ANTICANCER RESEARCH
International Journal of Cancer Research and Treatment
ISSN: 0250-7005

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Reprinted from
ANTICANCER RESEARCH *43*: 733-739 (2023)

ANTICANCER RESEARCH

International Journal of Cancer Research and Treatment

HighWire Press® STANFORD UNIVERSITY

ISSN (print): 0250-7005
ISSN (online): 1791-7530

Editorial Board

Editorial Office: International Institute of Anticancer Research, 1st km Kapandritiou-Kalamou Rd., Kapandriti, P.O. Box 22, Attiki 19014, Greece. Tel / Fax: +30-22950-53389.

U.S. Branch: Anticancer Research USA, Inc., 111 Bay Avenue, Highlands, NJ 07732, USA.

E-mails: Editorial Office: journals@iiar-anticancer.org
Managing Editor: editor@iiar-anticancer.org

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Publication Data: ANTICANCER RESEARCH (AR) is published bimonthly from January 1981 to December 2008 and monthly from January 2009. Each annual volume comprises 12 issues. Annual Author and Subject Indices are included in the last issue of each volume. ANTICANCER RESEARCH Vol. 24 (2004) and onwards appears online with Stanford University HighWire Press from April 2009. All published articles are deposited in PubMed Central.

Annual Subscription Rates 2023 per volume: Institutional subscription US$ 1,898.00 (online) or US$ 2,277.00 (print & online). Personal subscription US$ 897.00 (online) or US$ 1,277.00 (print & online). Prices include rapid delivery and insurance. The complete previous volumes of Anticancer Research (Vol. 1-42, 1981-2022) are available at 50% discount on the above rates.

Subscription Orders: Orders can be placed at agencies, bookstores, or directly with the Publisher. (e-mail: subscriptions@iiar-anticancer.org)

Advertising: All correspondence and rate requests should be addressed to the Editorial Office.

Book Reviews: Recently published books and journals should be sent to the Editorial Office. Reviews will be published within 2-4 months.

Articles in ANTICANCER RESEARCH are regularly indexed in all bibliographic services, including Current Contents Life Sciences and Medical Sciences, Science Citation Index Expanded, Index Medicus, Biological Abstracts, PubMed, PubMed Central, Chemical Abstracts, BIOSIS, Previews, Essential Science Indicators, Excerpta Medica, University of Sheffield Biomedical Information Service, Current Clinical Cancer, AIDS Abstracts, Elsevier Bibliographic Database, EMBASE, Compendex, GEOBASE, EMBiology, Elsevier BIOBASE, FLUIDEX, World Textiles, Scopus, Progress in Palliative Care, Cambridge Scientific Abstracts, Cancergram (International Cancer Research Data Bank), MEDLINE, Reference Update - RIS Inc., PASCAL-CNRS, Inpharma-Reactions (Datastar, BRS), CABS, Immunology Abstracts, Telegen Abstracts, Genetics Abstracts, Nutrition Research Newsletter, Dairy Science Abstracts, Current Titles in Dentistry, Inpharma Weekly, BioBase, MedBase, CAB Abstracts/Global Health Databases, Investigational Drugs Database, VINITI Abstracts Journal, Leeds Medical Information, PubsHub, Sociedad Iberoamericana de Información Científíca (SIIC) Data Bases.

D.T.P. BY IIAR

PRINTED BY ENTYPO, ATHENS, GREECE. PRINTED ON ACID-FREE PAPER

ANTICANCER RESEARCH *43*: 733-739 (2023)
doi:10.21873/anticanres.16212

Breast Conserving Surgery in Combination With Targeted Intraoperative Radiotherapy Compared to Mastectomy for In-breast-tumor-recurrence

