Ann Surg Oncol (2012) 19:519–526
DOI 10.1245/s10434-011-1879-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Neoadjuvant Chemotherapy Increases the Rate of Breast Conservation in Lobular-Type Breast Cancer Patients

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ABSTRACT

Introduction. Our study aims to determine whether patients with lobular-type breast cancer have significantly improved rates of breast conservation (BCT) after neoadjuvant chemotherapy (nCT).

Methods. Patients who received nCT and surgery within three prospective trials between 1995 and 2007 at the Medical University of Vienna were retrospectively analyzed.

Results. 325 patients had median follow-up of 53 months; 21% had lobular cancer, and 70% of these women were initially scheduled for mastectomy (MX). Twenty-one finally received BCT, yielding a MX–BCT turnover rate of 45%. Of patients primarily scheduled for BCT, 20% had to finally undergo MX in lobular cancer. The 256 patients with ductal-type breast cancer finally had a MX–BCT turnover rate of 52% ($p = 0.561$ versus lobular) and a BCT–MX turnover rate of 15% ($p = 0.933$ versus lobular). Secondary MX after initial BCT was necessary in 2% (ductal) and 10% (lobular, $p = 0.110$). There was no difference in local recurrence in lobular- as compared with ductal-type breast cancer patients after BCT (2.7% versus 10%, $p = 0.135$), nor was a difference seen in lobular breast cancer patients when comparing BCT with MX (2.7% versus 3.4%, $p = 0.795$). Tumor type was not an independent predictor for either BCT or local recurrence.

Conclusion. We do not suggest excluding patients with lobular-type breast cancer who are primarily scheduled for MX from nCT, since BCT rates may still increase by 45% without influencing the oncologic outcome.

Neoadjuvant chemotherapy (nCT) was originally introduced as a treatment option for patients with locally advanced breast cancer in an attempt to convert inoperable into operable disease.[1–3] Soon after achieving positive results, the concept was extended to earlier, operable stages, aiming to increase the rate of breast-conserving therapy (BCT), which is associated with less morbidity, better cosmetic results, and improved body image as compared with mastectomy.[4–6]

The benefit of nCT for lobular-type breast cancer is questioned, especially in terms of pathologic complete response (pCR) rate.[7] Thus, some authors suggested not to submit lobular-type, estrogen and progesterone receptor-positive breast cancer to nCT.[8] This reasoning was based on two observations. First, lobular breast cancer yielded only 1.7% pCR, while ductal type showed 11.6% in several randomized trials.[9] This finding was supported by a meta-analysis.[7] Second, the rate of breast conservation does not seem to be increased by nCT in lobular-type breast cancer.[10,11] While no benefit from nCT has been demonstrated in patients with lobular-type breast cancer, there are some promising results with neoadjuvant endocrine therapy (nET). However, available data regarding the increase in BCT rate are of limited use, as authors have failed to differentiate between patients primarily scheduled for BCT and those needing mastectomy (MX) before nCT. nET is presently not considered standard therapy and should only be administered within prospective trials. Thus, nET is not

First Received: 4 February 2011;
Published Online: 9 July 2011

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a treatment option for lobular-type breast cancer in hospitals without access to clinical trials.

The aim of this study is to investigate whether lobular-type breast cancer patients primarily scheduled for MX may experience increased BCT rates after nCT with similar oncologic outcome.

PATIENTS AND METHODS

Design

We analyzed our prospectively generated internal patient database. After each visit at the outpatient ward, our study nurse prospectively processes data into a pre-existing computer worksheet. Data are then transferred into an Excel spreadsheet for further statistical analyses.

