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Risk factors for seroma evacuation in breast cancer patients treated with intraoperative radiotherapy

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ABSTRACT

Background: Novel techniques in oncology provide new treatment opportunities but also introduce different patterns of side effects. Intraoperative radiotherapy (IORT) allows a shortened overall treatment time for early breast cancer either combined with whole breast radiotherapy (WBRT), or alone. Although the early side effects of IORT are well known, data on clinically important late side effects, which require medical intervention, are scarce.

Aim: In this study, we analyze risk factors for seroma evacuation more than 6 months after IORT.

Materials and methods: We evaluated 120 patients with a mean follow-up of 27.8 months (range: 7–52 months). Fifty-one patients received IORT only and 69 were additionally treated with WBRT.

Results: Seroma evacuation was performed 6–38 months after IORT. Two (3.9%) events were observed in the IORT group and 14 (20%) in the IORT + WBRT group. Univariate (Kaplan–Meier) analysis showed that addition of WBRT to IORT increased the risk of seroma evacuation [hazard ratio = 5.5, 95% confidence interval: 2.0–14.7, $P = 0.011$]. In a multivariate analysis (Cox proportional hazards regression), WBRT and axillary lymph node dissection were significant risk factors for seroma evacuation (model P value = 0.0025).

Conclusions: WBRT applied after IORT is associated with increased risk of seroma evacuation, which might be considered as a late side effect.

1. Background

Breast cancer is the second most common cancer worldwide and the most frequent cancer among women. It is estimated that about 1.67 million new breast cancer cases were diagnosed in 2012 (25% of all cancers).[1] Currently, most cases of breast cancer are treated with multiple modalities. Depending on tumor stage, molecular profile, and in certain cases patient preference, treatment options include

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surgery, chemotherapy, hormonal therapy, targeted therapy, and radiotherapy.

The role of adjuvant radiotherapy in the treatment of early-stage and locally advanced breast cancer has been demonstrated.[2,3] Whole breast radiotherapy (WBRT) is part of breast conservative treatment (BCT) and improves local control and overall survival.[3,4] WBRT with additional radiation dose to the tumor bed improves local control, although with moderately poorer cosmetic effect.[5–8] The risk of WBRT side effects depends on the volume of irradiated breast tissue, the dose given to the heart, lung, lymph node areas.[9–11] Omitting irradiation of the whole breast and delivering high-dose radiation only to the lumpectomy bed, with a 1- to 2-cm margin, in a shorter period of time, may reduce the risk of these side effects without compromising curability in selected patients. This concept of accelerated partial breast irradiation (APBI) after a lumpectomy has led to the development of various radiotherapy techniques (balloon catheter brachytherapy, multi-catheter interstitial brachytherapy, conformal external beam radiotherapy, and intraoperative radiotherapy) and dedicated equipment allowing delivery of the radiation dose in 1–7 days.

Intraoperative radiation therapy (IORT) is one of the APBI techniques that delivers a single fractional dose of radiation with megavoltage electrons (Mobetron, Sunnyvale, CA, USA; Novac, LIAC, Sordina IORT Technologies, SpA, Vicenza, Italy) or kilovoltage photons (Intrabeam, Carl Zeiss, Oberkochen, Germany) directly to the tumor bed during surgery. The technique and its clinical application were described by Vaidya.[12,13] IORT given as a boost is an effective option for breast-conserving treatment.[14] Data gathered in the Targeted Intraoperative radiotherapy (TARGIT) and Intraoperative radiotherapy with electrons (ELIOT) trials support the idea that some patients with breast cancer can be offered APBI as a sole radiation modality in BCT.[15–17] Recommendations for the selection of patients for APBI have been proposed by the American Society for Radiation Oncology (ASTRO) and the European Organisation for Research and Treatment of Cancer (EORTC).[18,19]

When introducing novel techniques such as APBI, we are faced with new data in imaging modalities[20–22] and different patterns of side effects.[23–26] Frequently reported side effects related to IORT are seroma, delayed wound healing, and fibrosis.[20,23,26–31] In mammography and breast ultrasonography, the most frequently reported side effects are hematoma or seroma, fat necrosis (manifesting as oil cysts), unspecific dystrophic calcifications, and parenchymal scarring (architecture distortions).[21,22] Most of these side effects are reported irrespective of the time of occurrence. It is widely accepted that side effects appearing later than 3–6 months after radiotherapy are considered as late. In our institution, seroma is the most frequently observed side effect that needs medical intervention.