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Abstract. *Background/Aim: Mastectomy is the standard treatment of in-breast-recurrence of breast cancer after breast conserving surgery (BCS) and external beam radiation therapy (EBRT). In selected cases, it is possible to preserve the breast if targeted intraoperative radiotherapy (TARGIT-IORT) can be given during the second lumpectomy. This is a comparative analysis of overall survival and quality of life (QoL). Patients and Methods: Patients in our database with in-breast-recurrence and either mastectomy or BCS and TARGIT-IORT were included. Identified patients were offered participation in a prospective QoL-analysis using the BREAST-Q questionnaire. The cohorts were compared for confounding parameters, overall survival, and QoL. Results: Thirty-six patients treated for in-breast-recurrence were included, 21 had received a mastectomy and 16 patients had received BCS with TARGIT-IORT. Mean follow-up was 12.8 years since primary diagnosis and 4.2 years since recurrence. Both groups were balanced regarding prognostic parameters. Overall survival was numerically longer for BCS and TARGIT-IORT, but the numbers were too small for formal statistical analysis. No patient had further in-breast-recurrence. Psychosocial and sexual wellbeing did not differ between both groups. Physical wellbeing was significantly superior for those whose breast could be preserved (p-value=0.021). Patient-reported incidence and severity of lymphedema of the arm was significantly worse in the mastectomy group (p=0.007). Conclusion: Preserving the breast by use of TARGIT-IORT was safe with no re-recurrence and no detriment to overall survival in our analysis and led to a statistically significant improvement in physical wellbeing and incidence of lymphedema. These data should increase the confidence in offering breast preservation after in-breast-recurrence of breast cancer.*

Local recurrence-free survival after breast conserving therapy for stage I-III breast cancer, *i.e.*, breast conserving surgery and breast irradiation, has been reported to be 89% after 5 years and 80% after 10 years of follow up (1). Patients remain at a risk for an ipsilateral in-breast tumor recurrence (IBTR) of 0.5% per year (2). The risk of local recurrence is significantly higher in patients younger than 70 than in older patients (3). The database guiding systemic treatment recommendations in the case of a local recurrence without distant disease is small. The only prospective trial investigating adjuvant chemotherapy in this situation, the CALOR trial, demonstrated a benefit in association with adjuvant chemotherapy only for hormone receptor negative patients (4). Data regarding the use of HER2-directed antibodies or tyrosine kinase inhibitors in the setting of an isolated local recurrence are missing and recommendations in this situation are based on extrapolations from early or metastatic breast cancer (5). The benefit of endocrine therapy in the situation of an endocrine responsive local recurrence is limited to disease-free survival without impact on overall survival (6-8). Not only is the systemic treatment approach in this situation subject to discussion and has to be decided individually, but the same is true for surgical treatment options. The more radical surgical approach (*i.e.*,

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Key Words: Breast cancer, in-breast-tumor-recurrence, IBTR, mastectomy, TARGIT-IORT, BREAST-Q, QoL.

mastectomy) results in a range of second local recurrence rates between 2-31% in comparably small datasets (9); however, it seems to be without prognostic impact if the regional lymph nodes are evaluated or not (10). The less radical solution of repeat breast conserving surgery without radiation leads to local failure in 19-50% (9). Interestingly a direct comparison of mastectomy and breast conserving surgery without radiation did not reveal significantly different rates of second recurrence in a series of 266 patients with a follow up of 51 months (breast conservation 38% *vs*. mastectomy 25%; p=0.27) (11). In another series comparing mastectomy with second breast conserving surgery with a median follow up of 70 months the difference in rates of second surgery in breast recurrence favoring mastectomy (4% *versus* 19%) did not influence overall and disease-free survival (12). A recent meta-analysis including 15 studies confirmed these results and demonstrated an increased rate of local failure for repeat breast conserving surgery compared to mastectomy but no impact on overall survival (13). Although the addition of whole breast irradiation to breast conserving surgery in case of a breast, which has already received a full course of radiation, was demonstrated to be feasible (14, 15), this approach was never really pursued due to fear of a high risk of severe toxicity not only for the breast tissue itself but also for adjacent structures, such as the lung. The application of techniques of partial breast irradiation to avoid an elevated toxicity risk in this situation yielded good control rates, acceptable toxicity and good cosmesis for external partial re-irradiation (16), brachytherapy (17-19) and for targeted intraoperative radiotherapy (TARGIT-IORT) with the 50kV-XRay-device (20, 21). These data did not only lead to the integration of breast conserving surgery in combination with partial breast irradiation in national guidelines as an option for selected patients in case of IBTR (and not as a replacement for mastectomy in general) (22-24), but have also convinced breast surgeons and radiation oncologists to offer this option to patients who want to preserve their breast (25).