Inclusion Criteria

Patients with histologically verified unilateral breast cancer and tumor diameter exceeding 2 cm were eligible for nCT within three clinical trials carried out at our institution. The analyses included 400 patients who had completed nCT and local therapy at the Medical University of Vienna and who had been operated between January 1995 and May 2007. Eligibility for BCT or MX prior to nCT was re-evaluated on the basis of the patients' reports (either outpatient ward report or operation report). Patients without a clear pretherapeutic decision for either MX or BCT were excluded from further analyses ($n = 75$). Patients were scheduled for MX in the presence of breast–tumor size ratio larger than 4:1 (more than one breast lump has to be excised). Accordingly, multicentricity seen on pretreatment radiological examinations was another factor for scheduling patients for MX either before or after nCT. Clinical assessment as well as mammography and ultrasound or magnetic resonance imaging (MRI) mammography were mandatory in terms of primary staging evaluation.

Exclusion Criteria

Patients with metastatic breast cancer, inflammatory breast cancer, infiltration of the thoracic wall, Eastern Cooperative Oncology Group (ECOG) >2 or bilateral breast cancer were not included in the present analysis. For additional inclusion and exclusion criteria, please refer to the original publications.[7,12,13]

Neoadjuvant Therapy

Most patients received nCT in one of three prospective randomized trials conducted by the Austrian Breast and Colorectal Cancer Study Group (ABCSG; trials ABCSG 7, ABCSG 14, and ABCSG 24) and approved by the local ethics committee.

ABCSG 7 In ABCSG 7 (1991–1999), 423 patients with hormone receptor-negative or high-risk endocrine-responsive disease were randomized to three cycles of CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2 on days 1 and 8, every 4 weeks) as either pre- or postoperative treatment. The overall response rate to neoadjuvant CMF was 56.2%, with 12 patients (5.9%) achieving pCR. While no difference in terms of overall survival was observed between the two groups, recurrence-free survival was significantly better in patients receiving chemotherapy postoperatively, leading to the conclusion that three cycles of CMF was insufficient for nCT.[13]

ABCSG 14 ABCSG 14 (2000–2004) compared three cycles of epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 (ED) on day 1, every 3 weeks, combined with granulocyte colony-stimulating factor on days 3–10 of each cycle, versus six cycles of the same regimen as neoadjuvant treatment for breast cancer. A total of 292 patients were accrued; six cycles of ED yielded a significantly higher pCR rate (18.6% versus 7.7%, $p = 0.0045$), a significantly higher percentage of patients with negative axillary status (56.6% versus 42.8%, $p = 0.02$), and a trend towards a higher BCT rate (75.9% versus 66.9%, $p =$ n.s.).[12]

ABCSG 24 Based upon a proposed synergistic effect of docetaxel and capecitabine, ABCSG 24 (2004–2008) compared six cycles of ED plus capecitabine (EDC; epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 on day 1, capecitabine 1,000 mg/m^2 bid days 1–14, every 3 weeks, plus pegfilgrastim 6 mg on day 2 of each cycle) with the standard six cycles of ED as established in ABCSG 14. A total of 512 patients were accrued to ABCSG 24. Significantly more patients reached pCR with ECD (23.8% versus 15.2%, $p = 0.036$).[7]

Clinical Response Evaluation

Clinical response was evaluated by palpation and radiologically by mammography and ultrasound or MRI imaging. Pathological response was evaluated from paraffin-embedded sections compared with the clinical size prior to nCT, as described earlier.[14]

Surgery

Four to six weeks after nCT, patients proceeded to surgery. Patients primarily underwent BCT except in the presence of:

- Initially questionable cosmetic result with BCT to achieve R0 resection (>1 mm or not on ink)
- Multicentric disease (MRI was done in patients with two or more lesions seen on the mammogram or breast ultrasound)

Patients primarily scheduled for BCT underwent secondary MX in cases of R1 (<1 mm or touching the ink) resection after BCT lacking the possibility for re-resection, with good cosmetic outcome (resection of two quadrants or more). Other patients were re-resected until R0 resection was accomplished (the decision for MX in part depending on patients' wishes).

