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Our intraoperative boost radiotherapy experience and applications

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ABSTRACT

Objective: To present our experience since November 2013, and case selection criteria for intraoperative boost radiotherapy (IObRT) that significantly reduces the local recurrence rate after breast conserving surgery in patients with breast cancer.

Material and Methods: Patients who were suitable for IObRT were identified within the group of patients who were selected for breast conserving surgery at our breast council. A MOBETRON (mobile linear accelerator for IObRT) was used for IObRt during surgery.

Results: Patients younger than 60 years old with <3 cm invasive ductal cancer in one focus (or two foci within 2 cm), with a histologic grade of 2-3, and a high possibility of local recurrence were admitted for IObRT application. Informed consent was obtained from all participants. Lumpectomy and sentinel lymph node biopsy was performed and advancement flaps were prepared according to the size and inclination of the conus following evaluation of tumor size and surgical margins by pathology. Distance to the thoracic wall was measured, and a radiation oncologist and radiation physicist calculated the required dose. Anesthesia was regulated with slower ventilation frequency, without causing hypoxia. The skin and incision edges were protected, the field was radiated (with 6 MeV electron beam of 10 Gy) and the incision was closed. In our cases, there were no major post-operative surgical or early radiotherapy related complications.

Conclusion: The completion of another stage of local therapy with IObRT during surgery positively effects sequencing of other treatments like chemotherapy, hormonotherapy and radiotherapy, if required. IObRT increases disease free and overall survival, as well as quality of life in breast cancer patients.

Keywords: Breast cancer, boost radiotherapy, intraoperative radiotherapy, local recurrence

INTRODUCTION

Breast conserving surgery (BCS) and radiotherapy (RT) has been the standard treatment in breast cancer therapy in appropriate cases, as a result of studies and improvements achieved especially within the last 30 years. Due to the high likelihood of recurrence rates if adjuvant RT is not applied, postoperative boost RT is applied to the tumor bed (1-3).

Whole breast irradiation (WBI) performed as an adjuvant therapy and again boost RT effectively controls the primary tumor site and the around of 1-2 cm where recurrence is the most common. However, in the postoperative treatment plan after pathologic examination sometimes the timing of chemotherapy (CT) (RT-CT sequence) and sometimes the location of the tumor bed are subject to change (4). This situation may result in detrimental results in terms of tumor recurrence. It is reported that intraoperative boost radiotherapy (IObRT) effectively reduces the likelihood of local recurrence as compared to adjuvant boost RT, and generates a significant difference (5, 6). Thanks to this effect of IObRT, WBI may possibly be performed later giving chemotherapy a priority.

Intraoperative boost radiotherapy is beneficial to the hospital both for the treatment of a particular patient and for the treatment of other patients being treated in the same center by enabling more time and improving service quality.

MATERIAL AND METHODS

Case Selection Criteria

Patients who were suitable for IObRT have been selected as a candidate in our hospital's breast council within breast cancer patients who were planned to undergo BCS. In this selection, the histologic features of the tumor, if the breast tissue will allow the required flap thickness to be created surgically, if it is fatty or pendular were taken into consideration. All patients under 60 years of age were regarded as candidates if their breast tissue complied with the above-mentioned features. Tumors smaller than 3 cm in diameter, clinical and radiologic N0 patients, those without an identified BRCA1 and/or 2 mutation, those with a high likelihood of local recurrence according to histopathologic variables, patients with invasive ductal carcinoma histologic and nuclear grade 2-3 were chosen as a espetially. The selection

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criteria taken into account for the cases presented in this paper for parcial breast radiotherapy were classified as those suitable for IObRT, those in whom it is possible to perform IObRT and those not suitable for IObRT (Table 1).