2. Aim

The aim of the present study was to analyze the risk factors for seroma evacuation more than 6 months after IORT.

Table 1 – Eligibility criteria for APBI.

Factor	Criterion
Patient factors	
Age	≥50 years
Pathologic factors	
Histology	NST, tubular, mucinous
Tumor size	≤20 mm
Margins	>2 mm
LVSI	No
ER status	Positive
Her-2 status	No overexpression
Pure DCIS	<5% within tumor
EIC	Not allowed
Nodal status	No

LVSI, lymphvascular space involvement; NST, no special type; ER, estrogen receptor; Her-2, human epidermal growth factor receptor 2; DCIS, ductal carcinoma in situ; EIC, extensive intraductal component.

3. Materials and methods

3.1. *Characteristics of patients and follow-up*

The research protocol was accepted by Bioethical Committee of Polish Chamber of Physicians and Dentists in Szczecin (Decision Number 08/KB/V/2015). The study is a retrospective medical records analysis of radiotherapy side effects and the data were analyzed and reported anonymously, thus, it did not require additional patients' informed consent.

One hundred and twenty-seven patients with breast cancer were treated in our institution using IORT from April 20, 2010 to February 19, 2014 based on the decisions of a multidisciplinary team. The criteria for APBI were in accordance with the ASTRO and EORTC recommendations (Table 1).[18,19] After APBI, patients were consulted by the multidisciplinary team and qualified for further treatment. Indications for WBRT included findings that did not match the criteria in Table 1. Two patients in the APBI group refused WBRT. Patients with sentinel lymph node metastasis were offered axillary lymph node dissection (ALND). Fifteen of 18 patients with sentinel lymph node metastasis underwent ALND, but it was omitted in three patients with micrometastasis. Enrolment for systemic treatment (chemotherapy, hormonal therapy, or other therapy) followed international recommendations.[18,19,32–34] Fourteen patients were given chemotherapy before WBRT. Eighty three patients were treated with tamoxifen, while 27 with aromatase inhibitors, 1 with LHRH analog and 9 patients did not receive hormonal therapy.

The patients were followed up prospectively every 3 months for 2 years and every 6 months thereafter. The data were collected in relation to treatment results and side effects using a modified LENT-SOMA scale (Late Effects in Normal Tissues Subjective, Objective, Management and Analytic scores). Seven patients were lost to follow-up. This analysis included 120 patients with a mean follow-up of 27.8 months (range: 7–52 months, median: 24 months). Fifty-one patients received APBI only and 69 were additionally treated with WBRT.

3.2. *Radiotherapy*

IORT was performed using the Intrabeam system, which emits low-energy photons (30–50 kV) with a steep dose fall-off in soft tissues. Installation of the applicator and dose prescription followed previous recommendations.[13] Prescription of radiation dose followed the TARGIT protocol. In short, a dose of 20 Gy was set on the surface of the applicator.[15,16] The rim of the skin was kept no less than 1 cm from the applicator surface. Neither oncoplastic nor lumpectomy cavity closure techniques were performed during the operation.

In a group of patients who underwent WBRT, the planning computed tomography scan was obtained with 5-mm-thick slices on a personalized immobilization device with one or two arms raised. The clinical target volume included whole breast tissue and was expanded by 5 mm to create the planning target volume. Organs at risk (OARs) included the lung, heart, coronary arteries, and contralateral breast. The plans were prepared in three-dimensional (3D) planning systems either by Prowess Panther (Radiology Oncology Systems, Inc., San Diego, CA, USA) or Oncentra Masterplan (Oncentra MasterPlan, Nucletron, Veenendaal, The Netherlands). Whole breast was treated with a total dose of 46–50 Gy in 2-Gy daily fractions. For each patient, dose–volume histograms for the target and OARs were obtained. Choice of irradiation technique (intensity modulated radiotherapy or 3D conformal radiotherapy) depended on the fulfillment of dose constrains for the OARs and target volume. Forty-one patients were treated with 3D conformal radiotherapy and 28 patients with intensity modulated radiotherapy. WBRT was performed on Siemens linear accelerators (Siemens Healthcare, Erlangen, Germany) using either 6 or 7 MeV photons. Mean time from IORT to the first fraction of WBRT was 77 days (17–244 days).

