

State of the art in breast intraoperative electron radiation therapy after intraoperative ultrasound introduction

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Background. Breast intraoperative electron radiation therapy (B-IOERT) can be used in clinical practice both as elective irradiation (partial breast irradiation – APBI) in low risk breast cancer patients, and as an anticipated boost. The procedure generally includes the use of a shielding disk between the residual breast and the pectoralis fascia for the protection of the tissues underneath the target volume. The aim of the study was to evaluate the role of intraoperative ultrasound (IOUS) in improving the quality of B-IOERT.

Patients and methods. B-IOERT was introduced in Trieste in 2012 and its technique was improved in 2014 with IOUS. Both, needle and IOUS were used to measure target thickness and the latter was used even to check the correct position of the shielding disk. The primary endpoint of the study was the evaluation of the effectiveness of IOUS in reducing the risk of a disk misalignment related to B-IOERT and the secondary endpoint was the analysis of acute and late toxicity, by comparing two groups of patients treated with IOERT as a boost, either measured with IOUS and needle (Group 1) or with needle alone (Group 2). Acute and late toxicity were evaluated by validated scoring systems.

Results. From the institutional patients who were treated between June 2012 and October 2019, 109 were eligible for this study (corresponding to 110 cases, as one patients underwent bilateral conservative surgery and bilateral B-IOERT). Of these, 38 were allocated to group 1 and 72 to group 2. The target thickness measured with the IOUS probe and with the needle were similar (mean difference of 0.1 mm, $p = 0.38$). The percentage of patients in which the shield was perfectly aligned after IOUS introduction increased from 23% to more than 70%. Moreover, patients treated after IOUS guidance had less acute toxicity (36.8% vs. 48.6%, $p = 0.33$) from radiation therapy, which reached no statistical significance. Late toxicity turned out to be similar regardless of the use of IOUS guidance: 39.5% vs. 37.5% ($p = 0.99$).

Conclusions. IOUS showed to be accurate in measuring the target depth and decrease the misalignment between collimator and disk. Furthermore there was an absolute decrease in acute toxicity, even though not statistically significant, in the group of women who underwent B-IOERT with IOUS guidance.

Key words: breast cancer; intraoperative electron radiation therapy; ultrasound; whole breast radiotherapy

Introduction

Breast cancer is the most common malignant disease among women and about 53 000 new cases were estimated in Italy in 2019.¹ It still represents the first cause of death for cancer among women, even though there is a downward trend in the mortality in recent years (0.8%/year), due to the spread of screening programs and to therapeutic progress.²

Adjuvant radiotherapy (RT) after breast conservative surgery is currently considered the standard treatment for early breast cancer and plays an important role to reduce local recurrences (LR) and to improve disease-free and overall survival.³

Traditionally whole breast radiation therapy (WBRT) consisted of a total dose of 50–50.4 Gy in 25–28 fractions. In recent years moderate hypofractionated WBRT has become the preferred dose-fractionation scheme, with a total dose of 40 Gy in 15 fractions or 42.50 Gy in 16 fractions, as loco-regional and survival endpoint analyses have demonstrated no inferiority compared to a conventionally fractionated schedule in several meta-analyses.^{4,5}

The use of an additional external boost, of 10–16 Gy to the tumor bed can reduce the local failure rate from 10.2% to 6.2% ($p < 0.0001$).⁶ This effect could be observed in all age-classes whereas the absolute gain is greatest in the group below 40 years. So far the impact of the boost has not yet been explicitly investigated in hypofractionation trials.^{4,5}



FIGURE 1. First case of breast intraoperative electron radiation therapy (B-IOERT) in Trieste using the dedicated electron beam accelerator Mobetron by IntraOp® Company.