Surgical Technique

The candidate cases were hospitalized after receiving written consent following information provided by at least two physicians, the surgeon and radiation oncologist. Surgery was started with sentinel lymph node biopsy (SLNB) by periareolar subcutaneous isosulphan blue dye injection method. Then an incision was made over the tumor and segmental mastectomy was performed. At this stage, the breast tissue was prepared at a desired distance from the tumor bed in accordance with oncoplastic surgery principles, in order to allow creation of intraglandular advancement or sliding flaps (6). The procedure was begun with subcutaneous dissection of the incision made according to the localization of the breast tumor, which is the first step in preparing an intraglandular advancement flap. The breast tissue was separated from the subcutaneous tissue in a thickness that will not impair skin vascularization and by careful attention to hemostasis. In the second step, the tumor was excised with negative surgical margins. The segmental mastectomy specimen was marked on the superior (short), lateral (long) and posterior wall (loop-silk), and was sent to pathology for evaluation of surgical margins and measurement of tumor size. In the third step, the surrounding breast tissue was dissected together with the fascia in order to prepare the tumor bed for IObRT application, and the cavity in the tumor bed was closed by the prepared advancement or sliding flaps. This last step was performed according to the information required from pathology evaluation. If surgical margins were adequate than flap application was completed, if not, i.e. a margin <2 mm, then at least 2 mm re-excision of that side was performed. While removing a tumor located near the pectoral fascia, the fascia that is accepted as a natural barrier was also removed with the tumor and if posterior wall surgical margin was <2 mm additional tissue excision was not performed in such cases. In preparing the breast tissue flaps, it was aimed for the tumor bed to be at 10-20 mm distance from the surface where electron beams reach the optimal effective dose, and maintaining >30 mm tissue thickness to the chest wall. Since in IObRT, the electron beam tissue penetration is decreased to <10% at 3 cm, preservation of intra-thoracic organs was possible (Figure 1) (7, 8).

Intraoperative Radiotherapy Boost Application

MOBETRON was used for boost RT application during surgery (mobile linear accelerator for IORT). The flap thickness, the thickness of the surface that will meet the conus to the tumor bed and the chest wall was measured and reported to the radiation oncologist and physicist. The conus diameter and the angle was selected based on these tissue-related data and the tumor related numerical values (tumor size and margin) obtained from pathology and the dose to be delivered was calculated according to the monitor unit (MU). The breast skin and wound edges were retracted by temporary suspension sutures and the skin was protected with moist sterile sponges and sterile sponges placed around the conus. When preparations regarding focus and irradiation were completed, the respiratory frequency of the patient was set to be low without creating hypoxia to limit movement during IObRT, and focused down by approximating the operating table with MOBETRON. For IObRT, electron beam equivalent to 10 Gy (6-9 MeV) was transferred through the selected conus to the tumor bed and 2 cm of surrounding tissue. When IObRT is applied to the tumor bed, in about two minutes the physicist, radiation oncologist, and anesthesiologist took their place in an insulated control room within the operating room. The surgical team and other officers waited outside the operating

Table 1. Patient selection criteria (for partial RT)

	Suitable	Possible	Not suitable
Age	<60	Breast tissue of all ages	
Tumor size	≤2 cm	<3 cm	
Histology	Invasive ductal carcinoma	Invasive ductal, mucinous, tubular, medullary and colloid carcinoma	Indifferentiated tm, <2 cm lobular type
Grade	Any	Any	
Pure DCIS	Not suitable	Not suitable	Not suitable
Diffuse intraductal component	Not suitable	Not suitable	Not suitable
Lobular carcinoma in situ	Applicable	Applicable	Diffuse LCIS
Multicentricity	Unicentric only	Unicentric only	Scattered and/or pure DCIS
Multifocality	Clinical unifocal	Clinical unifocal	Clinical multifocal scattered
Lymphovascular invasion	Not suitable	Not suitable	Not suitable
Oestrogen receptor	Positive	Any	Any
Surgical margin	≥2 mm	≥2 mm	<1 mm or adjacent to the SM
Lymph node status	pN0 (i-, i+)	pN0	<pN1
BRCA 1/2 mutation	Absent	Unidentified	Present
Neoadjuvant treatment	Not suitable	Not suitable	Not suitable

DCIS: ductal carcinoma in situ; SM: surgical margin; LCIS: lobular carcinoma in situ

