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Is oncoplastic surgery a contraindication for accelerated partial breast radiation using the interstitial multicatheter brachytherapy method?

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ABSTRACT

PURPOSE: To evaluate accelerated partial breast irradiation (APBI) in patients after oncoplastic surgery for early breast cancer.

METHODS AND MATERIALS: A retrospective analysis of 136 breasts of 134 patients, who received breast-conserving oncoplastic surgery for low-risk breast cancer between 2002 and 2010 in the Universities of Vienna and Luebeck followed by adjuvant APBI applying total doses of pulse dose rate of 50.4 Gy or high-dose rate (HDR) of 32 Gy over 4 days. Target volume definition was performed by the use of surgical-free margin data, related to intraoperatively fixed clip positions, pre- and postoperative imaging, and palpation.

RESULTS: At the time of data acquisition, 131 of 134 patients were alive. The median follow-up time was 39 months (range, 4–106 months). After high-dose rate treatment, 3 of 89 patients showed systemic progress after a mean follow-up of 47 months (range, 19–75 months) and 2 patients had a different quadrant in-breast tumor after 27 and 35 months. One patient died 7 months after treatment of unknown causes. After pulse dose rate treatment, 1 of 45 patients had a local recurrence after 42 months and 1 patient died because of another cause after 13 months. We observed mild fibrosis in 27 breasts, telangiectasia in 6, hyperpigmentation in 14 cases, and keloid formation in 1.

CONCLUSIONS: These preliminary results suggest the feasibility of multicatheter APBI after oncoplastic breast-conserving surgery in selected low-risk breast cancer patients; however, special attention to target volume definition is needed. Further prospective investigations with long follow-up are needed to define the real value of the procedure.

Keywords: Breast cancer; Brachytherapy; Oncoplastic surgery; Multicatheter brachytherapy; Partial breast irradiation (APBI)

Introduction

Accelerated partial breast irradiation (APBI) of early-stage breast cancer after breast-conserving surgery has been established in the last few years (1–4) as an alternative to whole-breast irradiation. In breast-conserving surgery, different surgical methods, such as open cavity, closed cavity, and oncoplastic tumor excisions, are practiced. Target definition for interstitial brachytherapy in the open cavity case is an easy procedure because the excision cavity is well seen postoperatively and the target could be easily defined. If the surgical cavity was closed by the surgeon, the use of preoperative imaging data combined with the information of the surgeon/pathologist and preoperative imaging and imaging at the time of implantation help to define the target of partial breast radiation. The use of

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pre- and postimplantation sets of CT scanning results in optimal dose distributions with respect to target coverage, dose homogeneity, and conformity (5). One of the advantages of oncoplastic surgery is the combination of oncoplastic and reconstructive surgery; therefore, oncoplastic surgery has become more frequent in the past few years because of excellent cosmetic results (6–8). Adjuvant radiotherapy procedures have to cope with breast tissue displacements in the postoperative target definition. The presented retrospective study intended to analyze the treatment results of adjuvant pulse dose rate (PDR) and high-dose rate (HDR) multicatheter partial breast implants to judge the feasibility of APBI after oncoplastic surgery and describe how to define the target volume in APBI after oncoplastic breast-conserving surgery.

Methods and materials

Between December 2002 and November 2010, 134 women with breast cancer as primary or recurrence were treated using multicatheter APBI using PDR (PDR/45 breasts) or accelerated and hypofractionated HDR (HDR/91 breasts) after oncoplastic conserving surgery in the Department of Radiotherapy and Radiobiology at the University Hospital of Vienna and in the Interdisciplinary Brachytherapy Unit at the University of Luebeck. Details of pathology parameters are listed in Table 1. This work is based on the retrospective evaluation of patient files. The recurrence rate was estimated by the Kaplan–Meier method.

Inclusion and exclusion criteria

Patient selection for APBI included low-risk breast cancer patients and was similar to the later published Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) recommendations (1). Furthermore, the following eligible criteria were implicated: Only women with early-stage unilateral or bilateral breast cancer ($n = 2$), who received a simple mammoplastic surgery and treated by PDR or HDR APBI were included. The maximum tumor diameter was ≤35 mm. All patients were informed on both the whole-breast external beam treatment and the partial breast radiotherapy procedure. Thus, patients who preferred the partial breast treatment with the multicatheter technique signed an informed consent.