Intraoperative electron beam radiotherapy (IOERT) in the treatment of early-stage breast cancer was introduced into the clinical practice at the end of the 1990s, when dedicated mobile linear accelerators (Linacs) became available.⁶ It can be used both as elective RT to the partial breast as accelerated partial breast irradiation (APBI) and as an anticipated boost.^{6–8} In this case, it shortens the total radiation treatment time by 1–1.5 weeks and improves the precision of dose delivery to the tumor bed, which provides high local in-breast control rates for patients allocated to every risk group.⁸

Clinical data and technical details for both possible types of IOERT application, as a boost and as APBI, were summarized and discussed extensively within recently published ESTRO-guidelines.⁹

Beside others, in breast intraoperative electron radiation therapy (B-IOERT) the protection of the tissues underneath the target volume, as the heart, lungs, and bony structures, is obtained by positioning a shielding disk between the residual breast and the pectoralis muscle. The two main criticalities in this step of the procedure are the misalignment and the wrong orientation of the disk.^{10,11}

B-IOERT was introduced in the “Azienda Sanitaria Universitaria Integrata” of Trieste in 2012 using the Mobetron® (IntraOp Medical, Inc. Santa Clara, CA), a “dedicated” electron beam accelerator, that produces electrons with nominal energies of 6, 9, and 12 MeV at dose rates up to approximately 10 Gy/min (Figure 1). Initially it was used as an anticipated boost in the treatment of early breast cancer and since March 2018 also as APBI in selected patients, according to the international recommendations.¹² Its technique was improved in 2014 with IOUS. Both needle and IOUS were used to measure target thickness; the latter was used even to check the correct position of the shielding disk.

The primary endpoint of this retrospective study was the evaluation of the role of IOUS in reducing the risk of the disk misalignment related to B-IOERT and the secondary endpoint was the analysis of acute and late toxicity, by comparing two groups of patients treated with IOERT as a boost, whose target was measured either with IOUS and needle (Group 1) or with needle alone (Group 2).

Patients and methods

This is a retrospective cohort analysis of prospectively recorded data involving patients who underwent B-IOERT as an anticipated boost between

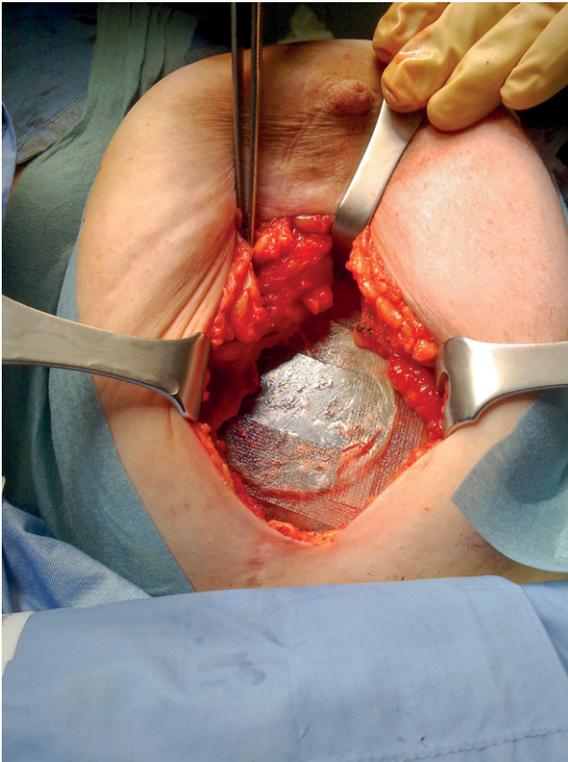


FIGURE 2A. The shielding disk positioned beneath the tumor bed during the operation.