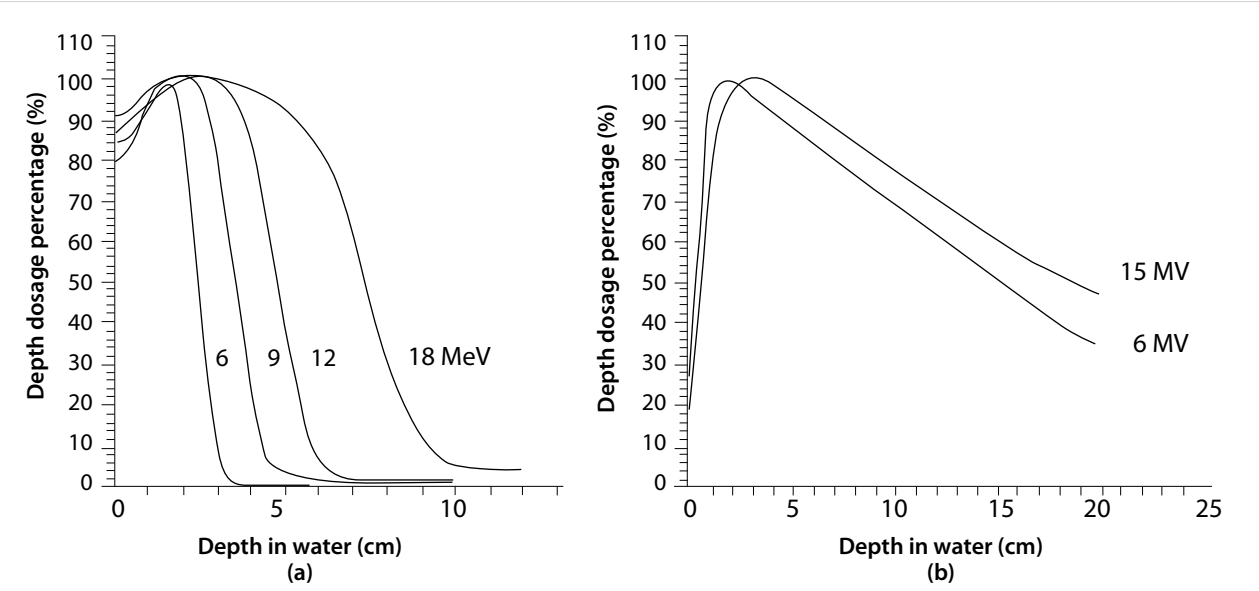

Figure 1. Isodose curves-isodose tissue thickness and efficiency curves (tissue penetration of the same energy dose electron beam and X rays)

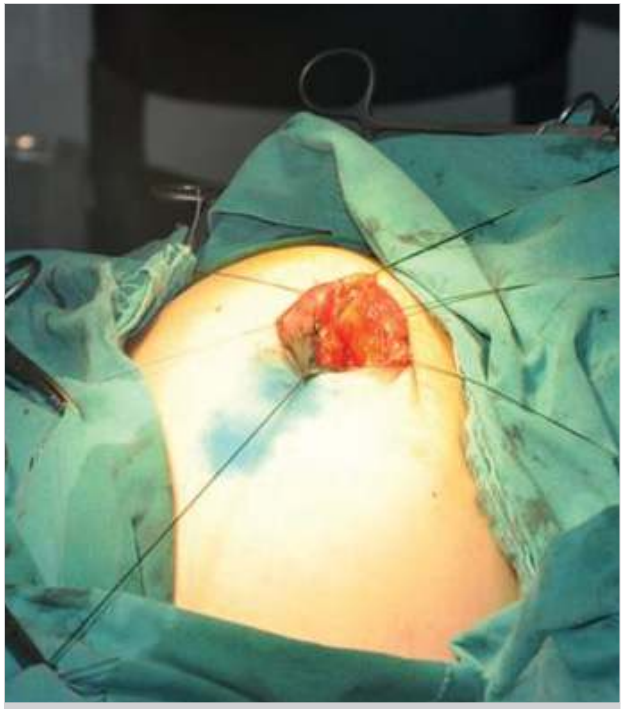

Figure 2. Skin edges were prepared with retraction sutures

room (Figure 2-5). The conus was separated from the tissue at the end of IObRT.

The operating table was re-positioned to its original place, according to SLNB results from pathology, three cases underwent Level 1 and 2 axillary lymph node dissection, the incision was closed in layers and the patient was sent to the ward.

RESULTS

The mean age of the 30 cases who underwent BCS and IObRT with a diagnosis of breast cancer in our hospital from October 11, 2013 to October 22, 2014 was 52 years. Ten cases were premenopausal, 20 were postmenopausal and in 29 the tumor was unifocal. Two combined foci were identified in one case. 24 patients had T1 and 6 had T2 tumors, the median tumor size was 16 x 12 mm (the largest 28 x 25 mm, the smallest 8 x 7 mm), the surgical margin was at least 1 mm and at most 10 mm, the patient with 1 mm margin underwent re-excision with at least 2 mm and the postoperative pathology result was reported with negative margins. The documentation of cases and the median values were presented in Table 2 and 3.