Eligible histology was invasive ductal, adenocystic, tubular, mucinous, squamous cell carcinoma, ductal carcinoma in situ (DCIS), and invasive lobular carcinoma. The resection margin had to be clear and free of microscopic tumor. Regarding nodal status, there were pN_{mi} ($n = 2$) and pN_{1b} ($n = 1$), pN_x ($n = 13$), and all other cases of pN_0. Sentinel node investigation was practiced. We enrolled women in the age of >40 years; however 2 patients in the age of 33 and 38 years wished to be treated by APBI and refused external beam radiation. They were informed of the potential of increased recurrence risk.

Table 1
Pathology data of the APBI cohort ($N = 136$)

Pathology data	($N = 136$)
Invasive ductal carcinoma	95
Invasive lobular carcinoma	18
Other invasive carcinoma	11
DCIS	12
WHO tumor grading system	
G1	43
G2	76
G3	16
n.d.	1
Nodal status (TNM classification)	
pNx	13 (APBI as second treatment + 11 DCIS)
pN0	120
pN1mi	2
pN1b	1
ER/PR status	
ER+/PR+	106
ER+/PR−	12
ER−/PR+	2
ER−/PR−	15
n.d.	1
Herceptin receptor status	
0	27
1	32
2	6
3	15
Negative	51
n.d.	3

APBI = accelerated partial breast irradiation; DCIS = ductal carcinoma in situ; WHO = World Health Organisation; G = tumor grade; n.d. = nondocumented; TNM = tumor classification system, T = size or extent of primary **t**umor, N = degree of spread to regional lymph **n**ode, M = presence of distant **m**etastasis; pN = **p**athologic lymph **n**ode status; ER = estrogen receptor; PR = progestarone receptor.

Patients with previous breast surgery, no clear resection margin and DCIS which was larger than 50% of the invasive part, and women with extensive intraductal component or multifocal carcinoma, or not being operated with the oncoplastic method, were excluded.

The mean tumor size was 14 mm (range, 3–35 mm). In the histopathology, data stated 95 invasive ductal, 18 invasive lobular, 11 other invasive carcinomas, and 12 DCIS cases, respectively. Most of the patients had a negative nodal status ($pN_0 - 120$, $pN_{mi} - 2$, $pN_{1b} - 1$), and pN_x was observed in 13 cases. Regarding grading, G1, G2, and G3 were observed in 43, 76, and 16 breasts, respectively. In one case, the grading status is unknown (Table 1).

APBI target definition

Brachytherapy was performed under general anesthesia, usually 3 weeks after breast-conserving surgery. All oncoplastic surgical procedures were breast tissue rotational techniques. If adjuvant chemotherapy was indicated, brachytherapy was started within 2 weeks after the last course of chemotherapy.

According to a consensus with the breast pathologist, the size of the specimen and the size of the surgical-free margins

(SFMs: distance between tumor and specimen surface) were given in several directions (ventral, dorsal, left, right, caudal, and cranial), and preoperative imaging was studied and the breast was palpated. If the surgeon did not place surgical clips to the tumor bed, the quadrant plus palpable postoperative scar region within the breast was implanted. Before implantation of the needles, intraoperatively (at the time of the breast-conserving surgery) placed surgical clips were visualized by radiography in the operation room and their projection on the skin was marked. Clinical target volume (CTV) was defined as the sum of relevant clipped area (RCA) and the distance of 20 mm minus the smallest SFM defined by the pathologist [CTV = RCA + (20 − SFM)]. Planning target volume was defined as the CTV + 10 mm (Fig. 1). The additional distance of 10 mm resulted from the interobserver delineation variability, which will be not influenced by setting clip markers (9). First needle was implanted parallel to the thoracic wall and its position relative to the clips was checked by radiography. In the next step, further necessary needles of the basal plane were implanted with a separation of 12−16 mm, regarding to the CTV size. Number of the needles was defined by the size of the CTV, the craniocaudal extension of the CTV needed to cover by the implantation. After repeated radiography control, additional needles in additional planes were implanted to cover the complete CTV. After finishing the implantation, needle geometry was documented by radiographs, and the needles were replaced by plastic tubes that were fixed by the use of buttons on both sides of the skin level.