Results regarding quality of life (QoL) after repeat BCS are not conclusive. In a study including patients after second BCS for IBTR with and without partial breast irradiation (PBI) demonstrated a QoL benefit for repeat BCS compared to mastectomy (26) whereas a trial comparing BCS and TARGIT-IORT with mastectomy with and without reconstruction found comparable QoL using the BREAST-Q™ questionnaire in all three groups (27). Here, we are presenting an analysis comparing long-term outcome, patient-reported side effects, and QoL between patients who received BCS and TARGIT-IORT and patients who received a mastectomy for IBTR.

Patients and Methods

This study included patients who were treated for IBTR after breast conserving surgery and whole breast irradiation in our certified breast cancer center between 2014 and 2020 and who had received either mastectomy or BCS and TARGIT-IORT for IBTR. Both options were discussed with the patients and patients chose their preferred procedure. Patients with distant recurrence and patients with breast reconstruction after mastectomy for IBTR were excluded from this analysis. All patients received a mammography, breast and axilla ultrasound, CT scans of the thorax and abdomen and a bone scan prior to surgery. Data regarding patient characteristics at the time of recurrence and follow-up were extracted from the patient files and transferred into an Excel-file after anonymization.

The analysis includes a retrospective part regarding patient characteristics and outcome parameters and a prospective part regarding QoL analysis. Patients had signed a written informed consent authorizing the use of their follow-up data for scientific reasons at the time of surgery for IBTR. For the prospective QoL analysis, patients were contacted *via* mail and offered participation in the study. After written informed consent, patients received the German version of the BREAST-Q™ questionnaire. The results of the completed BREAST-Q™ questionnaires were also transferred into the anonymized Excel-file.

Patient and tumor characteristics analyzed at the time of recurrence included (all at the time of IBTR) age, diameter, estrogen receptor status (ER), progesterone receptor status (PR), HER2neu status, nodal status, and use of neoadjuvant therapy for IBTR. Outcome parameters analyzed were overall survival defined as death by any cause after time of primary diagnosis and time of IBTR.

Parameters analyzed from the results of the BREAST-Q™ questionnaires were psychosocial, sexual, and physical wellbeing, lymphedema of the arm on the side of surgery, satisfaction with breast surgeon, medical team, and office staff, and adverse effects of radiation.

Values in the BREAST-Q™ questionnaires were added and transformed into a sum score between 0 and 100 with a higher sum score indicating a higher QoL. As an exception from this method, the item "lymphedema of the arm on the side of surgery" was transformed into a scale from 1 to 3 with 3 meaning that the patient had not suffered from a lymphedema at any time.

Mastectomy was performed as a modified radical mastectomy with removal of the skin, breast tissue, and fascia of the musculus pectoralis major. Patients with breast reconstruction were not included in this analysis. Breast conserving surgery was performed as segmentectomy. TARGIT-IORT was performed with the 50kV X-ray source Intrabeam™ (Carl Zeiss meditec, Oberkochen, Germany). The applied radiation dose was 20 Gray at the surface of the applicator resulting in 5-6 Gray in a depth of 1 cm. Axillary surgery was not performed as a standard procedure, only in cases of involved lymph nodes these were removed.

The two cohorts (mastectomy/BCS and TARGIT-IORT) were compared for confounding parameters, OS from primary diagnosis, and time of IBTR and QoL.

Statistical analysis. After transfer of the retrospective and prospective data into the anonymized Excel-file (Microsoft Excel®, Version 16.56, 2021) the statistical analysis was performed using the software SPSS® Statistics Version 28 (IBM Corp. Released 2021, IBM SPSS Statistics for Macintosh, Version 28.0. Armonk, NY, USA).

