

Influence of Age on Short-term Complications After Intraoperative Radiotherapy in Women after Breast-conserving Surgery

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Abstract. *Background: We investigated the influence of age on short-term complications in women undergoing intraoperative radiotherapy (IORT) for early breast cancer. Patients and Methods: We retrospectively analyzed data of 188 women who underwent IORT during breast-conserving surgery (BCS). The study group consisted of 54 patients aged 70 years or older. One hundred and thirty four patients aged less than 70 years served as the control group. Results: In both collectives, the acute toxicity was low. There were no significant differences regarding type and duration of surgery, and type of radiation treatment, comparing both collectives. The most frequent postoperative side-effects were haematoma/suggillation (13/54, 24.1% vs. 28/134, 20.9%; $p=0.633$). There was a significantly higher incidence of postoperative axillary haematoma in the study group (10/54, 18.5% vs. 10/134, 7.5%; $p=0.026$). Conclusion: Acute toxicity after BCS with IORT in women aged 70 years and older does not seem to be higher compared to younger patients.*

Breast cancer is one of the most frequent malignant neoplasms in women, responsible for 500,000 deaths every year in Europe (1). Mainstays in treatment of early breast cancer are breast-conserving surgery (BCS), surgical axillary staging and subsequent external whole-breast radiotherapy (EBRT). An additional boost radiation with 16 Gy targeted at the tumour bed reduces the risk of a local relapse, which is important since over 90% of in-breast relapses occur in tissue adjacent to the primary tumour (2). Furthermore, in

the course of time, considerably improved radiotherapy techniques have been developed, delivering higher effective radiation doses without increasing side-effects. With the introduction of intraoperative radiotherapy (IORT) the risk of missing the favoured target (tumour bed) can be minimised, surrounding healthy tissue can be protected and the interval between tumour excision and the beginning as well as the overall duration of an adjuvant radiotherapy can be shortened (3). In particular, shortening the postoperative duration of radiotherapy and thereby improving quality of life is of particular importance for elderly women living far from a radiation treatment facility or for patients relying on public transportation (4). These aspects are emphasized by the fact that 30-40% of breast cancer occurs in women aged more than 65 years, and due to further ageing of the population, the number of women of this age group will increase significantly over the next decades (5). In the elderly, breast cancer surgery-related mortality is low and ranges from 0-0.3%, allowing for alternative treatment options such as outpatient surgery or surgery under local anaesthesia (6). BCS, which is recommended as the standard-of-care in every age group, has a similar disease-free and overall survival but is associated with a better quality of life and is preferred for most elderly patients in comparison to mastectomy (6, 7). Although elderly individuals make up a large proportion of the breast cancer population, there is a paucity of evidence-based clinical trial data on older patients (6). Due to this fact, women of advanced age are less likely to be treated according to treatment guidelines, conceivably leading to under-treatment and negative effects on overall survival (6). Currently, in the ongoing TARGIT E(lderly) trial, the efficacy of single-dose IORT in women aged 70 years and older with small breast carcinomas and absence of risk factors is being investigated (8). It is known that advanced age impairs the outcome after breast-reduction surgery and also may negatively affect wound healing (9). Since the introduction of IORT as a novel

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Table I. Demographic parameters of the study (n=54) and control (n=134) collectives.

	Study group (range)	Control group (range)	p-Value
Median age (years)	76 (70-95)	57 (30-69)	<0.001*
Median body mass index (kg/m ²)	27 (18-38)	30 (18-42)	0.697
Smoking, n (%)	5 (9.3%)	27 (20.1%)	0.072
Diabetes mellitus, n (%)	7 (13.0%)	11 (8.2%)	0.316

*Significant difference.

approach, there is only limited evidence concerning influence of age on short-term toxicity after BCS. Hence the aim of this study was to investigate the impact of patient age on the postoperative outcome after BCS with IORT.