The operation lasted 2 hours and 15 minutes in the first case. There was no waste of time because the breast tissue was prepared while waiting for the response from pathology, and once the response was obtained the physicist selected the appropriate conus and calculated the dose required while the surgery team was preparing the skin and wound edges. The operating table and MOBETRON was simultaneously approximated and focused on the boost area, the time spent for these additional process was also taken into consideration. The habit of working together improved within the team gradually shortening the overall duration, and the mean time from the incision until the final suture was determined as 110 (90-135) minutes.

It has been nearly 13 months since our very first case, and 3 weeks from the last case, with a median follow-up of 26 weeks. Patients were discharged on postoperative day 1 or 2. Patients discharged on the second day were unremarkable except for their co-morbidities or social problems (living outside the city). In order to monitor wound healing closely, they were invited to the outpatient breast clinics on the 5th and 10th postoperative days where they were controlled by the surgeon and radiation oncologist who took place in the operation. We encountered minor complications in seven patients; 2 (6%) fat necrosis, and 2 (6%) hematoma occurred, one of which has been using anti-aggregant drugs, 3 (10%) patients had limited cellulitis at the site of SLNB injection (Figure 6). These problems were overcome conservatively with anti-inflammatory medication and dressings in about 2 weeks. There were no early complications related to major surgery or radiation therapy. In our cases, only a single-dose of antibiotic was administered

Figure 3. Skin edges were protected by sterile and moist gauze

Figure 5. Only the patient is within the room during IObRT

Figure 4. The conus approximated to the tissue

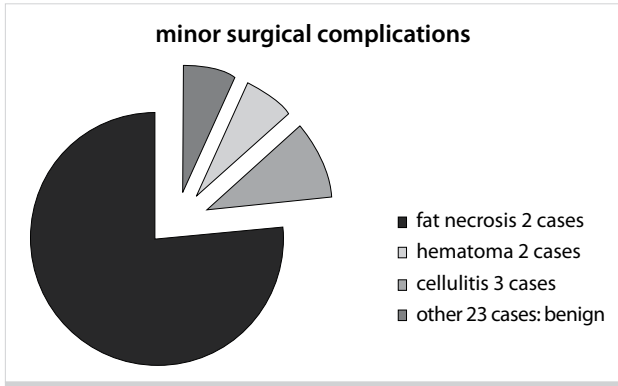

Figure 6. Surgical minor complications (n:30)

for prophylaxis, those with cellulitis were given therapeutic antibiotics for 5 days. In this study, SLNB was reported as positive in three of 30 patients (10%), and level 1 and 2 axillary lymphadenectomy was performed. According to the postoperative pathologic results, there were metastasis only in the SLN in two cases (1/12 and 1/10) and in three nodes (3/18) in the other patient. In these cases, adjuvant treatment was started with chemotherapy, while others were began with WBI. Whole breast irradiation was planned as 50 Gy to begin in the 5th-6th postoperative weeks (25 x 2 Gy). Additional irradiation to the axilla was not given.

DISCUSSION

The treatment of breast cancer must be planned according to a tumor's biological behavior. In this context, a different approach is used for each patient. If the primary treatment option is BCS, then sometimes RT or in some cases CT is given priority as adjuvant therapy according to the postoperative pathology report and prognostic markers (2, 7, 8). Being able to implement the boost fraction of radiotherapy as continuing/complementary treatment for breast cancer at once, directly and immediately after surgery provides effective control of the tumor bed as well as shortening postoperative treatment process significantly and allowing more accurate and effective timing of CT- RT (1, 3, 7, 9).

In centers with large population volume similar to our hospital, it may improve the quality of the service provided to the patient (and other patients) by partially reducing the workload.

The leading cause of local recurrence, which is a nightmare for the surgeon, is if the tumor bed received a proper and effective adjuvant RT. The timing sequence and appropriate implementation of treatment methods has a direct impact on prognosis (3, 8). Radiotherapy of the tumor bed, where the cells are contaminated with subclinical breast cancer, is therefore very important.

Intraoperative radiotherapy (IORT) refers to direct irradiation of high-risk areas in patients during surgical therapy. Its basic objectives and benefits include increasing the total dose and shortening the total treatment time. It can be performed alone or with consecutive external beam radiotherapy (7, 9). Patient groups who are suitable and not suitable for intraoperative partial breast RT have been described in large series. The selection criteria and the results of TARGIT, ASTRO, ESTRO and GEC-ESTRO studies describe selection criteria for single dose IORT as well as IObRT application (5, 7, 10-13).