Hormone receptor and HER2neu status, tumor morphology, nodal status, and the use of neoadjuvant therapy were compared with the Chi-square test in case of ≥5 observations and with Fisher's exact test in case of <5 observations. Metrical variables, such as

Table I. *Patient characteristics at the time of recurrence*.

	Mastectomy for IBTR	BCS + TARGIT-IORT for IBTR	*p*-Value
n	21	15	
Age at IBTR mean (SD)	62.9 (12.4)	68.4 (13.4)	0.214
Tumor diameter IBTR in mm mean (SD)	21.4 (19.4)	14.6 (9.6)	0.427
ER positive n (%)	16 (76.2)	11 (73.3)	>0.999
PR positive n (%)	11 (52.4)	9 (60.0)	0.741
HER2neu positive n (%)	4 (19.05)	3 (20.0)	>0.999
Involved nodes n (%)	3 (14.3)	6 (40.0)	0.122
Neoadjuvant therapy n (%)	5 (23.8)	5 (33.3)	0.709

SD: Standard deviation; ER: estrogen receptor; PR: progesterone receptor; IBTR: in-breast-tumor-recurrence; BCS: breast-conserving surgery; TARGIT-IORT: targeted intraoperative radiotherapy.

age, diameter of the IBTR, and scales of the BREAST-Q™ questionnaire were analyzed using the *t*-test for independent samples in case of a normal distribution and the Mann-Whitney *U*-test in case of a non-normal distribution. The analysis for normal distribution was performed by Q-Q-diagram. Kaplan–Meier (K-M) estimates for OS were calculated with a Cox proportional hazards model. A *p*-value of 0.05 was considered statistically significant.

Results

In total, 36 patients treated for IBTR were included in this analysis, 21 had a mastectomy while 15 patients chose to preserve their breast and were treated with BCS and TARGIT-IORT in compliance with an interdisciplinary tumor board decision. The Ethics Commission of the Faculty of Medicine at the University of Duisburg-Essen approved the project on June 23rd, 2021 (Approval No: 21-10061-BO).

Mean follow-up was 12.8 years since primary diagnosis and 4.2 years since recurrence. We observed no statistically significant differences between both groups regarding age, ER, PR, HER2neu, tumor size, nodal status, and the use of neoadjuvant therapy at the time of recurrence. The results of the comparison of patient characteristics at the time of recurrence can be found in Table I.

One patient in the BCS and TARGIT-IORT group (6.7%) and 3 patients in the mastectomy group (14.3%) died during follow up. Overall survival was numerically longer for BCS and TARGIT-IORT either calculated from primary diagnosis (mean BCS + TARGIT-IORT 24.4 years *versus* mastectomy 23.4 years) or from recurrence (mean BCS + TARGIT-IORT 7.7 years *versus* mastectomy 6.4 years), however, these differences were not statistically significant. No patient had a second local recurrence during follow-up. The results of the outcome analysis can be found in Table II.

Twelve of the 21 patients in the mastectomy group and 10 of the 15 patients in the BCS and IORT group returned the BREAST-Q questionnaire. Eight patients refused participation in the prospective QoL analysis, four patients had died, and two patients did not react at all, but were alive according to information from their general practitioners. Use of the BREAST-Q™ questionnaire, authored by Drs. Klassen, Pusic and Cano, was made under license from Memorial Sloan Kettering Cancer Center, New York, NY, USA. Psychosocial wellbeing, sexual wellbeing, and satisfaction with breast surgeon, office team, and medical staff did not differ between both groups. Physical wellbeing was superior for those whose breast could be preserved. The median score for this item in the BCS and TARGIT-IORT group was 91.0 [interquartile range (IQR)=71.0-100.0] *versus* 66.0 (IQR=57.2-100.0) for the mastectomy group. This difference was statistically significant with a *p*-value of 0.021. Whereas other side effects were comparable without significant differences in both groups, patient-reported incidence and severity of lymphedema of the arm on the side of surgery was significantly worse in the mastectomy group with a score of 2.0 (IQR=2.0-3.0) compared to 3.0 (IQR=3.0-3.0) in the BCS and TARGIT-IORT group. This difference was statistically significant with a p-value of 0.007. The full set of analyzed items from the BREAST-Q™ questionnaires and the corresponding scores are displayed in Table III.

