

Original Article

The Effect of Intraoperative Boost Dose Radiotherapy on Wound Complications in Breast Cancer Patients Operated with Upper Outer Quadrantectomy by Using Intraglandular Flap Mobilization Technique

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ABSTRACT

Aim: In this study, the technical aspects of intraoperative radiotherapy (IORT) application and its effect on early wound complications were evaluated.

Methods: Fifty consecutive patients operated with upper outer quadrantectomy and intraglandular flap mobilisation and given IORT between 2013 and 2014 were included. Radiotherapy at a boost dose of 10 Gy was given to 21 patients. The control group consisted of 29 patients who were operated with the same surgical technique but were not given IORT.

Results: The median age of the patients was 51.5±10.9 years. The average specimen weight was 266±83 g. The surgical resection margin evaluation with frozen section was negative in all patients. Four patients were reported to have involved margins at permanent sections. When both groups were compared in terms of early postoperative complications, there were 6 (28.5%) patients with seroma in the IORT group and 2 patients (6.8%) in the control group. While 5 (23.8%) patients were seen to have surgical site infection (SSI) in the IORT group, there was no SSI in the control group. There were 7 (33.3%) patients with delayed wound healing in the IORT group and 2 patients (6.8%) in the control group. While 2 (6.8%) patients had hematoma in the control group, there was no hematoma in the IORT group. While one (4.7%) patient was seen to have minor wound dehiscence in the IORT group, there was no wound dehiscence in the control group.

Conclusion: In this study, we concluded that IORT may negatively impact wound healing by increasing the incidence of seroma, SSI, and delayed wound healing in patients undergoing oncoplastic breast surgery. Increased awareness and preventive measures are necessary, especially in centers newly implementing IORT.

Keywords: Breast cancer, breast conserving surgery, complication, intraoperative radiotherapy

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Introduction

Loco-regional treatment of breast cancer aims to resect cancer with safe surgical margins and decrease local recurrences to the greatest extent possible. Nowadays, given the increased survival times, maintaining the body integrity of patients with an emphasis on aesthetic outcomes has become a target. With traditional breast conserving surgery (BCS) techniques, the preservation of the natural shape of the breast or the correction of deformities of previous biopsy sites is not always possible. Oncoplastic breast surgery (OBS) is one of the most intriguing areas of surgical oncology in recent years, with increasing applications to obtain better cosmetic results. OBS offers advantages such as wider surgical margins, fewer reoperation rates, and better cosmetic results [1]. The upper outer quadrant is the area where breast tumors are most frequently located. Therefore, the most common surgical procedures are performed in this quadrant. Volume displacement techniques are effective methods that are frequently used in OBS for upper external quadrant tumors, and the best-defined intraglandular flap technique is used with a racket incision [2].

Adjuvant whole breast irradiation and boost dose of radiotherapy to the tumor bed after OBS are a standard approach. Intraoperative radiotherapy (IORT), which is a type of partial breast irradiation (PBI), is increasingly used today because it shortens the duration of treatment and protects surrounding tissues such as the heart, lungs, and normal breast tissue [3]. In IORT implementation, intervening with external equipment occurs when a surgical open wound is present. The effects of the intervention on wound complications should be known, as these complications are the most important factors that negatively affect cosmetic results.

This study was planned to investigate the effect of IORT on early wound complications in patients operated on using OBS with a racket incision for the tumors located in the upper external quadrant of the breast.

Methods

Study Design

Fifty consecutive patients operated with the same surgical technique (upper outer quadrantectomy with intraglandular flap mobilisation) were included. Among these patients, the group of patients with IORT as a boost to the tumor bed with mobile Mobetron (Intraop Medical Incorporated, Santa Clara, CA), constituted the study group. Patients who did not receive IORT constituted the control group.

The incisions defined for upper external quadrantectomy were radial and fusiform, in shape, through the tumor bed, including the removal of the skin over the tumor. The incision was extended from the axillary hair area to the areola. The sentinel lymph node was found with the help of a gamma probe and guided to the frozen section using this incision.