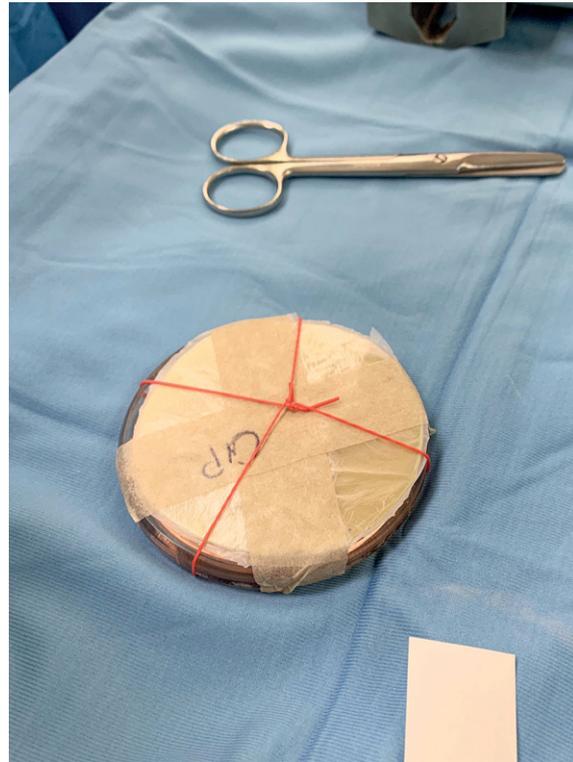


FIGURE 2B. The disk provided by IntraOp® Company, made up of three stacked layers.

June 2012 and November 2019 in the “Azienda Sanitaria Universitaria Integrata di Trieste”.

B-IOERT boost dose prescription was 10 Gy specified as maximum dose; the planning target volume (PTV) should be encompassed by 90% of the prescribed dose (*i.e.* 9 Gy); dose inhomogeneity: -10% within the target volume was allowed. It was followed by conventionally fractionated WBRT with a total dose of 50 Gy (2 Gy/25 fr.).

Since November 2014 we have taken part in the HIOB protocol (Hypofractionated Whole-Breast Irradiation preceded by Intra-Operative Radiotherapy with Electrons as anticipated Boost – Prospective one-armed multi-center-trial), after the approval of the Regional Ethics Committee.

The anticipated IOERT boost dose was 11,10 Gy, specified at the point of maximum dose on the central axis depth dose curve, and it was followed by hypofractionated WBRT with a total dose of 40,5 Gy in 15 fractions, 2,7 Gy/fr.¹³ First clinical results on treatment tolerance (toxicity and cosmetic outcome) were published in 2020.¹⁴

In the whole series before starting IOERT (either as a boost or as the unique radiation treatment), a shielding disk was positioned beneath the tumor bed on the pectoralis muscle (Figure 2A). A disk

provided by IntraOp® Company was employed, made by stacking a 5 mm polymethyl methacrylate (PMMA) layer, a 3 mm copper layer and 2 mm PMMA layer (Figure 2B).¹⁵

The optimum size of the shielding disk depends upon the electron applicator chosen for the treatment. As described in our research and in some recent studies, the set-up of normal tissue protection and applicator placement are closely correlated with two very relevant risks in IOERT treatments: misalignment and wrong orientation of the shielding disk.^{11,16,17} The low accuracy in the alignment of the disk would cause the delivery of an excess of dose to the underlying normal tissues. The surrounding healthy gland was sutured above the shielding disk.

Initially target depth was measured with a needle in 5 different points of the tumor bed and the average value was assumed in order to select the proper electron energy. Since the end of 2014, when HIOB Protocol was introduced, both needle and IOUS were used in a certain number of cases, to obtain 5 measures of the target thickness and the latter was used even to check the correct position of the shielding disk. An Esaote MyLab™One/Touch equipment with SL 3332 linear probe was applied.

The effectiveness of the correct localization by IOUS was verified employing “in vivo dosimetry”. A properly calibrated EBT3 radiochromic film can be fixed on both faces of the disk, allowing to obtain two images that provide a detailed bidimensional dose distribution. From the first image, obtained just below the target, it is possible to measure the absolute entrance dose in that position. Moreover, the visual analysis acquired within the prepared target tissue can provide the surgeon with an effective feedback about the actual homogeneity acquired in the reconstruction of the target. From the second image positioned beyond the shielding disk, it is possible to evaluate the fraction of the dose passing through the disk and arriving at the underlying healthy tissue.¹⁵

The post-processing analysis of the dose distribution measured on the films provides a quantitative estimate of the misalignment between the collimator and the disk.