Discussion

Early breast cancer carries a good prognosis with local recurrence-free survival at 10-years of about 80% (1). Because of this high rate of long-term survival, questions of patient satisfaction, long-term side effects, and QoL have come more and more into focus. Patient-reported outcomes are considered to be at least as if not more important than clinical and photographic assessments of results after breast conserving therapy (28). QoL and self-esteem are reported to be superior in patients treated with BCS compared to mastectomy for early breast cancer at the time of primary diagnosis. Interestingly this did not change if patients received a breast reconstruction (29). In the recurrent situation, patients are also reporting a better QoL if treated with a second breast conserving operation compared to mastectomy (30-32).

Table II. *Survival analysis*.

	Mastectomy for IBTR	BCS + TARGIT-IORT for IBTR	*p*-Value
n	21	15	
Mean OS since primary diagnosis in years (95%CI)	23.4 (17.9-29)	24.4 (21.6-27.4)	0.507
Mean OS since IBTR in years (95%CI)	6.4 (5.5-7.2)	7.7 (6.8-8.5)	0.402
Death n (%)	3 (11.1)	1 (6.7)	

CI: Confidence interval; OS: overall survival; IBTR: in-breast-tumor-recurrence; BCS: breast-conserving surgery; TARGIT-IORT: targeted intraoperative radiotherapy.

Table III. *Results of the BREAST-Q™ questionnaires*.

	Total	Mastectomy for IBTR	BCS + TARGIT-IORT for IBTR	*p*-Value
n	22	12	10	
Psychosocial wellbeing - median (IQR)	65.0 (53.5-74.7)	64.0 (50.5-68.2)	74.0 (60.0-80.0)	0.069
Sexual wellbeing - median (IQR)	39 (25.5-66.0)	40.0 (31.5-66.0)	34.0 (20.0-70.0)	0.813
Physical wellbeing - median (IQR)	71.5 (64.0-100.0)	66.0 (57.2-83.7)	91.0 (71.0-100.0)	0.021*
Lymphedema of the arm on the side of surgery - median (IQR	3.0 (2.0-3.0)	2 (1.25-3.0)	3.0 (3.0-3.0)	0.007*
Satisfaction with the breast surgeon - median (IQR)	96.0 (59.0-100.0)	100.0 (59.0-100.0)	92.0 (52.5-100.0)	0.71
Satisfaction with the medical team - median (IQR)	100.0 (69.0-100.0)	100.0 (69.5-100.0)	91.0 (67.7-100.0)	0.539
Satisfaction with office staff - median (IQR)	79.5 (66.7-100.0)	85.0 (64.2-100.0)	79.5 (66.7-100.0)	0.923
Adverse effects of radiation - median (IQR)	87.0 (61.5-100.0)	71.0 (58.0-100.0)	87.0 (69.0-100.0)	0.436

IQR: Interquartile range; IBTR: in-breast-tumor-recurrence; BCS: breast-conserving surgery; TARGIT-IORT: targeted intraoperative radiotherapy. *Statistically significant difference.

Intraoperative radiotherapy with a 50 kV X-ray-source (TARGIT-IORT) has become one standard of care in the local treatment of early breast cancer as an anticipated boost (33) but also as definitive radiation (34). This has led to the integration of TARGIT-IORT into national guidelines and recommendations (35) and it is also used in indications when radiation is problematic *e.g.*, in patients with implants who do not want them to be removed in the course of BCS (36). In Germany, access to treatment with the INTRABEAM™ -device is available in over 50 certified breast cancer centers.

In our analysis, overall survival was longer in the group of patients receiving BCS and TARGIT-IORT for IBTR compared to the group of patients with a mastectomy, although this result did not reach statistical significance. This trend for a better outcome without statistical significance has also been reported previously in studies comparing BCS and TARGIT-IORT with mastectomy in cases of IBTR (27). Although the numerical results hint to a benefit of BCS and TARGIT-IORT, we recommend a very cautious interpretation of these data. However, we believe it is safe to acknowledge that BCS and TARGIT-IORT is not detrimental to overall survival compared to the standard of care mastectomy in cases of IBTR and can thus be regarded a safe alternative.