Nonpalpable lesions were localized with a hook wire preoperatively. Intraoperative frozen section was done in all cases to determine the resection margins and thereby reduce the reoperation rate.[15,16] In unifocal disease, the resection was performed within new resection boundaries after response to nCT. In multifocal disease, resection boundaries were only smaller if all tumors responded to nCT and the total diameter was reduced. All patients underwent axillary level I and II dissection, except in some selected postmenopausal, clinically complete responders with no clinical evidence of axillary involvement before or after nCT. These patients underwent sentinel node biopsy only. Axillary dissection always followed sentinel node biopsy in the presence of a positive sentinel lymph node.

Histological Evaluation

Lobular histology was defined using E-cadherin staining. Estrogen and progesterone receptors were defined according to the Reiner score.[17] In this investigation, receptor positivity implies at least 10% positive tumor cells. Pathologic response was evaluated with paraffin-embedded sections. pCR was defined as no invasive tumor within the breast with or without in situ components within the breast and no axillary cancer burden (pCR±isN0).

Adjuvant Therapy

All patients received adjuvant therapy according to centers' policies. After 2004, all patients with human epidermal growth factor receptor 2 (HER-2)-positive tumors received trastuzumab for 1 year.

Statistical Analyses

Categorical data were described with absolute and relative frequencies. Chi-square tests were used to test categorical data between groups. In case of sparse data, Fisher's exact test was applied. Furthermore, effects between groups were quantified with odds ratios (OR) and corresponding 95% confidence intervals (CIs) calculated with univariate and multivariate logistic regression. In case of infinite odds ratio estimates for multiple logistic regression, exact odds ratios and corresponding CIs were estimated and mid-p values are given. Survival curves were described according to Kaplan–Meier, and differences between groups were tested by log-rank testing. Cox regression was used to model the prognostic factors in univariate and multivariate models. All p-values are two-sided, and $p \leq 0.05$ was considered significant. All calculations were performed using SAS® statistical software (version 9.2; SAS Institute Inc., Cary, NC, USA).

RESULTS

Nineteen lobular-type breast cancer patients received CMF, while the other 48 underwent taxane-based chemotherapy. The corresponding numbers for ductal-type breast cancer were 117 and 141, respectively.

Demography

Demographic data are presented in Table 1. The planned surgical therapy and the final surgical procedures are also presented in Table 1. We compared four groups: (1) patients who were scheduled for MX and finally underwent that treatment (MX–MX), (2) patients scheduled for MX who finally underwent BCT (MX–BCT), (3) patients undergoing BCT primarily scheduled for that treatment (BCT–BCT), and (4) patients scheduled for BCT who finally underwent MX (BCT–MX). Provided data show that there were no differences between the groups in terms of ductal- versus lobular-type breast cancer (Table 1).

Surgical Outcome

Forty-five percent ($n = 21$) of patients with lobular carcinoma (88% of whom were endocrine responsive) primarily scheduled for MX ($n = 47$) were finally operated with BCT (i.e., the MX–BCT turnover rate). Regarding ductal-type breast cancer, the MX–BCT turnover rate was 52%. There was, however, an increase in R1 resection at primary attempt in lobular-type breast cancer, leading to an insignificant increase in secondary MX (Fig. 1).

Eight out of 17 CMF-treated patients primarily scheduled for MX (47%) underwent BCT, while this was true for 13 out of 30 patients following taxane-based therapy (43%). The corresponding numbers for ductal-type breast cancer were 43% (36 out of 83) and 58% (53 out of 91).