In order to investigate possible differences in the target thickness between needle and IOUS, which could alter the results, we compared preliminarily these measures in a sample of 23 patients.

Between June 2012 and October 2019 a total of 109 women (corresponding to 110 cases, as one patient underwent bilateral conservative surgery and bilateral B-IOERT for two different cancers on both breasts) underwent B-IOERT as an anticipated boost and 35 of them entered the HIOB trial.^{13,14} In 38 cases both needle and IOUS were used (Group 1) and in 72 only the needle (Group 2).

Acute toxicity was rated according to the Radiation Therapy Oncology Group (RTOG) criteria¹⁸ and late toxicity to the LENT-SOMA score, respectively.¹⁹

This study was approved by the Institutional Review Boards of the Hospital and all patients signed preoperatively a specific informed consent.

Statistical analysis

The statistical analysis was performed by R software (version 3.5.0). Shapiro-Wilk test was applied to quantitative (continuous) variables to check for distribution normality. Continuous variables were reported as median with range (minimum-maximum). Qualitative (categorical) variables were reported as absolute frequencies and/or percentages. Measures of target thickness (in mm) between needle and IOUS were compared by paired student's *t* test for every patients and overall. Moreover, Lin's concordance correlation coefficient (ρ_c) was calculated to evaluate the agreement on target thick-

ness obtained by the two methods. ρ_c ranges from 0 to 1, with perfect agreement at 1 while values near to 0 indicates no agreement. The value of ρ_c was interpreted according to the Mc-Bride classification (< 0.90: poor; 0.90–0.95: moderate; 0.95–0.99: substantial; > 0.99: almost perfect). Categorical variables were compared by Chi-square test or Fischer's exact test whenever appropriate. All p-values were calculated from 2-sided tests using 0.05 as the significance level.

Results

Description of the population

Information on patient characteristics and adjuvant systemic treatments of the whole population and of the two groups are summarized in Table 1. Baseline characteristics are similar between treatment groups. The median age of the entire cohort of patients was 67 years (range: 43–85).

Two patients (one belonged to Group 1 and the other to Group 2) refused adjuvant radiotherapy and one (Group 2) performed it elsewhere.

Of note, two patients did not receive the allocated systemic therapy: one was discouraged for endocrine therapy due to severe osteoporosis and the second refused chemotherapy without compensating it by another oncological relevant medication.

With a median follow-up of 52 months (range: 5–87), 3 patients died of breast cancer and 4 of other causes; one patient is alive with progressive disease and another one was treated for a contralateral tumor and is disease-free at the last follow-up.

Effect of IOUS

The target thickness detected preliminarily with IOUS in a sample of 23 patients turned out to be completely in agreement with the measures obtained with the needle, with Lin's concordance coefficient $\rho_c = 0.98$, 95%CI: 0.96:0.99 and with a negligible average difference of 0.1 mm (range 0.1–1.2 mm) ($p = 0.38$) as described in Supplementary Table 1.

The EBT3 “in vivo dosimetry” showed that IOUS guidance achieved a reduction in the misalignment with an electron field area outside the shielding disk reduction from 5.6 cm² to 2.6 cm².

After IOUS introduction, the percentage of patients in whom the shield was perfectly aligned, defined as a field totally inside the shield, increased from 23% to more than 70%. The proper