Treatment modalities have been challenged with advances in pathology, and more accurate and detailed information on cancer biology. In 1985, Holland (13) showed that 60% of subclinical microscopic cancer cells are located in the tumor bed and within the surrounding 2 cm area. This information is very important since it forms the basis of boost RT logic. Subsequently, boost RT was introduced to treatment in addition to WBI. Marking the tumor bed with metal clips during BCS guides postoperative RT planning. However,

Table 2. Patient characteristics

Case	Side menopausal status	Age gender	Tumor stage (mm)	Surgical margin (mm)	Flap thickness/ to the fascia/ to the chest wall	Energy (MeV)/ conus diameter/ angle-degree	Dose Gy/ equivalent MU = monitor U
1-H.Ç.	R pre	41 F	T1 (13 x 10)	7	16/35/40	6/5.5/30	10/803
2-B.İ.	R post	60 F	T1 (12 x 11)	10	17/30/35	6/5.5/0	10/864
3-S.Y.	L post	52 F	T1 (10 x 10)	10	15/29/34	6/5.5/0	10/850
4-S.T.	L post	58 F	T1 (15 x 12)	8	16/35/40	6/5.5/0	10/863
5-Z.G.	R pre	47 F	T1 (18 x 15)	6	15/26/32	6/5.5/30	10/863
6-S.M.	R post	54 F	T1 two foci (12 x 10) and (4 x 5)	6	16/26/32	6/5/15	10/849
7-N.G.	L pre	46 F	T1 (13 x 10)	5	16/27/34	6/6/30	10/852
8-S.K.	R post	48 F	T1 (20 x 16)	4	15/35/40	6/6/30	10/933
9-N.G.	R post	66 F	T1 (12 x 10)	3	19/26/45	6/5.5/15	10/880
10-H.B.	R post	55 F	T2 (26 x 20)	5	16/26/30	6/7/15	10/926
11-Y.H.	L post	56 F	T2 (28 x 25)	4	14/24/30	6/7/15	10/926
12-S.D.	R pre	39 F	T1 (15 x 14)	5	16/24/30	6/5.5/0	10/773
13-A.İ.	R pre	44 F	T1 (15 x 14)	4	18x34x38	6/6/30	10/863
14-Y.K.	L post	53 F	T1 (19 x 15)	2	19/38/42	6/6/30	10/878
15-M.Ş.	R post	70 F	T2 (24 x 18)	5	17/37/42	6/6/30	10/829
16-K.O	R post	56 F	T1 (11 x 14)	4	20/18/38	6/0/30	10/868
17-L.Ç.	R post	41 F	T1 (18 x 15)	5	13/21/34	6/6/30	10/878
18-T.A.	R pre	44 F	T1 (20 x 17)	3	16/19/35	6/5.5/30	10/815
19-B.M.	R post	52 F	T1 (10 x 9)	4	16/20/36	6/4/15	10/878
20-Ş.Ç.	L pre	42 F	T1 (20 x 16)	2	17/19/38	6/6/30	107828
21-A.A.	L pre	34 F	T1 (15 x 14)	4	20/16/36	6/5.5/30	10/828
22-I.E.	L post	52 F	T1 (8 x 9)	5	18/17/35	675/30	10/878
23-G.Ç.	L post	61 F	T1 (20 x 14)	2	16/16/32	6/5/15	10/878
24-E.G.	R post	50 F	T2 (21 x 18)	1	16/18/34	6/6/30	10/878
25-Z.A.	L post	50 F	T1 (7 x 8-)	3	16/22/38	6/5/15	10/804
26-H.K	R post	68 F	T1 (13 x 12)	4	15724/39	6/5/30	10/828
27-NE	R post	50 F	T2 (26 x 20)	2	14/18/32	6/5/5	10/828
28-A.C.	L post	67 F	T1 (11 x 10)	3	13/22/35	6/4/15	10/878
29-HG	L pre	48 F	T1 (8 x 6 x 7)	2	17/17/34	6/5/15	10/903
30-YK	R post	50 F	T2 (21 x 18)	5	14/18/32	6/6/0	10/878