Patients and Methods

We retrospectively analysed peri- and postoperative data of 188 women who underwent IORT during BCS between 2002 and 2007. IORT was applied using the mobile device Intrabeam® (Carl Zeiss Surgical, Oberkochen, Germany). In 135 women (71.8%), IORT was applied as a boost irradiation and 53 patients (28.2%) received IORT only without an additional EBRT. This allocation was due to participation of women in the prospective international TARGIT-A trial, in which IORT as a sole treatment in an investigated low-risk collective (10). The German Association for Geriatric Medicine specifies an age of 70 years or more as one criterion of its definition of a geriatric patient (11). Thus, the study group consisted of 54 patients aged 70 years or older. One hundred and thirty-four patients aged less than 70 years served as the control group. The Intrabeam® system is composed of a miniature (1.6 kg) x-ray source having a probe of 10 cm in length and 3.2 mm diameter, a set of spherical applicators from 1.5 to 5.0 cm in diameter, a carrier system and a control unit. Accelerated electrons aimed at a gold target produce a spherical radiation field with an isotropic dose distribution around the tip of the probe. Using this method low-energy x-rays (50 kV) are generated. Due to the steep dose fall-off, this mobile device can be used in unmodified operating rooms. Prior to use, mechanical stability, dose rate and homogeneity of the emitted radiation were checked in detail. The patients received a perioperative intravenous single-shot antibiotic treatment with 1.5 g cefuroxime. After informed consent was given by every woman for whom radiotherapy was planned, the surgical and radiotherapeutic procedures were performed as a standardized operating procedure. Histological findings were assessed at the Department of Pathology at the University Medical Center Mannheim. Demographic and surgical parameters, as stated below, were analyzed retrospectively by checking the patients' charts. Clinical outcomes, as well as the cosmetic results were evaluated every day throughout the first week after surgery. Toxicities were assessed using the CTC/EORTC score (12). Other findings were documented without grading. These findings include: haematoma/suggillation, palpable seroma, mastitis, the necessity for therapeutic application of antibiotics, prolonged prophylactic antibiotic therapy for three days, breast induration, induration of the

Table II. Surgical parameters of study (n=54) and control (n=134) collectives. Data are given as n (%).

	Study group	Control group	p-Value
Type of axillary surgery			
SNB	30 (55.6%)	69 (51.5%)	0.614
ALNE (primary or after SNB)	27 (50.0%)	78 (58.2%)	0.305
Duration of surgery (min)			0.643
<60	0 (0%)	1 (0.8%)	
60-90	1 (1.9%)	4 (3.0%)	
90-120	8 (14.8%)	24 (17.9%)	
120-180	37 (68.5%)	76 (56.7%)	
>180	8 (14.8%)	29 (21.6%)	
Intraoperative antibiotic treatment	49 (90.7%)	126 (94.0%)	0.312
Radiation treatment			0.661
IORT-only	14 (25.9%)	39 (29.1%)	
IORT boost	40 (74.1%)	95 (70.9%)	
Duration of irradiation (min)	35 (18-55)	30 (10-60)	0.530

SNB=Sentinel node biopsy; ALNE=axillary lymphadenectomy.

tumour bed, retraction of the scar, postoperative fever, postoperative nausea, pre- and postoperative blood count, and the use of postoperative pain relievers. All data were collected in an Excel TM (Microsoft Corporation, Redmond, Seattle, USA) datasheet. After careful examination for faulty entries and extreme values, the data were transferred into SPSS (SPSS® version 17.0; SPSS Inc. Chicago, USA) for statistical analysis. Quantitative data are presented as the median and range, qualitative data as frequencies. All computations were carried out using the SPSS statistics software. A p-value less than 0.05 was considered significant.

Results

In both collectives, the acute toxicity was low and no severe intra- or postoperative complications occurred in the observation period. There were no significant differences regarding body/mass index (BMI), diabetes mellitus and smoker status comparing both collectives, as shown in Table I. In both groups most carcinomas occurred in the upper outer quadrant of the breast. In the study collective of elderly patients the upper outer quadrant of the left breast was affected more often (left 17/54, 31.5% vs. right 15/54, 27.8%), whereas in the control group cancer occurred more often in the right side (left 42/134, 31.3% vs. right 43/134, 32.1%). Type of axillary surgery, duration of surgery and type of radiation treatment revealed no significant differences comparing the two collectives. In 53 women aged 70 years or more (98.1%) and in 132 of the younger patients (99.2%), wound drainage was inserted during surgery, and in 35 (64.9%) and in 104 (78.2%) patients, respectively, it was left for three to five days. Surgical parameters are presented in detail in Table II. Regarding the tumour characteristics, most women suffered invasive ductal breast cancer stage cT1c

Table III. Tumour characteristics of study (n=54) and control (n=134) collectives. Data are given as n (%).