Subsequently, skin flaps were prepared medially to the upper border of the mammary gland and laterally to the breast sulcus using the subcutaneous plan employed in mastectomy. A fusiform-shaped excision centered on tumor tissue was made with inclusion of subcutaneous tissue and pectoral fascia. After removal of specimen, a frozen section evaluation was performed for 4 sides and the base. Metallic clips were placed for the pectoral muscle, and lateral surgical margins. Later, the breast tissue was mobilized from the pectoral fascia to the limits prepared by the flaps. In the control group, the cavity was closed with glandular flaps sewn together with absorbable sutures (Figure 1). In patients with IORT, the flaps were temporarily approximated by placing an acrylic disc underneath. Subsequently, IORT was administered by placing the appropriate applicator with a 10 Gy boost dose (Figure 2). After completion of radiotherapy, temporary sutures of the flaps were opened, acrylic disc removed, and mobilized glandular flaps were sutured to each other and to the muscle. The crescent-shaped skin was de-epithelialized at the areola opposite the incision. The Nipple areola complex, is sewn to the de-epithelialized area in the center of the re-shaped breast. Skin was closed at subcutaneous plane. Level 1-2 axillary dissection was performed using the same incision for sentinel lymph node biopsy (SLNB) positive disease. There was no drain in the lumpectomy field. A negative pressure aspiration drain was placed in patients undergoing axillary dissection. Adjuvant external radiotherapy was applied in all patients in the study and control groups.

The age, radiological, and pathological tumor size, the distance of tumor to areola, skin and pectoralis muscle, flap thickness, hormone receptors and CEB-B2 status, and co-morbid diseases of the patients were recorded. Wound complications were evaluated in two groups: minor complications and major complications. Seroma, hematoma, surgical site infection (SSI), delayed wound healing, and minor incisional dehiscence were studied in the minor group. Major wound dehiscence was studied in the other group.

The study was conducted according to the principles of the Declaration of Helsinki, and approval was obtained from the Ethics Committee of University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision no: 2014/356, date: 15.05.2014). Written informed consent was obtained from all individual participants included in the study.

Statistical Analysis

The Statistical Package for the Social Sciences software, version 17, (Inc, Chicago, USA) was used for statistical analysis. The Kolmogorov-Smirnov and Levene tests were used to assess the homogeneity and normality of the scaled data. Pearson's chi-square and Fisher's tests were used to evaluate each group's nominal data; $p < 0.05$ was deemed statistically significant.



Figure 1. Incision, resection site, reconstruction with intraglandular flaps and postoperative view



Figure 2. Temporary fixation of the flaps after placement of the acrylic disc, placement of the applicator and application of IORT
IORT: Intraoperative radiotherapy

Results

Fifty consecutive patients operated with the same surgical technique (upper outer quadrantectomy with intraglandular flap mobilisation) and who received IORT (n=21) or did not receive IORT (n=29) were included. The median age of the patients included in the study was 51.5 ± 10.9 years. While the median size of the tumors at radiological examination was 16 ± 5.9 mm, it was 19.5 ± 8 mm at pathological examination. The average distances of the tumors to the skin, areola and pectoralis major muscle were measured as 2 cm, 4 cm and 2 cm, respectively. While the average skin flap thickness was 1.6 cm, the average specimen weight was 266 ± 83 g. The

incision sizes in the IORT group and the control group were 11.9 ± 2.3 and 12.1 ± 1.9 , respectively. Estrogen receptor, and progesterone receptor were positive in 41 and 27 patients, respectively, and CEB-B2 was negative in 33 patients. The grade distribution of the patients from 1 to 3 was 5, 32, and 13 patients, respectively. The surgical resection margin evaluation with frozen section was negative in all patients. The general characteristics of the patients in both groups are summarized in Table 1.

The preparation time for IORT after resection in patients in the IORT group was 25 minutes. The average RT duration was 2 minutes. SLNB was performed in 46 of 50 patients. Four patients with clinically present axillary metastases were

treated with dissection. Axillary dissection was applied in 11 of the SLNB treated patients, as the frozen result proved to be carcinoma metastasis. There was no statistically significant difference between IORT and control group, with respect to age, radiological and pathological tumor size, the distance of tumor to areola, skin and pectoralis muscle, flap thickness, weight of the specimen and tumor characteristics (hormone receptors, grade and CERB-B2 status) (Table 1).

When both groups were compared in terms of early postoperative complications, there were 6 (28.5%) patients with seroma in the IORT group and 2 patients (6.8%) in the control group ($p<0.05$). While 5 (23.8%) patients were seen to have SSI in the IORT group, there was no SSI in the control group ($p<0.05$). There were 7 (33.3%) patients with delayed wound healing in the IORT group, and 2 patients (6.8%) in the control group ($p<0.05$). While 2 (6.8%), patients had hematoma in the control group, there was no hematoma in the IORT group. While one (4.7%) patient was seen to have minor wound dehiscence in IORT group, there was no wound dehiscence in control group. There was no statistically significant difference between the groups, with respect to hematoma and minor wound dehiscence incidence ($p>0.05$). There was no major wound dehiscence in either group (Table 2).