Table 3. Mean values of all patients

Menopausal status-side	Age	Tumor size (mm) stage	Surgical margin (mm)	Flap thickness/to the fascia/ to the chest wall	Energy (MeV)/conus diameter/angle-degree	Dose Gy/equivalent MU = monitor U
10 premenopausal	52	16.25 x 12 T1	4.46	15.5/17/34 mm	6/5/variable	10/840.5/862
20 postmenopausal		One case two foci				
9 left breast		Total diameter 21 mm				
21 right breast						

studies on WBI and boost RT showed that the postoperative changes in breast tissue during the period from surgery until implementation of RT influence the tumor bed (4, 13). This situation may cause adverse effects in terms of tumor recurrence by leading to target dismissal. The most important benefit of IObRT is the application of boost RT immediately after surgical removal thus providing direct access to the target and elimination of possible contaminated cells from the tumor bed (5). 1109 patients were examined in the International Society of Intraoperative Radiation Therapy

(ISIORT pooled) study that included seven centers, and the results were released in May 2013. Patients in the IObRT group, i.e. those diagnosed with breast cancer and selected for IObRT, underwent BCS+IObRT+WBI and have been followed-up for an average of 72 months (0.8-239 months). This protocol was determined to be advantageous in terms of local recurrence as compared with postoperative boost RT. According to the results of this study that included patients from every risk group, the local recurrence control rate of IObRT was high (99.2%), with significant effectiveness (p=0.0031) (5). The safe surgical margin limit has been reported as 2 mm for invasive cancer and as >5 mm for in situ cancer by both the ISIORT study and case series on 156 patients by Reitsamer et al (14). We also used these criteria in our cases, the mean surgical margin in invasive cancers was determined as 4.5 mm, two adjacent foci were detected in one case one of which was an in situ cancer and the margin was <5 mm (Table 3) (5).

The consensus report by the German Society for Radiation Oncology (DEGRO), emphasized IObRT application as an important component of local treatment in breast cancer. It is also being implemented in all 7 breast centers within the ISIORT study (5, 8). Single dose IORT was evaluated in the TARGIT-A study on 3000 cases, and the international randomized controlled trials known as ELIOT that was terminated in 2000 patients. The method was reported to be unreliable and insufficient according to the results of both studies. It was concluded that it can be used in some cases with very low risk, but that more evidence is required. Superiority as compared to conventional adjuvant RT in terms of local recurrence was not identified (15). IObRT is the application of the postoperative adjuvant WBI and boost section of the boost RT at once and during surgery, and is a different approach known to have a positive impact on reducing local recurrence rate by its direct application to the tumor bed immediately following surgery (5, 15).

Intraoperative RT application requires efficient teamwork. This team includes radiology, pathology, oncology and surgical specialists, physics expert and technician, anesthesiologist, operating room nurse and operating room personnel. There is no radiation within the environment in the absence of irradiation, there is radiation only in a limited area during irradiation, the tissue penetration is low, and the electron beam energy is decreased below 10% in about 3 cm. There are no personnel within the room during irradiation, there is no radiation outside the room, and the process takes approximately 2 minutes (5, 10). During the procedure, while the physicist and oncology specialists impose and control irradiation in an additional insulated chamber within the room that is safe in terms of radiation, the anesthesiologist monitors the patient from within the same place. The surgery takes 15-20 minutes longer than an average BCS + SLNB and axillary dissection in case of necessity. This period is reduced with increasing experience.

Postoperative pathology results of the patients were taken into consideration in the breast council as in the preoperative period, and adjuvant treatment and follow-up plan was carried out. Within the mean 26-week follow-up of our initial cases no significant postoperative complications of surgery or radiation toxicity was encountered except for minor surgical problems presented in Figure 7. Surgical complications are reported at similar rates in series in the literature (5-8%). Kraus et al. (17) reported the potential problems in the first months as hematoma, cellulitis, and fat necrosis, while late complications after 1 year are reported to be due to radiation (5, 16).

Surgery and oncology specialists should perform the follow-up of these patients simultaneously. Their radiologic follow-up also requires expertise. It is suggested that radiologic follow-up should be carried out by a radiologist with experience in characteristics of the patient and changes during the timeline of RT.

CONCLUSION

Intraoperative boost RT therapy is known to reduce local recurrence rates in breast cancer patient who underwent BCS. The duty of the surgeon in the team is both to prepare the breast tissue containing the tumor bed and the 2 cm surrounding area where local recurrence is most frequent with an intraglandular flap so as to achieve optimum efficient isodose during irradiation, and to reshape the remaining breast after the tumor is removed.

The completion of a stage of local treatment with IObRT in surgery positively affects the timing of adjuvant CT, HT, and RT that will be used in case of necessity, as well as increasing patients' quality of life by shortening the total treatment duration.

Ethics Committee Approval: Local Review Board decision is not required due to the retrospective nature of study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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