Postoperatively, we performed a planning CT (2-mm slice thickness) for treatment planning purposes. To better visualize the plastic tubes, equal to bone density, mandarins were introduced for the time of the investigation. After the three-dimensional reconstruction of the anatomy and the plastic tubes, manual geographic dose optimization was performed. In this procedure, we followed two dose prescription rules: The reference isodose line should be in a maximum distance from the lateral tubes of 1 cm and the contact dose on the surface of the tubes should not be higher than 4× the reference isodose. These rules were derived from the Paris system for low-dose-rate implants.

The average mean reference isodose volume was 83.92 cc (range, 25−211), the mean/median number of needles was 12/11 (range, 5−21), and the mean and median number of planes was 3 and 4 (range, 1−4).

Total PDR dose of 50.4 Gy (63 hourly pulses, 0.8 Gy single doses) or HDR 32 Gy (treatment over 4 days, 4 Gy twice a day, interfraction time minute 6 hours) was applied. Two of the HDR patients were treated with 7 × 4.3 Gy (one 34.4 Gy per eight fractions) in 4 days, which results in comparable biological equivalent dose values as 8 × 4.0 Gy in the same total treatment time. Regarding the documentation of dose inhomogeneity of the treatment, we used the dose nonhomogeneity ratio (DNR = V_{200} divided by the V_{150}value), which was intended to be kept under 0.38. After completing radiation therapy, the plastic tubes were explanted without the need of anesthesia.

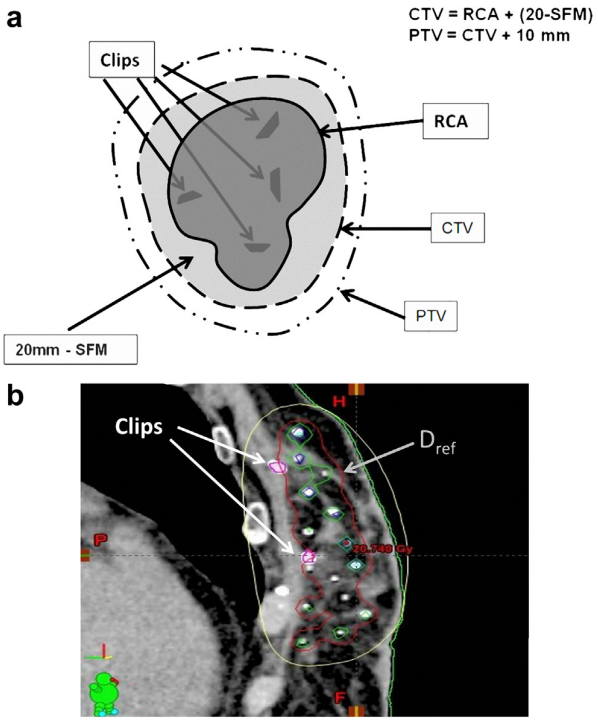

Fig. 1. (a) Schematic description of target definition for APBI after oncoplastic surgery. (b) Typical dose distribution of APBI using the multicatheter method after oncoplastic surgery. D_{ref}, reference isodose line; outer line, 50% isodose; inner line, 200% isodose; white dots, marked plastic tubes. APBI = accelerated partial breast irradiation; CTV = clinical target volume; RCA = relevant clipped area; PTV = planning target volume; SFM = surgical-free margin.

Results

After an average follow-up of 39 months (mean/median, 39.91/39.00 months), 131 of 134 patients were alive. The minimum follow-up time was 4 months and the maximum was 106 months. In the group of women who were treated by HDR (n = 89, two bilateral), 3 patients had a systemic progress, and 1 patient died in intercurrent disease 20 months after completing APBI. One patient died 7 months after the treatment of unknown causes. Two patients had an in-breast tumor located in a different quadrant after 27 and 35 months (five clips; DNR, 0.24 and 0.18). In the group of PDR-treated women (n = 45), 1 patient had a local recurrence after 42 month (no clips), and 1 patient died because of intercurrent disease after 13 months (Figs. 2 and 3). Median DNR was 0.26 (mean, 0.28; minimum, 0.16; and maximum, 0.56), V_{100} median 76 cc (mean, 83.92 cc; range, 25−211 cc), V_{150} median 20.0 cc (mean, 23.64 cc; range, 7−100 cc), and V_{200} median 7.00 cc (mean, 8.72 cc; range, 3−58 cc). We observed 27× fibrosis, 6× telangiectasia, 14×