TABLE 1. Description of the population

Variables	All cohort (n = 110)	Group 1 (n = 38)	Group 2 (n = 72)	p-value
Age (years) Median (range)	67 (43–85)	67 (48–80)	67 (43–85)	p = 0.51
Clinical stage				
cT1a N0	2 (1.8%)	1 (2.6%)	1 (1.4%)	p = 0.42
cT1b N0	47 (42.8%)	20 (52.6%)	27 (37.5%)	
cT1c N0	59 (53.6%)	17 (44.8%)	42 (58.3%)	
cT1b N1	1 (0.9%)	0 (0.0%)	1 (1.4%)	
cT2 N0	1 (0.9%)	0 (0.0%)	1 (1.4%)	
Histological type				
Ductal carcinoma in situ (DCIS)	1 (0.9%)	1 (2.6%)	0 (0.0%)	p = 0.46
Invasive ductal carcinoma	70 (63.6%)	26 (68.4%)	44 (61.1%)	
Invasive lobular carcinoma	19 (17.3%)	5 (13.2%)	14 (19.45%)	
Others	20 (18.2%)	6 (15.8%)	14 (19.45%)	
Multifocal disease	6 (5.4%)	4 (10.5%)	2 (2.8%)	p = 0.21
Pathological Stage pT				
pTis	1 (0.9%)	1 (2.6%)	0 (0.0%)	p=0.40
pT1a	3 (2.7%)	0 (0.0%)	3 (4.2%)	
pT1b	41 (37.3%)	16 (42.1%)	25 (34.7%)	
pT1c	59 (53.6%)	20 (52.6%)	39 (54.2%)	
pT2	6 (5.5%)	1 (2.6%)	5 (6.9%)	
Pathological Stage pN				
pN0	88 (80.0%)	32 (84.2%)	56 (77.8%)	p=0.71
pN1mi	7 (6.4%)	3 (7.9%)	4 (5.6%)	
pN1a	14 (12.7%)	3 (7.9%)	11 (15.3%)	
pN3	1 (0.9%)	0 (0.0%)	1 (1.4%)	
Grading				
G1	15 (13.7%)	7 (18.4%)	8 (11.1%)	p = 0.67
G2	68 (61.8%)	24 (63.2%)	44 (61.1%)	
G3	21 (19.1%)	6 (15.8%)	15 (20.8%)	
Gx	6 (5.4%)	1 (2.6%)	5 (7%)	
Adjuvant therapy*				
None	2 (1.8%)	0 (0.0%)	2 (2.8%)	p = 0.92
Chemotherapy	6 (5.5%)	2 (5.4%)	4 (5.6%)	
Endocrine therapy	85 (78%)	29 (78.4%)	56 (77.7%)	
Chemotherapy + Endocrine therapy	12 (11%)	4 (10.8%)	8 (11.1%)	
Chemotherapy + Trastuzumab	4 (3.7%)	2 (5.4%)	2 (2.8%)	

* Calculated on 109 patients

alignment with IOUS improved the absolute dose accuracy and tripled the number of patients without disk misalignment. The results of post processing analysis of the dose distribution measured on film, the collimator used, the estimated dose, the area outside the shielding disk and the dose map distribution are presented in Figure 3.

In the whole series acute toxicity, detected 4 weeks after WBRT, occurred in 49 patients (44.5%): G1 in 36 (32.7%) and G2 in 13 (11.8%) of them. The most common acute reaction was erythema due to postoperative WBRT. As perioperative complications the occurrence of seroma (one case), hematoma (2 cases) and lymphocele (2 cases) were identified. With regard to clinical collateral effects, patients allocated to group 1 developed less radiation induced acute toxicity compared to group 2 (36.8%

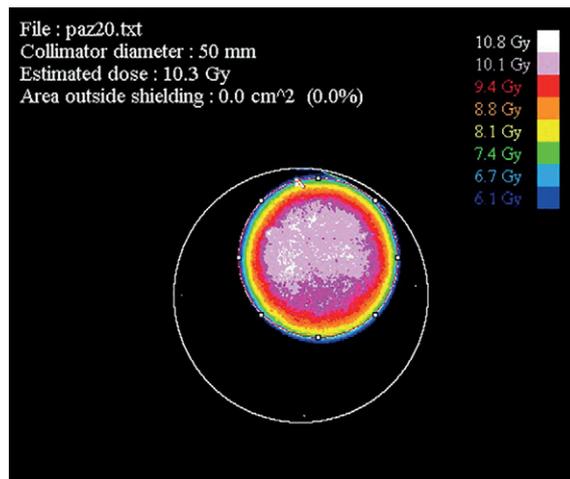


FIGURE 3. Post processing analysis of the dose distribution measured on film.