3.3. *Statistical analysis*

The endpoint of the study was the formation of seroma, defined as encapsulated serous fluid diagnosed by ultrasound or mammography >6 months after IORT (thus fulfilling the criteria for late side effect), and evacuated because of discomfort (pain and palpable mass) reported by the patient during follow-up visits. This definition of the study endpoint describes only a clinically important seroma that needs additional medical intervention and thus affects quality of life.

χ^2 or Fisher's exact tests and *t* tests were used to compare differences between APBI (IORT only) and WBRT (IORT + WBRT) groups (Table 2). The level of significance was set at 5%. Pearson's correlation coefficient was used to compare correlation between the volume of resected tissues and applicator diameter. The volume of resected tissues was calculated by multiplication of three dimensions obtained from histopathology reports. Although this method of resected tissue volume assessment is error prone, it is a simple approach that gives a rough estimate of tissue loss after lumpectomy.

Probability of seroma evacuation >6 months after IORT was estimated using the Kaplan–Meier method and log-rank test (Table 3; Figs. 1 and 2). Variables included in the analysis were: chemotherapy (Yes vs. No), WBRT (Yes vs. No), ALND (Yes vs. No), tamoxifen-based hormone therapy (Yes vs. No), applicator diameter (<3.5 cm vs. 3.5 cm vs. >3.5 cm), and volume of resected tissues ($\geq$108 cm^3 vs. <108 cm^3).

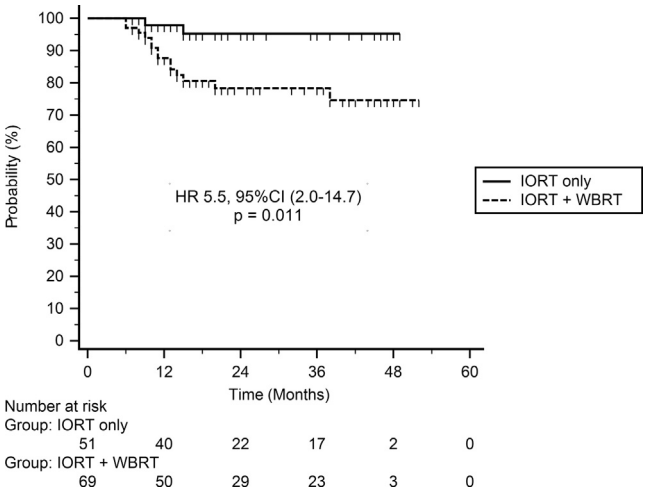

Fig. 1 – Kaplan–Meier probability curves of seroma evacuation after IORT in patients treated with IORT alone (APBI) and IORT + WBRT.

Cox proportional hazards regression (backward method) was used to create a model that predicted the risk of seroma evacuation >6 months after IORT (Table 4). Analyzed variables were age (continuous variable), chemotherapy (Yes vs. No), WBRT (Yes vs. No), ALND (Yes vs. No), tamoxifen-based hormone therapy (Yes vs. No), applicator diameter (continuous variable), and volume of resected tissues (continuous variable). Variables with $P < 0.1$ were included in the model.

Statistical analyses were performed using MedCalc for Windows, version 14.10.2 (MedCalc Software, Ostend, Belgium).