While 8 patients in the IORT group experienced early wound complications, complications were observed in 4 patients in the control group. While 9 (42.8%) patients underwent axillary dissection in the IORT group, 6 (20.6%) patients had axillary dissection in the control group. Axillary dissection application

($p>0.05$) and comorbidities ($p>0.05$) had no effect on early wound complications.

Discussion

Application of 45-50 Gy to whole breast after BCS, followed by 10-16 Gy boost to tumor bed, is accepted as standard in early breast cancer. The role of boost application on local control has been shown in several studies [4]. In a randomized trial by EORTC comparing patients with BCS who received and did not receive boost radiotherapy, it was found that 50 Gy of whole breast radiotherapy followed by 16 Gy of boost application to the tumor bed showed a significant improvement in local control [5]. While the target volume for boost dose is being determined, the resection borders of the tumor bed are very important [6]. There may be shifts in the tumor bed during the mobilization of glandular flaps, prepared to fill the cavity required for reconstruction. The clips placed in the tumor bed can also be displaced. When boost area is determined by external radiotherapy techniques, there are some concerns about the location and the larger volume of the tumor bed. With IORT, the entire dose of therapeutic radiotherapy can be given in a single fraction, to the surgical bed directly in the operating room. As the patient selection criteria are still not clear, only the boost dose is given as IORT in our center, while whole breast irradiation is given in the form of external radiotherapy. Immediately after the tumor has been surgically removed, the necessary boost dose can be applied directly as

Table 1. Distribution of demographic and clinical factors according to IORT and control groups

Demographic and clinical factors	No. of patients (%) IORT control (21 patient 42%) (29 patient 58%)		p
Age, year, median, range	51	49	$p=0.4^u$
Radiological dimension, mm, median	17	15	$p=0.2^u$
Pathological dimension, mm, median	20	19	$p=0.1^u$
Distance to pectoral muscle, mm, median	25	28	$p=0.4^u$
Distance to areola, mm, median	35	40	$p=0.3^u$
Distance to skin, mm, median	20	27	$p=0.2^u$
Flap thickness, mm, median	15	15	$p=0.1^u$
Incision size, mm, median	11	12	$p=0.09^u$
Weight, gr, median	260	240	$p=0.4^u$
ER status: n (%)			
Absent	3 (14.2%)	6 (20.6%)	$p=0.42$
Present	18 (85.8%)	23 (79.4%)	
PR status: n (%)			
Absent	9 (42.8%)	14 (48.2%)	$p=0.42$
Present	12 (57.2%)	15 (51.8%)	
Her 2 status: n (%)			
Absent	15 (71.4%)	19 (65.5%)	$p=0.42$
Present	6 (28.6%)	10 (34.5%)	
Grade: n (%)			
Grade 1	4 (19.1%)	1 (3.4%)	$p=0.12$
Grade 2	11 (52.3%)	21 (72.4%)	
Grade 3	6 (28.6%)	7 (24.1%)	

SD: Standard deviation, χ^2 : Chi-square test, u : Mann-Whitney U test, IORT: Intraoperative radiotherapy, ER: Estrogen receptor, PR: Progesterone receptor

Table 2. Distribution of general complications

Complications	No. of patients (%) IORT control (21 patient 42%) (29 patient 58%)		p
Seroma status: n (%)			
Absent	15 (71.4%)	27 (93.1%)	p=0.042
Present	6 (28.6%)	2 (6.9%)	
Surgical site infection: n (%)			
Absent	16 (76.1%)	29 (100%)	p=0.0052
Present	5 (23.9%)	0 (0%)	
Hematoma: n (%)			
Absent	21 (100%)	27 (93.1%)	p=0.22
Present	0 (0%)	2 (6.9%)	
Minor wound dehiscence: n (%)			
Absent	20 (95.2%)	29 (100%)	p=0.12
Present	1 (4.8%)	0 (0%)	
Delayed wound healing: n (%)			
Absent	14 (66.6%)	27 (93.1%)	p=0.0062
Present	7 (33.4%)	2 (6.9%)	

χ^2 : Chi-square test, IORT: Intraoperative radiotherapy

IORT without any further intervention on the tumor bed. In this way, tissue displacement problems seen during OBS can be avoided and an effective and homogeneous dose was applied with high accuracy to a smaller volume compared to external radiotherapy with complete protection of surrounding tissues (heart and lung). As a result, the skin can be moved away from the irradiated area, skin reactions are reduced, and better cosmetic results can be obtained [7]. Tumor proliferation and invasion can be prevented by the destruction of tumor cells in the microenvironment, through instantaneous high-dose administration to the tumor bed with IORT. Moreover, as the interval between surgery and radiotherapy disappeared, repopulation of microscopic residual cells was blocked. Because the rich vascular structure and aerobic metabolism are not distorted yet, compared to externally administered boost treatment, IORT boost treatment is considered more effective in terms of radiobiology [8]. However, during IORT, while an open wound is present, manipulations are performed and radiation is given. This situation raises increased concern about the early postoperative infective and non-infective complications that pose a risk of deterioration of cosmetic results.

