








Long-term results of breast cancer patients who received IOERT as boost during BCS: A single-institution retrospective analysis

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ABSTRACT

Objective: Intraoperative electron radiotherapy (IOERT) applied as boost to the tumor bed during breast conserving surgery is advantageous in terms of local recurrence in breast cancer patients. In addition, it has other advantages over the adjuvant boost RT such as no risk of tumor bed change, ease of sequencing radiotherapy chemotherapy, and reduced workload of the radiotherapy clinic. This study aimed to evaluate the long-term results of our patients who were treated with this method in our institution and are still being followed up.

Material and Methods: One hundred and three patients enrolled in this study received IOERT equivalent to 10 Gy as boost during BCS and were subsequently given adjuvant WBI according to the biological subtype of the tumor systemic therapy. These patients were analyzed using their files and hospital records. Patients were evaluated for overall survival, local recurrence, distant metastasis, and cosmetic outcome (using LENT-SOMA scale).

Results: Median age was 53,5 (27-74), mean follow-up time was 75 (48-106) months. Mean pathological tumor size was 18 mm (4-30), 90 of the patients had invasive ductal carcinoma, eight of them were lobular and five of them had mixed histological structure. Ninety-three of the patients presented histological grade II, 15 grade III; 74 patients were luminal A-like, 15 luminal B-like, eight HER2 positive and six triple negative breast cancer. According to the LENT-SOMA scale, 35 had grade 0, 42 each had grade I, 23 had grade II, and two had grade III. All patients underwent whole breast irradiation after surgery, 81 received chemotherapy and 90 endocrine therapy. There was one local recurrence, distant recurrence was seen in four patients and one patient died of non-breast cancer causes. Overall survival was %99, and event free survival %96.

Conclusion: IOERT for breast cancer treatment during BCS is a safe option with low chronic toxicity and the cosmetic outcome gets better over time.

Keywords: Breast cancer, breast conserving surgery, boost radiotherapy, intraoperative electron radiotherapy, LENT-SOMA

INTRODUCTION

Currently, breast conserving surgery (BCS) and radiotherapy (RT) have become the standard approach in every case who is eligible for BCS regardless of stage in the regional treatment of breast cancer. Whole breast irradiation (WBI) as adjuvant therapy and boost RT applied to the tumor bed effectively control the tumor bed and around 1-2 cm where local recurrences are most common (1-4).

Thanks to the developments in the field of radiotherapy, intraoperative electron radiotherapy (IOERT) is an important option to reach the required effective dose in the tumor bed in a short time during the operation, which is applied as a boost to the tumor bed by direct visualization during breast-conserving surgery and is advantageous in terms of local recurrence in patients with breast cancer. In addition, it has other advantages over the adjuvant boost RT, such as no risk of tumor bed changes. After the final pathology report, the treatment plan may differ in chemotherapy (CT) and RT sequence and may require modification. The marker clip, which is placed in the original location of the tumor during surgery, can be displaced in the postoperative period because of the seroma and etc., and focus on a different area in boost planning, also healthy breast tissue can be exposed to extra RT (4-7). It gives an excellent sequencing chance where adjuvant chemotherapy takes precedence over external boost RT, IOERT is more likely to have local control (5,7). When compared with external adjuvant boost RT, it has been reported that there is a positive difference in favor of the patient, especially in terms of

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local recurrence after four years (8-10). In our previous study, the average follow-up period was three years, and local recurrence was less in the group that underwent IOERT (7). Another advantage is that by shortening the duration of adjuvant RT, it contributes to the correct use of time and resources allocated for the treatment of other patients treated in the same center (1,2,5,7).

The aim of this study was to evaluate the long-term results of our patients who were treated with this method in our institution and are still being followed up.

MATERIAL and METHODS

One hundred and three patients who were treated with the diagnosis of breast cancer in our clinic between October 2013 and June 2018 were included in this study. After a treatment plan was made in the multidisciplinary breast cancer committee, the patients were selected among those eligible for IOERT. They received IOERT as boost during BCS followed by WBI and, if necessary, systemic therapy. IOERT as boost, an electron equivalent to 10 Gy was applied via Mobetron with an average 865 (773-954) monitor unit (MU) and 90% reference isodose with 6 MeV energy (Table 1). Mobetron® (registered trademark of IntraOp Medical, Inc., USA) is an electron linear accelerator designed to deliver electron beam IOERT to treat cancer during surgery. These patients were analyzed using their files and hospital records. Patients were evaluated for overall survival, local recurrence, distant metastasis, and cosmetic outcome.