Regarding QoL and patient reported toxicity, our data demonstrated a significantly superior physical wellbeing in the BCS and TARGIT-IORT. This is in line with other data in this situation, demonstrating that TARGIT-IORT is associated with superior (26) or at least non-inferior (26) QoL of BCS and partial breast irradiation compared to mastectomy. The study that did not demonstrate a superior QoL included three groups (BCS + TARGIT-IORT *versus* mastectomy without reconstruction *versus* mastectomy with reconstruction) whereas our inclusion criteria did not include patients with reconstruction after mastectomy. It is possible that the group of patients with mastectomy and reconstruction led to the differing findings regarding QoL because these patients are exposed to a higher possibility of postoperative complications and this may have influenced the analysis of QoL. In another retrospective series including patients with primary tumors the failure of reconstructions was significantly associated with the application of radiation (37) and a failed reconstruction can be expected to have a detrimental effect on how patients feel about their therapy.

We also could demonstrate a significantly lower rate of postoperative lymphedema in the group of patients who received BCS and TARGIT-IORT compared to mastectomy. To our knowledge, this is the first time this benefit is reported. Considering the fact that lymphedema does not only have the expected effects on arm movement and pain but also leads to a rate of 58.8% of sleep disturbances and a rate of 29.7% of

depression in affected patients (38), this result should be mentioned in the process of decision making in cases of IBTR.

Of course, our analysis has limitations that have to be kept in mind when interpreting the data. It was a retrospective analysis and the patient numbers are small. However, prospective data in this situation are missing and comparable analyses have patient numbers in the same range. Although studies like ours have to be interpreted with caution, they give confidence when discussing the alternatives of mastectomy and BCS and TARGIT-IORT with a patient in case of an IBTR.

The majority of patients with breast cancer including those with local recurrence are highly reluctant to lose their breast. In our analysis, we found that breast preservation by use of TARGIT-IORT was safe with no re-recurrence and no detriment to overall survival. This approach led to a statistically significant improvement in physical wellbeing as well as the rate of lymphedema. Our results carry the potential to increase the confidence in offering breast preservation in combination with TARGIT-IORT for local therapy of IBTR of breast cancer.

Conflicts of Interest

HCK has received honoraria from Pfizer, Novartis, Roche, Genomic Health/Exact Sciences, Amgen, AstraZeneca, Riemser, Carl Zeiss Meditec, TEVA, Theraclion, Janssen-Cilag, GSK, LIV Pharma, Lily, SurgVision, Onkowissen, Gilead, Daiichi Sankyo and MSD, travel support from Carl Zeiss Meditec, LIV Pharma, Novartis, Amgen, Pfizer, Daiichi Sankyo, Tesaro and owns stock of Theraclion SA and Phaon Scientific GmbH. HN has nothing to disclose. JSV has nothing to disclose. LAB has nothing to disclose. AM has nothing to disclose. OH has nothing to disclose. GL has nothing to disclose. MS has nothing to disclose. CKL reports stock by Phaon Scientific, honoraria by Roche, AstraZeneca, Celgene, Novartis, Pfizer, Lilly, Hexal, Amgen, SonoScape, consulting to Roche, Novartis, Pfizer, Celgene, Phaon Scientific; research funding by Roche, Novartis, Pfizer as well as travel and accommodation by Roche, Daiichi Sankyo.

Authors' Contributions

The design of the analysis was developed by HCK, CKL, and HN. Data collection and statistical analysis were performed by HCK and HN. Interpretation of the data, writing and correction of the manuscript were performed by HCK, HN, JSV, LAB, AM, OH, GL, MS, and CKL. All Authors approved the final version of this manuscript.

Acknowledgements

Use of the BREAST-Q™ questionnaire, authored by Drs. Klassen, Pusic and Cano, was made under license from Memorial Sloan Kettering Cancer Center, New York, U.S.A.

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Received December 5, 2022
Revised December 13, 2022
Accepted December 14, 2022

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