TABLE 2. Acute toxicity of radiotherapy in the two groups

	Group 1 (n = 38)	Group 2 (n = 72)	Total (n = 110)
Grade 0	23 (60.5%)	36 (50%)	59 (53.6%)
Grade 1	8 (21.1%)	28 (38.9%)	36 (32.7%)
Grade 2	6 (15.8%)	7 (9.7%)	13 (11.8%)
Grade X	1 (2.6%)	1 (1.4%)	2 (1.9%)
Grade 1-2	14 (36.8%)	35 (48.6%)	49 (44.5%)

Group 1 = cases treated with breast intraoperative electron radiation therapy (B-IOERT) as a boost in which both needle and intraoperative ultrasound (IOUS) were used; Group 2 = cases treated with B-IOERT as a boost in which only the needle was used

TABLE 3. Late toxicity of radiotherapy in the two groups

	Group 1 (n = 38)	Group 2 (n = 72)	Total (n = 110)
Grade 0	22 (57.9%)	43 (59.7%)	65 (59.1%)
Grade 1	12 (31.6%)	24 (33.3%)	36 (32.7%)
Grade 2	3 (7.9%)	3 (4.2%)	6 (5.5%)
Grade X	1 (2.6%)	2 (2.8%)	3 (2.7%)
Grade 1-2	15 (39.5%)	27 (37.5%)	42 (38.2%)

Group 1 = cases treated with breast intraoperative electron radiation therapy (B-IOERT) as a boost in which both needle and intraoperative ultrasound (IOUS) were used; Group 2 = cases treated with B-IOERT as a boost in which only the needle was used

vs 48.6%), which turned out as not statistically significant ($p = 0.33$) (Table 2).

Late toxicity, evaluated at the last follow-up, was observed in 42 patients (Grade 1: 36 cases; Grade 2: 6 cases). There was a negligible difference in the two groups of patients: 39.5% (Group 1) vs. 37.5% (Group 2) ($p = 0.99$). (Table 3). The most common type of sequelae were: fibrosis/fat necrosis (G1/2: 21.8%) and breast edema (G1/2: 6.4%). In the whole population no Grade 3 acute and late toxicity occurred.

Detailed results for late toxicity according to LENT-SOMA score are summarized in Supplementary Table 2. As regards the different WBRT schedules, no significant differences were detected for acute and late toxicity (Supplementary Table 3A, 3B).

Discussion

The primary objective of this analysis was to evaluate the role of IOUS in improving the quality and in reducing the risks related to B-IOERT.

We could demonstrate that IOERT is a safe treatment modality; the target thickness measures

performed with the needle were comparable with those obtained with IOUS. Moreover IOUS contributed considerably to optimize the alignment of the shielding disk.

At present, a commercially available treatment planning system (TPS) for IOERT, which allows to accurately illustrate a dose distribution within the target as well as the surrounding tissues, is used only by a small number of Centers.²⁰ The process leading to intraoperative radiation treatment, without TPS, is mostly the result of a sequence of manually handled actions involving the Surgeon, the Radiation Oncologist, the Medical Physicist, the Technicians and the Nurses of the operating room.^{9,11}

Some papers examined the importance of risk assessment analysis applied to IOERT procedure: in the Italian publications a dedicated mobile Linac was used, while in the Spanish analysis the irradiation was performed with a conventional Linac.^{11,16,17} In all of the studies the highest risk was associated with the alignment of the shielding disk, as it was observed in our experience.

The low accuracy in the alignment of the disk would cause the delivery of an excess of dose to the underlying normal tissues and is mainly related to the lack of direct visual disk control.¹¹ Selecting a plate much larger than the applicator size and fixing it to the pectoralis fascia is some effective corrective actions. The introduction of intraoperative ultrasound allows to check the position of the shielding disk as well as to better define the target thickness and is an important strategy for reducing the risk of shield misalignment and incorrect thickness measures.