The risks of overall survival, local recurrence and event-free survival were performed by the Kaplan-Meier method and late effects normal tissue/subjective objective management

Table 1. Patient and tumor characteristics

Patient and tumor characteristics	n= 103
Age (median) range (27-74)	53.5
Follow-up time	75 (48-106)
Tumor diameter (mm)	18 (4-30)
T1a	3
T1b	16
T1c	66
T2	18
Histology-	
Invasive ductal	90
Invasive lobular	8
Mixt	5
Tumor grade (0-III)	2
Luminal A	74
Luminal B	15
HER2 neu positive	8
TNBC	6

Table 2. LENT-SOMA scale V06, 7/2003, for breast carcinoma radiotherapy: Post radiation fibrosis

Grade 0	None
Grade I	Rarely palpable/increased density
Grade II	Definite increased density and firmness
Grade III	Marked density, retraction and fixation

analytic [LENT-SOMA (V06-7/2003)] scale was used for cosmetic scoring (Table 2) (7). The study was approved by the ethics committee of the hospital, with the decision dated 17.10.2022/278.

RESULTS

Median age was 53.5 (27-74) years and mean follow-up was 75 (48-106) months. Mean pathological tumor size was 18 (4-30) mm, 90 of the patients had invasive ductal carcinoma, eight had lobular and five had mixed histological structure. Ninety-three of the patients presented histological grade II, 15 grade III; and 74 patients showed luminal A-like, 15 luminal B-like, eight HER2-positive, and six triple-negative molecular subtypes; and finally, 35 of them were evaluated as 0, 42 of them as first, 23 of them as second and two of them as third grade according to LENT-SOMA scale.

All patients underwent whole breast irradiation after surgery, 81 received chemotherapy and 90 received endocrine therapy (Table 2).

While adjuvant treatment of the patients whose loco-regional treatment is completed continues, they are monitored every three months for the first two years and every six months in the following years in terms of systemic and cosmetic outcome. During the follow-up period, one patient died from causes other than breast cancer, one patient showed local recurrence and four patients showed distant metastasis.

A 62-year-old patient died due to sepsis at the hospital where she was treated for a broken femur fracture that occurred after a traffic accident at the end of the postoperative second year. The patient who underwent mastectomy for local recurrence at 92 months had invasive ductal carcinoma in the first operation, the subtype of the tumor was HER 2+, Ki 67 35%, and nuclear grade III. Histopathological examination after mastectomy showed luminal A like invasive ductal carcinoma, nuclear grade II, Ki 67 25%.

The patients with distant metastases were treated with chemotherapy, nephrectomy and radiotherapy, respectively, due to one lung, one liver, one kidney and one bone metastasis. They are still being followed up event free. Overall survival was 99% and event-free survival was 96% (Table 3). When evaluated in terms of total (a), disease-free (b), local recurrence (c), and distant metastasis (d) at 75-month follow-up, the following estimated values with 95% [confidence interval (CI)] were reached:

Table 3. Treatment and follow-up characteristics

Treatment and follow-up characteristics	n= 103, median follow-up for all patients was 75 (range 48-106) months.
BCS	103
SLNB	103
ALND	7
IOERT dose: Gray-equivalent MU= monitor U	10/862
Applicator surface median (mm)	5.4 (4-7)
WBI	103
Adjuvant chemotherapy	81
Adjuvant endocrine therapy	90
Local recurrence/time: 92 M	1 (Mastectomy)
Distant metastasis/time Liver-94.M Lung-88.M Kidney-44.M Bone (Vertebra)-59.M	4 Chemotherapy Chemotherapy Nephrectomy RT
OS	99%
DFS	96%
Cosmetic outcome: LENT-SOMA scale	75% excellent- 23% good/satisfactory 2% poor
Grade 0	35
Grade I	42
Grade II	23
Grade III	2

Overall survival; 109.1 ± 0.8 , (CI= 107.5-110.7), local recurrence free survival; 109.5 ± 0.4 , (CI= 108.6-110.4), disease' other causes'-free survival; 107.6 ± 1.02 (CI= 105.6-109.6), distant disease-free survival 108.1 ± 0.9 months (CI= 106.3-109.9) respectively (Figure 1).