Uni- and multivariate analyses showed that none of the following factors demonstrated significant predictive value

TABLE 1 Demographic data

	Ductal ($n = 258$)		Lobular ($n = 67$)		χ^2
	n	%	*n*	%	
Age (years)					
<40	45	17	4	6	
>40	213	83	63	94	0.032
TNM					
cT1/2	150	58	34	51	
cT3/4	107	41	33	49	0.326
pT0/is/1/2	211	82	43	64	
pT3/4	47	18	24	36	0.003
N0	119	46	30	45	
N1	139	54	37	55	0.952
G1/2	122	47	47	70	
G3/x	135	52	18	27	<0.001
Tumor biology					
ER- and PgR-negative	121	47	8	12	
PrG/ER-any positive	137	53	59	88	<0.001
HER-2/neu-positive	9	3	3	4	
HER-2/neu-negative	247	96	57	85	0.868
Tumor response					
pCR(±is)	24	9	1	1	
pPR	181	70	44	66	
pNC	46	18	17	25	
pPD	7	3	5	7	0.027
Surgery					
Patients primarily scheduled for MX	$n = 171$		$n = 47$		
MX–BCT	89	52	21	45	
MX–MX	82	48	26	55	0.465
Patients primarily scheduled for BCT	$n = 84$		$n = 20$		
BCT–BCT	71	84	16	80	
BCT–MX	13	16	4	20	0.877 (Fisher)

pCR(±is) pathologic complete response in breast, with or without in situ cancer, *pPR* pathologic partial remission (included are pT0 with pN1), *pNC* pathologic no change, *pPD* pathologic progressive disease [using Response Evaluation Criteria in Solid Tumors (RECIST)]

for finally undergoing BCT: grading (G3 versus G1/2), tumor type (lobular versus ductal), menopausal status (premenopausal versus postmenopausal), endocrine responsiveness (estrogen/progesterone receptor-negative versus any positive), clinical response to nCT [clinical complete response (cCR) versus clinical partial response (cPR)/no change (NC)/progressive disease (PD)], and HER-2/neu status (HER-2/neu positive versus negative) (Table 2a). We further analyzed only lobular breast cancer patients and predictive factors for reaching BCT. In this regard, G3 was nearly predictive in uni- ($p = 0.0659$) but not multivariate analyses while clinical response was the only prediction for BCT in lobular breast cancer ($p = 0.0003$).

pCR

One out of 67 lobular breast cancers achieved pCR in our study. This patient presented with HER-2/neu overexpression and received trastuzumab antibody treatment. Univariate logistic regression showed that ductal tumors had 6.5 times (OR) higher chance for pCR, 4.4 times higher chance for pCR when estrogen receptor (ER)/progesterone receptor (PgR) was negative, and 3.6 times higher chance for pCR when HER-2/neu status was positive. Multiple logistic regression with all factors included again showed increased chances for pCR (±isN0) for ductal tumors and ER/PgR negativity, but also when BCT was rated possible before nCT (Table 2b).

No patient with lobular-type breast cancer and CMF treatment achieved pCR, while this was true for 2% of women administered a taxane-based regimen. The corresponding numbers for ductal-type breast cancer were 6 and 12%.

Oncologic Outcome

Median follow-up was 53 months. Lobular breast cancer patients finally undergoing BCT had similar 5-year local (97% versus 90%; Fig. 2), distant (92% versus 80%), and