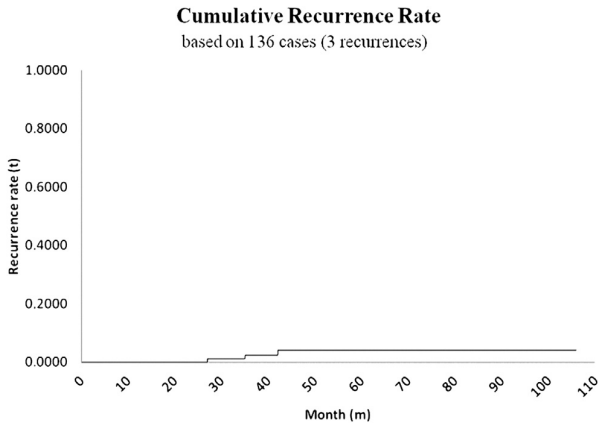

Fig. 2. Kaplan–Meier curve of cumulative recurrence rate.

hyperpigmentation, and 1× keloid at three insertion points in one patient. All side effects were Grade 1, and no higher grade toxicity was observed.

Discussion

Although the type of breast-conserving surgery (6–8) is a major influencing factor in target definition for APBI, there is less literature dealing with the influence of surgical methods on partial breast radiation target definition than with the different techniques of APBI (10–18). Although full-thickness wound closures result in improved cosmesis (19), there is growing recognition that immediate tissue reconstruction in carefully selected patients can combine an oncological and esthetic procedure in one operation with excellent outcome (20). Oncoplastic techniques for breast conservation range from simple reshaping and mobilization

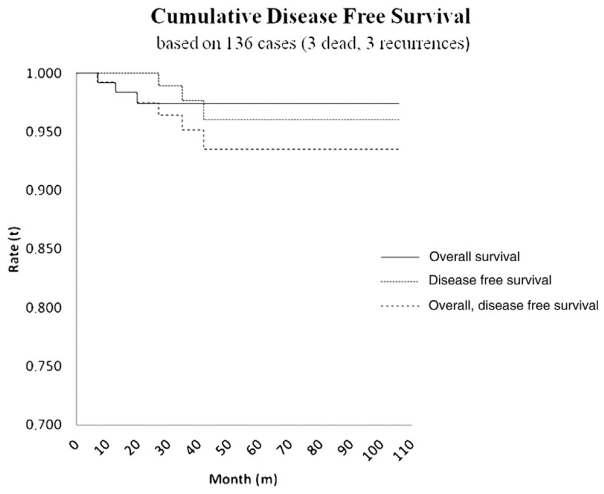

Fig. 3. Kaplan–Meier curves of cumulative disease-free survival, overall survival, and overall disease-free survival.

of breast tissue to more advanced mammoplasty techniques that allow resection of up to 50% of the breast volume (21). Reconstruction techniques are subdivided into simple volume displacement and displacement of local or distant flaps. The simple volume displacement includes mobilization of the parenchymal tissue from the original area around the excision up to whole breast plate. The replacement of tissue by local flaps is indicated for woman with small volume breasts (22). Because of the partly displacement of the originally tumor covering tissue, most radiation oncologists do not indicate APBI after oncoplastic surgery; however, immediate replacement of breast tissue usually results in improved cosmetic of the breast and therefore is nowadays more frequently used.

Intraoperatively positioned surgical clips serve as a stable surrogate for excision cavity over time; however, clips only define points on the excision cavity walls such that the remaining breast tissue/excision cavity interface must be derived by interpolation (23). In oncoplastic surgery, displacement of potentially tumor-infected margins occurs as well. Another problem is represented by the similarity of surgical clips: It is hardly possible to define on the postoperative radiographs dedicated geographic position of the different surgical margins. Although, for a better understanding and involvement of different surgical techniques in to the target definition of APBI, the need for placing at least six markers was suggested (24), there is no published consensus on target definition methods in the case of APBI performed by interstitial brachytherapy.