DISCUSSION

BCS followed by WBI is applied as the standard method in the locoregional treatment of early-stage breast cancer. Based on the knowledge that more than 70% of local recurrences occur around the 2 cm radius of the tumor bed's focus, additional doses of Rt have been given to the tumor bed with different methods since 1985 (3). It has been shown in many studies that this approach significantly reduces local recurrence (1,4,6,8). By adding an additional dose of 16 Gy to the tumor bed, the EORTC 'boost versus no boost' trial reported a reduction of the 10-years LR rate from 10.2 to 6.2% (3).

We also know from other published studies that when IOERT is administered as a boost during BCS, it is clear that the risk of local recurrence is relatively low and toxicity rates seem accept-

able (2,3,8-11). In other words, the results of patients receiving IOERT as a boost during BCS show the similar or better overall and disease-free survival than postoperative external boost RT. The strongest influence on these results is the effect on the microenvironment, including the microvasculature or cytokine model, without tumor cell proliferation before and during radiotherapy, with the dose delivered as boost directly to the tumor bed immediately after tumor removal during surgery (1,2,9).

Blank et al. have reported that IOERT, as a tumor bed boost during BCS, decreases the risk of local recurrence and that the toxicity rates seem to be acceptable (6). Follow-up of 197 patients who received IOERT as boost, with a median duration of 37 months, had five local recurrences, six secondary cancers, and 11 distant metastases, resulting in a five-year disease-free survival of 81.0% and overall survival of 91.3%. Local recurrence-free survival at three and five years (invasive cancers) was 97.0% (6).

In our series, when we look at the results of the first three-year follow-up, no local recurrence or distant metastasis was detected in the IOERT group, while local recurrence was detected in one patient at the 20th month in the external boost RT arm, and distant metastasis was detected in another patient at the 32nd month. Mean follow-up was 35 and 38 months (7).

The greatest experience for electron-using IOERT is available in a single-institution retrospective study comparing preliminary results of IOERT as boost. Accordingly, the results of the study, although with mild toxicities, have favorable early oncologic outcomes for the breast (8). A retrospective study compared 188 external boost RT with 190 IOERT patients at five-year follow-up, the rate of intramammary recurrence in the external boost group was 4.3% compared to 0% in the IOERT group. This difference was statistically significant and was due to the reduction in true local recurrences previous index quartile (10).

In a series of 46 patients with a median tumor size of 16 mm and mean follow-up of 62 months, there was no local recurrence after equivalent to 10-12 Gy IOERT as boost during BCS, followed by WBI, but two patients (4.3%) showed distant recurrence. In this article, it was reported that the patients were evaluated with Common Terminology Criteria for Adverse Events (CTCAE) 4.0 for chronic radiation toxicity in the late period, fibrosis was detected in six patients, and it was scored as grade II, and there was no patient with grade III (11).

Retrospective analysis of 400 patients with IOERT, followed by whole breast irradiation were in terms of adverse events, evaluated prospectively over a period of up to 15 years (LENT-SOMA scales). Median follow-up was 78 months (2-180). Local recurrence occurred in 15 patients, resulting in a local recurrence rate of 2.0%, 6.6%, and 10.1% at five, 10, and 15 years, respec-