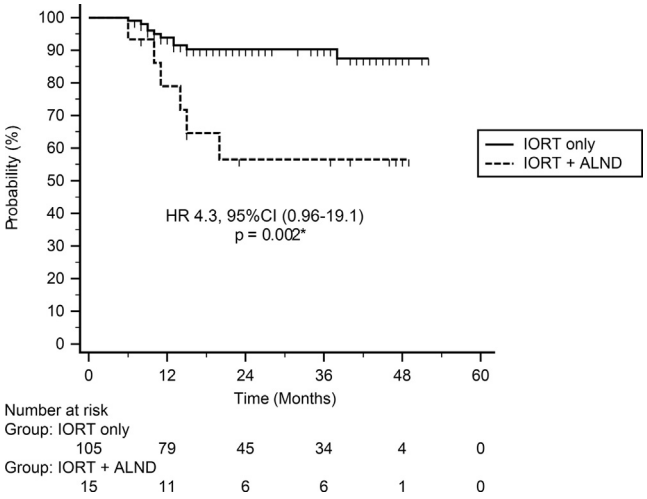

Fig. 2 – Kaplan–Meier probability curves of seroma evacuation after IORT in patients treated with IORT alone and IORT + ALND. *Result considered as statistically insignificant because 95% CI included the value of 1.0.

Table 2 – Clinical characteristics of patients treated with IORT only (APBI) and IORT + WBRT.

	IORT only	IORT + WBRT	Total	*p*-Value
Number of patients	51	69	120	–
Follow-up time [months]				
Range	7–49	7–52	7–52	n.s.
Mean	27.3	28.2	27.8	
Median	24	25	24	
Age [years]				
Range	48–86	32–79	32–86	0.0004
Mean	65.6	59.8	62.3	
Median	65	60	63	
Time to WBRT [days]				
Range	–	17–244	–	–
Mean		77	–	
Median		62		
WBRT time [days]				
Range	–	26–38	–	–
Mean	–	32	–	
Median	–	31	–	
ER status [*] [**]				
Positive	50 (98)	61 (91)	111	n.s.
Negative	1 (2)	6 (9)	7	
Her2 receptor overexpression [*] [**]				
Yes	2 (4)	4 (6)	6	n.s.
No	47 (96)	62 (94)	109	
Resected volume (cm^3)				
Range	20–320	12–384	12–384	n.s.
Mean	115	118	131	
Median	90	101	120	
Applicator diameter [*]				
2–3 cm	19 (37)	17 (25)	36	n.s.
3.5 cm	23 (45)	33 (48)	56	
4–4.5 cm	9 (18)	19 (28)	28	
ALND [*]				
Yes	2 (4)	13 (19)	15	0.03
No	49 (96)	56 (81)	105	
Chemotherapy [*]				
Yes	1 (2)	14 (20)	15	0.0065
No	50 (98)	50 (80)	105	
Tamoxifen [*]				
Yes	35 (69)	48 (70)	83	n.s.
No	16 (31)	21(30)	37	

* Number of patients (%).
** Too low amount of tumor tissue for some patients to perform all assays.
n.s., not significant; ER, estrogen receptor; Her-2, human epidermal growth factor receptor 2.

4. Results

Early side effects were uncommon. Four (3.3%) patients had infection related to the surgical procedure and two (1.6%) of them had delayed wound healing. Seroma was observed in 19 (15.8%) patients. During the early period (≤6 months from IORT), seroma was evacuated only in three (2.5%) patients.

In 16 (13.3%) patients, seroma was evacuated >6 months after IORT. This procedure was performed once in 10 patients,

Table 3 – Univariate analysis of seroma evacuation risk (log-rank test).

Variable	Direction	HR	95%CI	*p*-Value
WBRT	Yes vs. No	5.5	2.0–14.7	0.011
ALND	Yes vs. No	4.3	0.96–19.1	0.002[a]
Resected volume (cm^3)	≥108 vs. <108	1.7	0.6–4.6	n.s.
Applicator diameter (cm)	<3.5 vs. 3.5 vs. >3.5	–	–	n.s.
Tamoxifen	Yes vs. No	0.5	0.2–1.6	n.s.
Chemotherapy	Yes vs. No	2.3	0.5–9.9	n.s.

[a] Considered as not significant due to 95% CI which includes the value of 1.0.
n.s., not significant; HR, hazard ratio; 95% CI, 95% confidence interval for the estimated hazard ratio.

Table 4 – Results of the Cox proportional-hazards regression model: predictors of seroma evacuation after six months from IORT.