The secondary endpoint of the study was the evaluation of early and late toxicity in the whole series with the comparison between the group of patients who underwent IOUS examination vs. the group who underwent only needle measures.

The target volume with IOERT boost is smaller than the volume with conventional EBRT boost. This leads to a reduction in the radiation exposure of the subcutaneous tissues and intra-thoracic organs (i.e. lungs and heart). Besides it avoids the irradiation of the skin and of the contralateral mammary gland, reducing both the short-term and long-term sequelae correlated with RT and resulting in good cosmesis.⁹

To date various papers have been published on IOERT boost in the treatment of early-stage breast cancer, with the largest deriving from a pooled analysis of the International Society of Intraoperative Radiation Therapy (ISIRT)

Europe, which was updated for the Salzburg cohort with a 10 year follow-up in 2018.^{21,22} Excellent local control was reported in all the studies and side effects were generally low and acceptable. Merrick *et al.* reported 11% delayed fibrosis around the tumor bed and late breast or arm pain in 8% of patients; Lemanski *et al.* Grade 2 subcutaneous fibrosis in 14% and late breast or arm pain in 8% of patients.^{23,24} In the Salzburg experience less than 2% of patients developed G3 late toxicity.⁸ In the prospective study by Wong *et al.*, there was no G3 acute toxicity; two patient developed G3 late toxicity (3.8%) and 5 patients (9.6%) fat necrosis.²⁵ In these studies conventionally fractionated WBRT (total dose: 50–56 Gy/25–28 fr.) was delivered. In a retrospective German study 14 of 157 patients (8.9%) were treated with hypofractionated WBRT; the whole acute skin toxicity was evaluable in 153 patients: G1 in 75.2%; G2 in 15.7% and G3 in 4.6%, 6–8 weeks after WBRT.²⁶

In three prospective investigations, IOERT boost was combined with hypofractionated WBRT. In the report by Ivaldi *et al.* G1 and G2 acute toxicity were found in 79/132 (59.8%) and in 22/132 (16.7%) respectively, and G3 in 3/132 (2.3%) patients one month after the end of WBRT.²⁷ The recorded late skin toxicity was Grade 4 in one patient, Grade 3 in another one and Grade 2 or less in 106/108 cases (98.2%) with a median follow-up of 11 months. In the study by Bhandari *et al.* only 24 patients underwent IOERT as a boost; after a short follow-up (12 months), G1 and G2 acute toxicity was present in 47.8% and 4.4% of the cases, respectively; late toxicity in 40% (G1) and in 10% (G2) of the cases.²⁸ In the recent paper from HIOB prospective multicenter trial, G0–1 acute effects were noted in 92% of patients and G3 in one patient, 4 weeks after the end of WBRT; G0–1 late toxicity in 93%, G2 in 4.3% and G3–4 in 2.7% of cases at 4 years.¹⁴

Our results are similar to the data reported in the other series and even better than the results of the early published reports. Additionally the effectiveness of IOUS application during IOERT procedure was analyzed and less acute toxicity, even if not statistically significant, was observed in the group of women who underwent B-IOERT with IOUS guidance. As regards G1–G2 late toxicity, no differences in the two groups of patients were detected. No grade 3 and 4 acute and late toxicity were present in both treatment groups.

To our knowledge no other studies evaluated shielding disk misalignment and possible correlations with acute or late toxicity in B-IOERT procedure. However, these results should be taken with

caution. First of all this is a retrospective study; besides the analysis was carried out on a small series of patients and median follow-up is rather short. A longer follow-up is advisable, to monitor the incidence of late toxicity.

Conclusions

In this study, IOUS turned out to be an excellent intraoperative imaging modality that allows to measure the thickness of the tumor bed, to optimize the position of the shielding disk and it possibly contributes to decrease adverse effects in term of acute toxicity. Its application is advisable also in other areas of intraoperative radiation treatments.

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