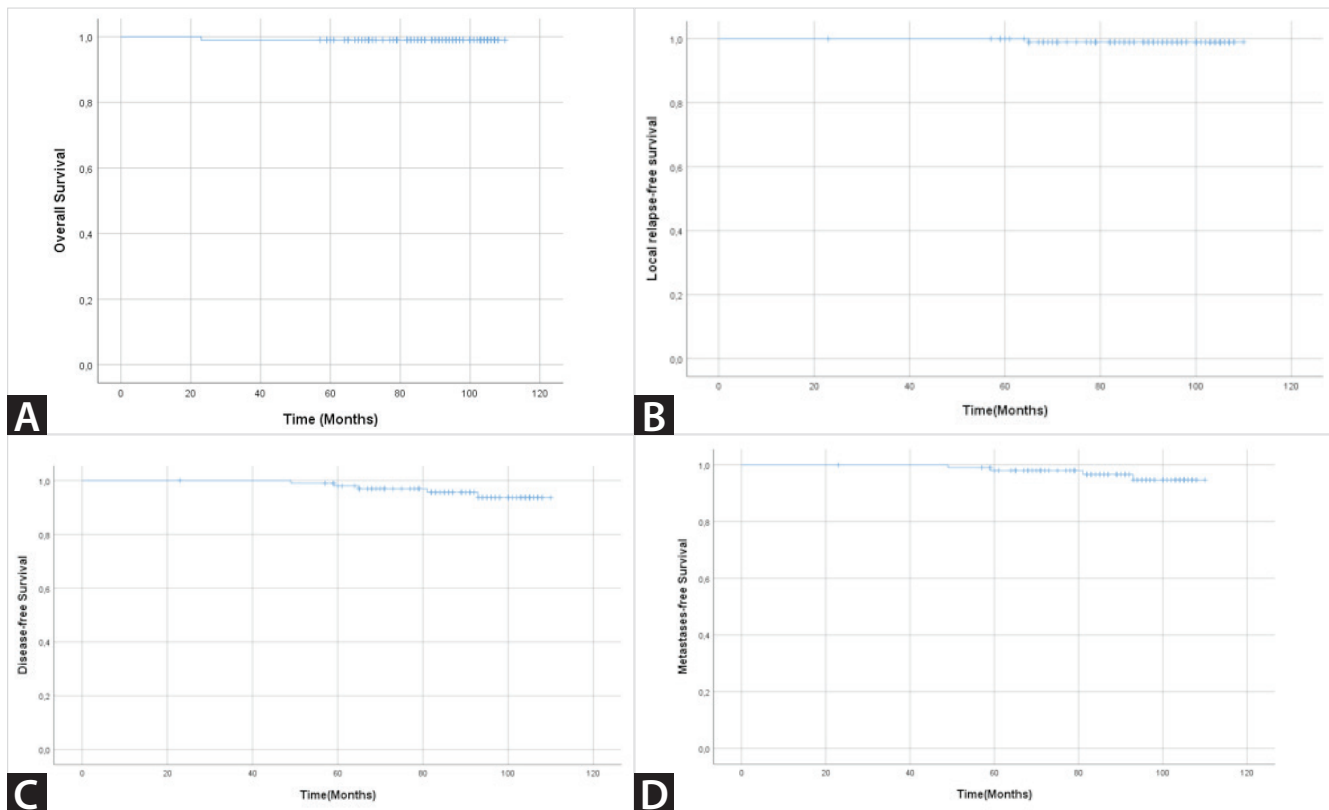


Figure 1. A. Overall survival: 109.1 ± 0.8 (107.5-110.7). B. Local recurrence-free survival: 109.5 ± 0.4 (108.6-110.4). C. Disease-free survival: 107.6 ± 1.02 (105.6-109.6). D. Distant metastase-free survival: 108.1 ± 0.9 (106.3-109.9).

tively. Overall survival rates at five, 10, and 15 years were 92.1%, 81.8%, and 80.7%, respectively (12). Local recurrence and overall survival were found to be better in our patients who had more than six years of follow-up. Side effects were similar to or less than expected from external beam boost RT, both in the Pez et al. series and in our patient group (13).

The results of studies published on this topic are also noteworthy: A correlation between breast size, tumor size, and cosmetic results has been reported. Similar results were obtained in our series and shared in the literature (13).

The series we presented with this study showed very low recurrence rates at an average follow-up of 75 months, as well as very few side effects such as fibrosis and pain. Those with fibrosis were defined as grade II, and the same patients reported pain relief when asked, but these side effects did not increase after three years. In our IOERT series, one patient had local recurrence at the 92nd month and mastectomy was performed, and distant metastasis was detected in four patients, and they are being followed up after their treatment. One of our patients died of a cause other than breast cancer (intra-abdominal sepsis).

Better overall and event-free survival results were obtained in our series when the articles reporting IOERT late outcomes with

similar follow-up times were reviewed. These studies, including our series, were designed retrospectively. We believe that this may be due to careful patient selection and better prognostic factors depending on molecular subtypes.

In a prospective study, 133 breast cancer patients received IOERT during BCS and compared 112 patients treated with postoperative external boost RT for local recurrence. While recurrences were observed in the IOERT arm at over 100 months of follow-up, the mean time to relapse was much earlier in external boost RT (55.2 months) group. The cumulative risk of IBTR at five and 10 years was 0.8% and 4.3%, respectively. IOERT group comparison with 4.2% and 5.3% after EBRT boost RT. Cosmetic results are significantly better in IOERT group compared to EBRT group and difference remained significant at any time. Cosmetic results are evaluated by both physicians and patients, both were similar and significantly better in IOERT group compared to external boost RT group and difference remained significant at any time (14).

At the end of a mean follow-up period of 36 months, only two of our patients were scored at grade III according to LENT-SOMA. Likewise, there was no change in the following years, and according to our patient records, it was observed that the cosmetic result was better tolerated in grade III patients.