Variable	Direction and unit	Coefficient	S.E.	Wald χ^2	p-Value	HR	95%CI
WBRT	Yes vs. No	1.57	0.77	4.2	0.040	4.8	1.07–21.49
ALND	Yes vs. No	1.27	0.53	5.7	0.017	3.6	1.26–10.07
Tamoxifen	Yes vs. No	−0.92	0.53	3.0	0.081	0.4	0.14–1.12

Variables excluded from the model due to p-value >0.1 (backward method): age, applicator diameter, chemotherapy, resected tissue volume. Overall model fit: Chi-squared 14.3, $p = 0.0025$ (degrees of freedom = 3). Coefficient = mathematical weighting of each variable in the model; S.E. = standard error; Wald $\chi^2 = [(\text{Coefficient})/(\text{standard error})]^2$; p-value is the probability value obtained by comparing the Wald χ^2 with the χ^2 distribution with 1 degree of freedom; HR = hazard ratio; 95% CI = 95% confidence interval for the estimated hazard ratio.

twice in one patient, and more than three times in five patients (four to six times). Evacuation was performed at a mean 13 months after IORT (range: 6–38 months, median: 11 months). Two (3.9%) events were observed in the APBI group and 14 (20%) in the WBRT group.

Addition of WBRT to IORT increased the risk of seroma evacuation in comparison to patients treated solely with IORT [hazard ratio (HR) = 5.5, 95% confidence interval (CI): 2.0–14.7, $P = 0.011$] (Fig. 1). Although seroma evacuation was more frequently observed among IORT patients additionally treated with ALND (HR = 4.3, 95% CI: 0.96–19.1, $P = 0.002$), the result was considered as statistically insignificant because of the 95% CI including the value of 1.0 (Fig. 2). Applicator size, resected volume, and tamoxifen were not associated with the risk of seroma evacuation (Table 3).

The correlation between resected tissues volume and the applicator diameter used during IORT was weak but significant (correlation coefficient = 0.34, 95% CI: 0.18–0.49, $P = 0.0001$) (Fig. 3).

There were no significant differences between the APBI (IORT only) and WBRT (IORT + WBRT) groups in respect to follow-up time, receptor status (estrogen, her-2), resection margin, applicator size, and volume resected. Patients in the WBRT group were younger, and more frequently underwent ALND and chemotherapy (Table 2).

Radiotherapy technique was not associated with the risk of seroma evacuation. Analyses of the dosimetric characteristics of WBRT plans showed that neither maximal dose in lumpectomy cavity nor volume receiving more than 48.3 Gy (105% of prescribed dose) influenced seroma evacuation risk.

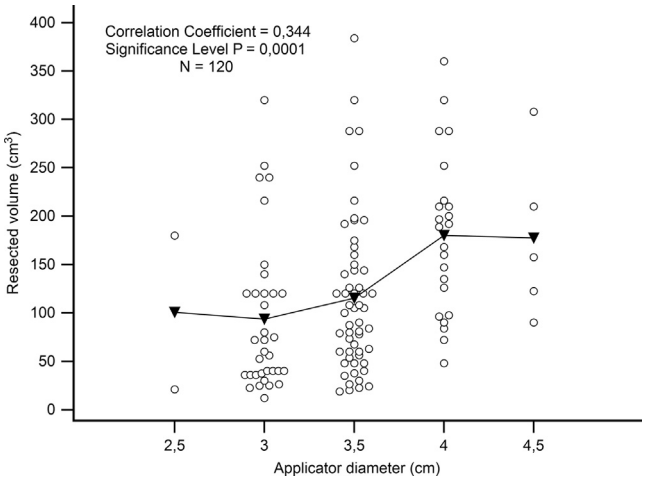

Fig. 3 – Comparison of resected tissue volume with applicator diameter used during IORT.

The final Cox model showed that only WBRT and ALND were significant risk factors for seroma evacuation, after adjusting for tamoxifen use (model P value = 0.0025) (Table 4).