In the TARGIT study comparing external radiotherapy with IORT, the rates of hematoma, seroma, wound dehiscence, and SSI in the IORT group were 1%, 2.1%, 2.8% and 1.8%, respectively. These rates were reported as 0.6%; 0.8%; 1.9%; and 1.3% in the external radiotherapy group. Statistically, only seroma formation was found to be significantly higher in the IORT group [9]. In this study, hemorrhages requiring surgical exploration were considered a hematoma, while SSI was defined as that requiring antibiotherapy and surgical drainage. The low rates of wound complications in this study may be related to the descriptions of complications. Ruano-Ravina et al. [10] reviewed 15 reports and investigated the safety of IORT in comparison with external radiotherapy. In this review, seroma was the most common wound complication following

fibrosis and skin reactions in patients receiving IORT. These complications are significantly higher than in patients receiving external radiotherapy, and the rates vary between 3-25%. In a study of 55 patients reported from Australia investigating early IORT complications, seroma was encountered in 28 patients (51%) [11]. In a study reported from China and including 72 patients who underwent IORT, the mean time for complete healing of the BCS incision was 13-22 days in the IORT group and 9-14 days in the EBRT group [12].

The effects of administering high doses of radiation to a radiobiologically limited area have been studied *in vitro* and may account for increased infective and non-infective complications. This suggests that in the new microenvironment created after radiotherapy, tissue composition is altered and signaling pathways to initiate wound healing are not activated. In addition, a decrease in blood circulation due to vascular damage after radiotherapy is a mediator of this process [13,14].

In our study, the rates of seroma, SSI, and delayed wound healing were significantly higher in the group receiving IORT compared to the group not receiving IORT among patients who underwent OBS for an upper outer quadrant tumor. In addition to the effects of high-dose radiotherapy applied to a limited area, possible factors should also be questioned in this procedure where manipulative procedures are performed. After resection, the protective disk and the appropriate applicator are placed in the surgical field, and then the operating table is shifted towards the IORT device and adjustments are made. In addition to the surgical team, radiotherapy specialists, technicians, and physical engineers are also involved in the operating room. After resection, the IORT procedure takes approximately half an hour to perform. Prolonged operation time, loss of sterility during procedures, and the presence of excess personnel beyond the surgical team in the room may be other factors that increase the complication rates.

Study Limitations

This study has several limitations that should be acknowledged. First, the sample size was relatively small (n=50), which may limit the statistical power and generalizability of the findings. Second, the analysis focused only on early postoperative wound complications, without long-term follow-up data on late complications, cosmetic outcomes, or oncological efficacy. Third, as this was a single-center study, the results may reflect the specific surgical and radiation techniques, patient selection criteria, and institutional protocols used in our center, limiting broader applicability. Additionally, this study represents the early experience with IORT in our institution, and procedural learning curves or increased operating room traffic during IORT delivery may have influenced complication rates. Finally, potential confounding factors such as surgeon variability, perioperative antibiotic protocols, and wound care practices were not analyzed in detail and could have impacted outcomes.

Conclusion

The effect of IORT on complications in patients who underwent OBS may indirectly and negatively affect treatment outcomes and cosmetic results. In this study, which represents our first experience with IORT, we concluded that IORT has negative effects on seroma, SSI, and wound healing. Consider that wound complications may increase in centers where IORT is newly applied. Necessary precautions should be taken to prevent compromise of sterile conditions in the operating room, and wound healing of the patients should be carefully followed. With increasing experience in this field, better outcomes can be achieved. Reporting the results of studies with higher patient volumes from centers where IORT has been applied for a long time will contribute to the understanding of this treatment approach.

Ethics

Ethics Committee Approval: The study was conducted according to the principles of the Declaration of Helsinki, and approval was obtained from the Ethics Committee of University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (decision no: 2014/356, date: 15.05.2014).

Informed Consent: Written informed consent was obtained from all individual participants included in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.K., L.D., M.A.G., Concept: M.A.G., Design: M.T., Data Collection or Processing: L.D.,

Analysis or Interpretation: L.D., Literature Search: M.T., Writing: N.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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