of teletherapy. However, some authors deliver BT boost using Iridium-192 implants at the time of surgery before whole breast irradiation.[23,80-81] The advantage of the intraoperative implantation is that it is possible to place the afterloading catheters more accurately in the tumor bed (***Figure 2***). In addition, the implant can be loaded within 24 hours after the surgery and the overall treatment time is shortened by 2 weeks. However, limitation of this procedure is that at the time of implantation there is lack of detailed histological information about whether boost is indicated at all. On the other hand, intraoperative implantation require good collaboration and time management between the surgeons and radiation oncologists.

Intraoperative radiation therapy (IORT)

The preliminary results of a dose escalation study to investigate the feasibility of applying single doses of IORT from 10 Gy up to 22 Gy have been reported very recently from the European Institute of Oncology, Milan.[82] A dedicated portable IORT equipment with different electron energies was used. Eighteen patients, treated with 10 and 15 Gy IORT, received an additional

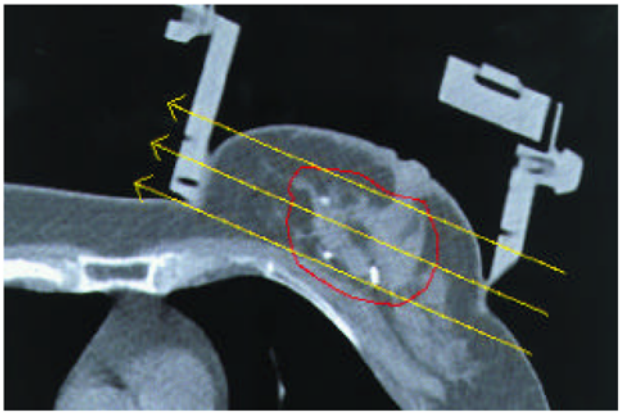

Figure 1. *3D virtual brachytherapy – preimplant CT-scan with template on the breast. Three titanium clips mark the boundaries of the excision cavity. Target volume is delineated (red); preplanned position of implant needles in three planes (yellow arrows).*

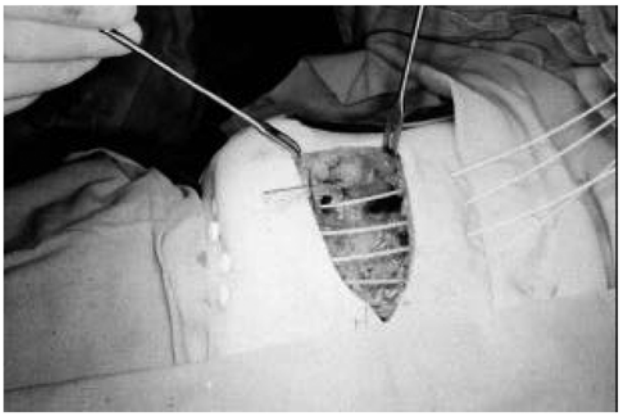

Figure 2. *Intraoperative implantation with 4 flexible afterloading catheters for perioperative HDR brachytherapy of the tumor bed.*

whole breast RT of 44 and 40 Gy postoperatively. No acute side effects, or intermediate untoward effects after a follow-up from 3 to 9 months, related to IORT were observed.

The authors concluded that long-term follow-up is necessary to demonstrate whether large single fractions of IORT might have the potential of sufficient LTC without major side effects. However, IORT has the same advantages and disadvantages as with perioperative BT. Furthermore, a dedicated linear accelerator is also needed, exclusively used for IORT.

Consensus statements of the GEC-ESTRO and guidelines of the American Brachytherapy Society

Based on the evolving retrospective data and recently published results of randomized trials, the European brachytherapy society (GEC-ESTRO) organized a consensus meeting on breast cancer in June 2001 to answer the question "To boost or not to boost and how to do it".[31] Statements from this meeting has not been published yet.[83] However, a consensus have been established by the participants for most aspects of boost irradiation. It was generally accepted that all patients should be routinely boosted for whom the 5-year local recurrence rate after BCS and whole breast RT assumed to be > 5%. This high risk subset of patients involves all women with age less than 50 years, with positive or close resection margins, and with EIC. It was also stated that intraoperative clip demarcation of the excision cavity should be routinely used as a minimal requirement for target volume definition.

The American Brachytherapy Society (ABS) has also published their guidelines specifically for the use of brachytherapy in breast carcinoma.[24] They stated that if a boost was deemed necessary, either electrons or BT could deliver the desired dose. BT should be used selectively as a boosting technique in situations in which a higher dose may be required because of larger tumor burden include:

- close, positive, or unknown margins
- an EIC
- a younger patient.

Conclusions, controversies, and future prospects

The results of numerous retrospective and some prospective studies suggest that boost dose increases LTC for patients treated with BCS and whole breast RT. At least two randomized trials have shown that boost significantly reduced local recurrence rate, even after excision of the primary tumor with clear surgical margins. Young age (< 50 years), positive or close surgical margins, and EIC should be viewed as absolute indications for boost irradiation. Interstitial BT boost (either LDR or HDR) can be used in the conservative therapy of breast cancer with low incidence of late side effects and with at least similar LTC as with percutaneous boost techniques. Furthermore, BT is preferable in some anatomical situations, especially in cases of deep-seated tumor bed in large volume breasts. Minimal requirement for boost target localization is the use of titanium clips to mark the walls of the excision cavity intraoperatively. Recently established guidelines for boost irradiation will help clinicians in their medical decisions on this issue. However, some aspects of boost irradiation still remain controversial. The final results of prospective boost trials with longer follow-up, involving analyses based on pathologically defined subgroups, will clarify the value of other possible prognostic factors for local recurrence. A metaanalysis of randomized studies would be also recommended. Preliminary results with recently developed boost techniques (IORT, CT-image based 3D conformal BT, and 3D virtual BT) are promising. However, more experience and longer follow-up are required to define whether these methods might improve LTC for breast cancer patients treated with BCS and RT.

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