This result is compatible with the data of the articles reported as the late outcome of the IOERT as boost group, namely that the cosmetic result is the same or better in subsequent years and that RT-related side effects occur most frequently in the first three years (5,8,11,12).

CONCLUSION

IOERT for breast cancer treatment during BCS is a safe option with low chronic toxicity and cosmetic outcome gets better over time. It also means less effort for the patient, fewer hospital visits and limits the use of healthcare resources.

Ethics Committee Approval: This study was approved by Istanbul Prof. Dr. Cemil Taşçıoğlu City Hospital Clinical Research Ethics Committee (Decision no: 278, Date: 17.10.2022).

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Author Contributions: Concept - SG, ÖK; Design - SG, ÖK; Supervision - SG, ÖK; Fundings - SG, BG, AA; Materials - SG, BG; Data Collection and/ or Processing - SG, BG; Analysis and/ or Interpretation - SG, BG, ÖK, AA, OY; Literature Search - SG, BG, ÖK; Writing Manuscript - SG; Critical Reviews - OY.

Conflict of Interest: The authors have no conflicts of interest to declare.

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**ORJİNAL ÇALIŞMA-ÖZET**

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Meme koruyucu cerrahi sırasında boost olarak IORT almış meme kanserli hastaların uzun dönem sonuçları: Tek merkez retrospektif analiziSemra Günay¹, Berk Gökçek², Özge Kandemir³, Arzu Akan¹, Orhan Yalçın¹¹ Sağlık Bilimleri Üniversitesi, Prof. Dr. Cemil Taşçıoğlu Şehir Hastanesi, Meme ve Endokrin Cerrahisi Kliniği, İstanbul, Türkiye² Sağlık Bilimleri Üniversitesi, Prof. Dr. Cemil Taşçıoğlu Şehir Hastanesi, Genel Cerrahi Kliniği, İstanbul, Türkiye³ Sağlık Bilimleri Üniversitesi, Prof. Dr. Cemil Taşçıoğlu Şehir Hastanesi, Radyasyon Onkolojisi Kliniği, İstanbul, Türkiye**ÖZET**

Giriş ve Amaç: Meme koruyucu cerrahi sırasında tümör yatağına boost şeklinde uygulanan intraoperatif elektron radyoterapi (IOERT) meme kanseri hastalarında lokal nüks açısından avantajlıdır. Biz de bu yöntemle tedavi edilen ve halen takipleri devam eden hastalarımızın uzun dönem sonuçlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışmaya alınan 103 hasta, BCS sırasında boost olarak 10 Gy'ye eş değer IORT aldı. Daha sonra tüm meme ışınlandı ve tümörün biyolojik alt tipine göre sistemik tedavi verildi. Bu hastalar dosyaları ve hastane kayıtları kullanılarak analiz edildi ve genel sağkalım, lokal nüks, uzak metastaz ve kozmetik sonuç açısından LENT-SOMA ölçeği kullanılarak değerlendirildi.

Bulgular: Yaş ortalaması 53,5 (27-74), ortalama takip süresi 75 (48-106) aydı. Ortalama tümör boyutu 18 mm (4-30), hastaların 90'ında invaziv duktal karsinom, sekizinde lobüler ve beşinde mikst histolojik yapı vardı. Hastaların 93'ü histolojik derece II, 15'i III; 74 hasta luminal A, 15 luminal B, sekizi HER2 pozitif ve altısı üçlü negatif meme kanseriydi. LENT-SOMA ölçeğine göre 35 kişi 0, 42 kişi 1, 23 kişi 2 ve iki kişi 3 puan almıştır. Tüm hastalara ameliyattan sonra tüm meme ışınlaması yapıldı, 81'i kemoterapi ve 90'ı endokrin tedavisi aldı. Bir lokal nüks oldu, dört hastada uzak nüks görüldü ve bir hasta meme kanseri dışı nedenlerle öldü. Genel sağkalım %99 ve olaysız sağkalım %96 idi.

Sonuç: BCS sırasında meme kanseri tedavisi için IOERT, düşük kronik toksisite ve zaman geçtikçe kozmetik sonuç açısından daha iyi hale gelen güvenli bir seçenektir.

Anahtar Kelimeler: Meme kanseri, meme koruyucu cerrahi, boost radyoterapi, intraoperatif elektron radyoterapi, LENT-SOMA

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