In the present investigation, we retrospectively analyzed the outcome of a pooled multicentric cohort to find out the feasibility of adjuvant multicatheter APBI after oncoplastic breast-conserving surgery in low-risk breast cancer patients. Target definition was influenced by multiple factors, such as the size of SFMs (distance between microscopic tumor extension and specimen margin in multiple dedicated directions) and the value of dedicated clip positions. Partial breast trials continue to use a 10- to 15-mm tumor bed—CTV margin based mainly on the spatial relationship between the residual disease and the index primary reported in mastectomy and re-excision studies (23, 25). The aim of the treatment in APBI is to treat at least >20 mm microscopic tumor-free margin around the tumor volume (1, 4, 26, 27). To our understanding, this margin should be the sum of both, surgery and radiotherapy cleared tissue depth. Therefore, we used in the CTV definition the addition of 20-SMF and the RCA. Regarding the SFM distances, if it is not to define, which clip belongs to a certain part of the tumor cavity, the smallest SFM distance from the pathology report becomes relevant for all clips. If one clip was positioned adherent to the *Mellontha pectoralis* on the chest wall and the surgeon performed a fascia resection which was not infiltrated by the tumor, in this position, we do not need to cover any additional distance to the tumor bed. Furthermore, sometimes singular clips can be clearly dislocated from the position

which fits to the description of the surgical procedure—such a clip was defined as irrelevant for the target definition. As a result of this, planning target vloume is the addition of CTV + 10 mm which intends to cover the potential of geometric inaccuracy influenced by a potential of clip movement and/or delineation interobserver variability and intraobserver variation in the delineation (9, 28, 29). A schematic summary of the used target definition is shown in Fig. 1a and the resulting typical dose distribution in Fig. 1b.

We also analyzed the potential correlation between number of clips, number of needles, and relevant changes in the treated volume; however, in 15 of 136 cases, we could not reconstruct if clips were used or not (Table 2). Approximately half of the cohort (n = 121) was clipped at the time of the operation by the surgeons. We did not find significant relationships between clipped vs. nonclipped targets, the number of clips, and size of treated volumes and number of needles; however, the authors have the feeling that nonclipped targets are larger than others. A potential reason for this could be the relatively small number of cases, the short follow-up, and the high number of variables. Maybe this could also serve as an explanation, why we could not find any differences in toxicity among the various dose rates used in our study at the moment.

The outcome and toxicity results of this retrospective observation show that it seems to be possible to select eligible patients for APBI after oncoplastic surgery. Careful target definition, which is based on the synopsis of different imaging and pathology data and on the clinical observations of experienced brachytherapy specialists, has the potential to offer effective treatments for low-risk breast cancer patients. The close cooperation between surgeons, pathologists, and brachytherapy experts within an interdisciplinary breast team is mandatory for the success.

Table 2
Mean and median values and quality indices of clipped and nonclipped patients (n = 121, in 15 of 136 cases data not complete)

N_{clip}	$N_{Pat.}$	V_{100}	V_{150}	V_{200}	DNR	N_{needle}	N_{planes}
Mean (n = 121)							
0	55	75.29	20.56	7.75	0.28	11.27	2.84
1	13	95.77	21.92	6.85	0.24	15.00	3.38
1–6	66	92.65	26.21	9.65	0.29	13.35	3.09
2	3	63.00	19.67	7.33	0.30	9.00	2.00
3	7	83.00	27.29	10.71	0.34	12.00	3.14
4	17	89.76	31.76	12.71	0.33	12.00	2.76
5	25	100.04	25.24	9.00	0.26	14.52	3.28
6	1	73.00	24.00	10.00	0.33	8.00	3.00
Median (n = 121)							
0	55	68.00	19.00	8.00	0.27	11.00	3.00
1	13	88.00	20.00	6.00	0.24	15.00	3.00
1–6	66	85.00	21.00	7.00	0.26	13.00	3.00
2	3	63.00	18.00	6.00	0.29	9.00	2.00
3	7	97.00	24.00	7.00	0.33	12.00	3.00
4	17	80.00	21.00	8.00	0.29	11.00	3.00
5	25	85.00	22.00	7.00	0.24	15.00	3.00
6	1	73.00	24.00	10.00	0.33	8.00	3.00

N_{clip} = number of clips; $N_{Pat.}$ = number of patients; V_{100} = volume treated with 100% of prescribed dose; V_{150} = volume treated with 150% of prescribed dose; V_{200} = volume treated with 200% of prescribed dose; DNR = dose nonhomogeneity ratio; N_{needle} = number of needles; N_{planes} = number of planes.

Conclusion

These preliminary and retrospective results suggest the feasibility of multicatheter APBI after oncoplastic breast-conserving surgery in selected low-risk breast cancer patients; however, special attention to target volume definition is needed. Further prospective investigations with long follow-up to evaluate late toxicity are needed to define the real value of the procedure.

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