Parameter	Study group	Control group	p-Value
Tumor size			0.484
T1a	1 (1.9%)	1 (0.7%)	
T1b	4 (7.4%)	22 (16.4%)	
T1c	32 (59.3%)	74 (55.2%)	
T2	17 (31.5%)	37 (27.6%)	
Histology			0.838
Ductal-invasive	30 (55.6%)	79 (59.0%)	
Lobular-invasive	12 (22.2%)	25 (18.7%)	
Tubulo/lobular-invasive	5 (9.3%)	9 (6.7%)	
Other	7 (13.0%)	21 (15.7%)	
Grading			0.875
1	7 (13.0%)	17 (12.7%)	
2	35 (64.8%)	80 (59.7%)	
3	11 (20.4%)	31 (23.1%)	
Unknown	1 (1.9%)	6 (4.5%)	
Nodal involvement			0.140
N0	39 (72.2%)	92 (68.7%)	
N1mic	6 (11.1%)	26 (19.4%)	
N1a	0 (0%)	6 (4.5%)	
N2a	1 (1.9%)	0 (0%)	
N3a	0 (0%)	1 (0.7%)	
Unknown	8 (14.8%)	9 (6.7%)	
Hormone receptors (ER, PR)			0.819
Positive	46 (85.2%)	115 (86.5%)	
Negative	8 (14.8%)	19 (14.2%)	

ER, Estrogen receptor; PR, Progesterone receptor.

(59.3% vs. 54.5%; $p=0.484$). In the elderly as well as in the control group, the majority of the tumours were rated as intermediate grade (G2) and were hormone receptor - positive. A detailed description of tumour characteristics is shown in Table III. The postoperative haemoglobin values showed no statistically significant differences between the two groups. The most frequent postoperative side-effects were haematoma/suggillation in the breast. These appeared in 13 women of the study collective and in 28 patients of the control group (13/54, 24.1% vs. 28/134, 20.9%; $p=0.633$). A surgical revision due to a haematoma in the breast was necessary in 2 women of the younger collective (0/13, 0% vs. 2/28, 7.1%; $p=0.367$). There was a significantly higher incidence of postoperative axillary haematoma in the elderly (10/54, 18.5% vs. 10/134, 7.5%; $p=0.026$). In one case of the control collective, surgical revision was necessary due to this complication. Grade I-II erythema arose in 7 women of the study collective and in 17 of the control collective (7/54, 13% vs. 17/134, 12.7%; $p=0.959$). None of them were classified as grade III or IV. In only 3 patients aged more than 70 years and in 3 younger patients was mastitis diagnosed (3/54, 6.5% vs. 3/134, 2.2%; $p=0.242$). There was

Table IV. Postoperative complications and clinical parameters of study (n=54) and control (n=134) collectives. Data are given as n (%).

Parameter	Study group	Control group	p-Value
Palpable seroma breast	2 (3.7%)	4 (3.0%)	0.114
Needle aspiration	1 (50%)	0 (0%)	
Palpable seroma axilla	12 (22.2%)	15 (11.2%)	0.051
Needle aspiration	8 (66.7%)	13 (86.7%)	0.314
Haematoma/suggillation breast	13 (24.1%)	28 (20.9%)	0.633
Surgical revision	0 (0%)	2 (7.1%)	0.367
Haematoma axilla	10 (18.5%)	10 (7.5%)	0.026*
Surgical revision	0 (0%)	1 (10.0%)	0.524
Inconspicuous woundhealing	26 (48.1%)	48 (35.8%)	0.117
Erythema	7 (13.0%)	17 (12.7%)	0.959
Mastitis	3 (5.6%)	3 (2.2%)	0.242
Fever	3 (5.6%)	13 (9.7%)	0.357
Therapeutic antibiotic treatment	17 (31.5%)	52 (38.8%)	0.311
Induration of tumour bed	6 (11.1%)	7 (5.2%)	0.150
Retraction of the scar	1 (1.9%)	1 (0.7%)	0.504
Postoperative pain reliever			
On demand	9 (16.7%)	19 (14.2%)	0.862
Regular	18 (33.3%)	54 (40.3%)	
Postoperative nausea	0 (0%)	3 (2.2%)	0.268
Duration of hospital stay			
<3 Days	4 (7.4%)	6 (4.5%)	0.400
3-5 Days	36 (66.7%)	78 (58.2%)	
>5 Days	14 (25.9%)	50 (37.3%)	

*Significant difference.

no significant difference in groups in regard to the incidence of fever, which was defined as elevated body temperature $>38.3^{\circ}\text{C}$ measured with a tympanic thermometer, within the first seven postoperative days (13). The majority of women in both groups stayed 3-5 days as in-patients (36/54, 66.7% vs. 78/134, 58.2%). A detailed description of postoperative events is given in Table III.