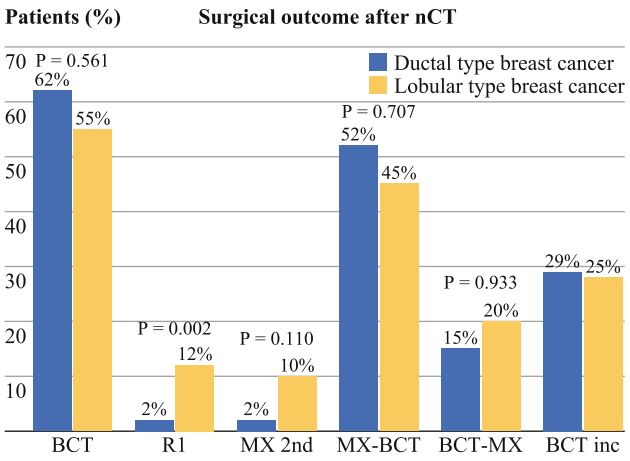

FIG. 1 Surgical outcome after nCT. *BCT* final breast-conservation rate, *R1* patients who had positive resection margin (tumor on ink) after the first operation, *MX 2nd* patients who had to undergo a second operation with mastectomy due to positive resection margin at the first operation, *MX–BCT* patients who were primarily scheduled for mastectomy but finally underwent breast conservation (true increase in BCT rate), *BCT–MX* patients who were primarily scheduled for breast conservation but finally underwent mastectomy, *BCT inc* the final percentage increase in breast-conservation rate (or patients who really profited from nCT) in the whole cohort after neoadjuvant therapy, taking into account the MX–BCT and the BCT–MX turnover rates no matter whether they were scheduled for MX or BCT

overall survival rates (97% versus 92%) as compared with ductal-type breast cancer patients. The 5-year local recurrence rate did not differ among lobular breast cancer patients when comparing MX with BCT (97% versus 97%), as shown in Fig. 2. Univariate and multivariate analyses demonstrated that there were no independent predictors for local recurrence-free survival in our patient cohort, as presented in Table 3.

DISCUSSION

Our retrospective analysis demonstrates that, among all lobular-type breast cancer patients randomized within three prospective neoadjuvant trials at a single cancer center (Medical University of Vienna), 70% were primarily scheduled for MX. However, after receiving three to six cycles of nCT, 45% of these women finally underwent BCT. This rate was similar in ductal-type breast cancer patients (52%). Ten percent of lobular-type breast cancer patients primarily undergoing BCT received secondary MX due to positive resection margin at the first attempt, as compared with 2% in ductal-type breast cancer patients, which was nonsignificantly higher. The BCT–MX turnover rate (patients who were primarily scheduled for BCT but finally received MX) was similar in the two groups (lobular, 20%; ductal, 15%). The 5-year local recurrence rate was insignificantly lower in lobular-type breast cancer as compared with ductal-type breast cancer after BCT (2.7% versus 10%). There was no difference in local recurrence within lobular-type breast cancer when comparing BCT with MX. In general, every second patient in either group (ductal and lobular type) showed a benefit from nCT due to an increase in BCT without comprising oncologic outcome.

Increase in BCT after nCT in Lobular Cancer

Boughey et al. evaluated BCT rates in lobular-type breast cancer patients with and without nCT.[11] The former group had mean tumor diameter of 4.9 cm and BCT rate of 17% after nCT, whereas patients without nCT had tumor diameter of 2.5 cm with BCT rate of 43%. After adjusting for initial tumor size, the authors found no difference in the rates of initial BCT, failure of and final BCT between the two groups. However, their analysis lacks data regarding the number of patients primarily scheduled for MX, such that the authors fail to show clearly that there may not be patients who could finally undergo BCT after primary MX scheduling. Size alone does not matter as far as decision-making in surgical strategy is concerned.[18] In our investigation, we clearly demonstrate that both ductal and lobular breast cancer patients experience an increase in BCT rate after being primarily scheduled for MX. Every second patient may be spared an ablative procedure, irrespective of the type of their cancer. We could not identify any certain subgroup of lobular type breast cancer showing improved response to nCT in a multivariate analyses including grading and receptor as well as her2neu status. We thus suggest that nCT may increase the BCT rate in lobular- as well as ductal-type breast cancer patients. Moreover, recent data from a Netherlands Cancer Institute cohort also demonstrated that every fifth patient with lobular breast cancer showed a benefit from nCT.[19]

Two older retrospective trials with small patient numbers showed that lobular-type breast cancer is an independent predictor of BCT ineligibility.[20,21] Our study showed no independent predictability of cancer subtype regarding BCT eligibility. This difference may be explained by the use of different chemotherapies.