5. Discussion

Eligibility criteria for APBI affected the results as shown in Tables 2 and 3. Patients who did not fulfill the criteria shown in Table 1 were offered adjuvant systemic treatment or WBRT. Factors such as lymph node status, age, and steroid receptor status are decisive for systemic treatment.

The TARGIT trial confronted physicians with a new profile of side effects associated with IORT. Data on late side effects of IORT in breast cancer patients are limited. Most of the published research has focused on early side effects of IORT, such as delayed wound healing (~3%), seroma/hematoma (17–25%), erythema, and wound infections. It is estimated that 25% of all seromas require medical intervention immediately after IORT.[29] The frequency of seroma is also affected by the reporting criteria.[25] The present study is believed to be the first to investigate risk factors for seroma requiring evacuation >6 months after IORT. We chose the study endpoint to be at least one evacuation of seroma affecting quality of life. Because of the mean time interval between IORT and WBRT or WBRT time (Table 2), we defined side effects as late when they occurred >6 months after IORT, and excluded seroma that occurred within 3–4 months after IORT (three cases).

According to Wenz et al., a time interval between IORT and WBRT of <36 days carries a risk of long-term toxicity.[25,35] Six of our patients were irradiated <36 days after IORT and two of them needed seroma evacuation (30%). In contrast to Wenz et al., our result was not statistically significant, probably because of the small number of cases treated for a shorter time interval between IORT and WBRT. On the other hand, in fourteen patients interval between IORT and WBRT was longer than 93 days because of chemotherapy administration.

Total dose of postoperative radiotherapy to the breast affects the risk of late side effects, such as fibrosis.[7,8] The Intrabeam system uses low-energy photons with relative biological effectiveness for late reactions increasing as the absorbed dose decreases with increasing distance from the applicator surface.[36] The median effective dose for fibrosis is estimated to be reached at the depth of 3–6 mm depending on the applicator diameter.[36] Goble et al. measured with ultrasound the seroma wall thickness and obtained values of 3–5 mm.[20] This leads to the hypothesis that increased density of tissue surrounding the tumor bed impairs local interstitial serous fluid circulation. WBRT might act in a similar way but

in the whole breast tissue, disrupting lymphatic drainage. The subclinical damage caused by IORT and WBRT alone becomes clinically important if both of those modalities are applied in conjunction. Another treatment modality that might perturb lymphatic drainage is ALND. Although in this study ALND was not a significant risk factor in univariate analysis, in multivariate analysis it was a risk factor for seroma evacuation, together with WBRT when adjusted for tamoxifen use. Only 15 patients were treated with ALND; therefore, this result should be explored in further studies.

Senthi et al. examined the incidence of seroma using the Intrabeam device for IORT boost followed by WBRT and found 28/55 patients (51%) developing seroma, with 33% requiring at least one aspiration for symptomatic relief. They subsequently examined the association of a variety of factors with seroma formation. The only risk factor for seroma development was primary tumor location in the upper inner quadrant.[37] In our study additional analysis of tumor location showed no impact on seroma evacuation risk (data not shown).

Goble et al. showed two cases of seroma evacuation among 71 patients that had undergone IORT only at follow-up of 6–12 months.[20] Similarly, we reported two (3.9%) cases of seroma evacuation among 51 patients that had received IORT only. In our study, most seroma evacuations were performed in the IORT + WBRT group (14/69, 20%). Ruch et al. analyzed mammographic images of patients given IORT (74% were treated additionally with WBRT). In comparison to WBRT alone, seroma was observed more frequently in the IORT group (4% vs. 22%).[21] Engel et al. evaluated mammographic changes in the tumor bed after IORT. They showed that seroma was more frequently observed if WBRT was added to IORT (6% vs. 40%). Owing to the small sample size, this result was not statistically significant. In Engel et al. study, seroma was more frequently observed in the patients treated with IORT (37% were given WBRT additionally) when compared with WBRT alone (19% vs. 0%).[22]

6. Conclusions

Our data are consistent with those from the above-mentioned studies[20–22] and lead us to conclude that addition of WBRT to IORT is associated with increased risk of seroma evacuation, which might be considered as a late side effect.

Conflict of interest

None declared.

Financial disclosure

None declared.

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