Discussion

Due to improved medical care, especially in developed countries, in addition to increased health awareness, the average life expectancy has steadily risen during past decades (14). The incidence and mortality of breast cancer has increased with increasing age. Although elderly women represent a large part of the breast cancer population, they have been excluded from many clinical trials because of advanced age, associated comorbidities, or both (6). Some studies deal with a therapeutic approach of less-invasive treatment of breast cancer in the elderly, including omission of surgery, performing hormonal treatment only. A Cochrane analysis revealed that primary hormonal treatment of breast cancer with tamoxifen is inferior to surgery (with or without hormonal treatment) for local control and progression-free

but not overall survival in medically-fit older women (15). Postoperative radiotherapy as one mainstay in the treatment of early breast cancer reduces the risk of local recurrence after BCS, as well as absolute breast cancer mortality (16). Although absolute benefits of adjuvant radiotherapy are less in older patients, the rate of local recurrence after BCS is significantly lower in women who receive adjuvant radiotherapy compared to women who receive treatment with tamoxifen only (5). Despite such evident benefit, elderly are treated less frequently with postoperative radiotherapy compared to a younger collective (6). This may be due to many reasons but probably in particular to a high logistical expenditure for the elderly, organizing a daily drive to the Department of Radiation Oncology. Sawin showed that older rural women suffering from breast cancer are confronted with problems such as driving to the oncologic department, which on one hand leads to increased healthcare costs and on the other hand is an additional strain on the already stressed patient (17). With introduction of IORT, it is possible to begin adjuvant radiotherapeutic treatment during surgery, with a low incidence of short-term complications, as shown in a recent study of our group (18). Vaidya *et al.* showed that IORT as a sole treatment in a low-risk collective (women with primary unifocal ductal invasive breast cancer, aged 45 years or older) is not inferior to EBRT regarding local recurrence (10). This is obviously of particular interest for elderly patients, as defined in our investigation. Therefore the prospective international multicentric trial TARGIT E(lderly) was initiated. This investigation should confirm the efficiency of a single IORT in a group of elderly patients with small breast carcinomas and absence of risk factors (8). Regarding acute toxicity after external radiation, tolerability is known not to be the limiting factor for radiotherapy in elderly women. Huguenin *et al.* and Whykhoff *et al.* analyzed the toxicity of postoperative radiotherapy in patients aged 65 years and older and showed no higher toxicity comparing this collective to younger women (19, 20). Nevertheless, data focusing on the influence of age on acute toxicity after IORT is still scarce. In our investigation, the overall toxicity was low and no grade 3/4 toxicity occurred. We showed that age does not influence acute toxicity after BCS with IORT. Our findings confirm the results of Kraus Tiefenbacher *et al.* (21). In their study, a series of 84 women treated with IORT as a boost using IntraBeam[®] were assessed, evaluating acute toxicity after one week, and 1, 2 and 4-6 months after surgery. The mean tumour size was 15 mm and the most frequently used applicator size was 4.5 cm. One week after surgery and IORT the most frequent side-effect was haematoseroma in 6%, followed by erythema, which occurred in 3% of the patients. There were no statistically significant differences regarding the observed toxicities due to age or tumour size. In our study, the incidence of erythema was slightly higher at

12.7% and 13%, respectively. A reason for the higher incidence may be the difference in timing of clinical evaluation (daily assessment starting from the first postoperative day *vs.* first postoperative evaluation seven days after BCS and IORT). Hence, after one week, the initial acute phase reaction after the physical trauma during surgery had declined and any haematoma of the skin had been absorbed. Kraus-Tiefenbacher *et al.* showed that in an external-radiation setting after BCS, age and BMI do not influence the toxicity after EBRT. Factors associated with higher toxicity after ERBT were large breast target volume, smoking and absence of allergies (22). Regarding age, our findings are consistent with this, because we also did not find a correlation of increased acute toxicity with advanced age in women undergoing BCS with IORT. The fact that there were significantly more axillary haematomas in the study group cannot be anatomically attributed to the IORT, as the irradiation to the breast does not affect the anatomical structures concerning the blood supply of the axilla. The higher incidence can be ascribed to an increased vulnerability and a reduced homeostatic capability in elderly, as shown by Gosain *et al.* (23). We know from the literature that elderly women undergoing surgery due to breast cancer are more likely to have a mastectomy and are less likely to undergo breast reconstruction (5). Although cosmesis seems to be less important in this group compared to younger patients, most would choose BCS despite the actual need for radiotherapy (24). Hence in our opinion, BCS in combination with IORT is a feasible alternative treatment option for women who decline or are incapable of undergoing postoperative radiation. Furthermore, shortening the overall postoperative treatment time of radiotherapy by using IORT in the elderly could contribute to solving logistical and psychological problems of women with early breast cancer, particularly for those living far from a radiation oncology center.

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