Clearly, the divergence of such chemotherapies may be a certain bias in our analyses. However, after comparing between CMF and non-CMF (taxane-based) regimens, we were unable to find any significant differences regarding pCR or MX–BCT turnover rate. These subgroup analyses should, however, be interpreted with great caution due to the very small number of patients. Similarly, Cocquyt et al. investigated this issue in a very small number of lobular-type breast cancer patients ($n = 26$) and showed that CMF was not superior to CAF (cyclophosphamide, doxorubicin, fluorouracil).[22] However, this finding remains to be substantiated in larger prospective studies.

TABLE 2 Factors predicting (a) BCT and (b) pCR(±isN0)

	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
(a)				
Grading				
G3 vs. G1/G2	0.88 (0.52–1.49)	0.6335	1.00 (0.55–1.81)	0.9892
Tumor type				
Lobular vs. ductal	1.33 (0.69–2.54)	0.3915	1.32 (0.65–2.68)	0.4503
Menopausal status				
Pre- vs. postmenopausal	0.88 (0.51–1.51)	0.6405	0.92 (0.52–1.61)	0.7615
Endocrine tumor status				
ER/PgR negativity vs. any positivity	0.79 (0.46–1.344)	0.414	0.87 (0.48–1.61)	0.6628
Clinical response				
cPR/NC/PD vs. cCR	1.88 (0.75–4.67)	0.1758	2.45 (0.90–6.70)	0.0800
HER-neu/2 status				
HER-2/neu positivity vs. negativity	0.99 (0.47–2.09)	0.9779	1.23 (0.56–2.72)	0.6033
(b)				
Grading				
G3 vs. G1/G2	1.79 (0.76–4.42)	0.1832	0.98 (0.37–2.74)	0.9724
Tumor type				
Ductal vs. lobular	6.51 (1.33–117.58)	0.0156	>100 (1.32–∞)	0.0269
Menopausal status				
Pre- vs. postmenopausal	1.28 (0.56–2.90)	0.5615	0.89 (0.35–2.20)	0.7962
Endocrine tumor status				
ER/PR negativity vs. any positivity	4.39 (1.85–11.56)	0.0007	5.22 (1.82–17.73)	0.0017
Tumor–breast relation[a]				
BCT possible vs. mastectomy necessary	1.75 (0.75–3.99)	0.1912	2.67 (1.04–6.90)	0.0421
HER-2/neu status				
HER-2/neu positivity vs. negativity	3.55 (1.42–8.44)	0.0078	2.11 (0.77–5.45)	0.1421

There is no odd ratios estimate for tumor type, as approximating zero

BCT breast-conserving therapy, *pCR(±isN0)* pathologic response with or without in situ components in the breast with negative final lymph node status

[a] Confidence intervals (CI) based on profile likelihood. *p* values based on likelihood-ratio tests

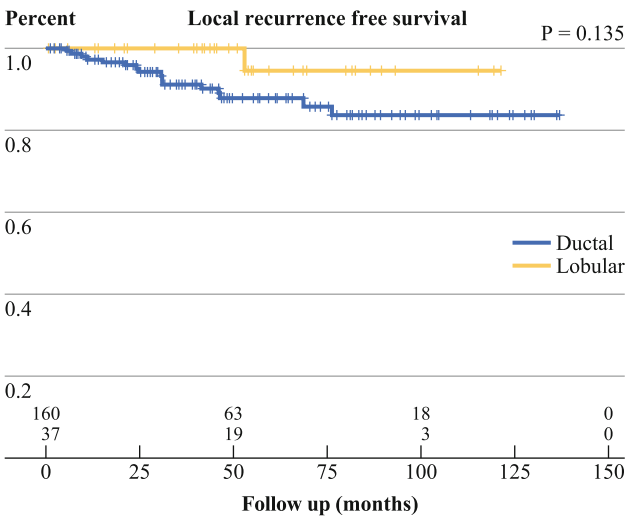

FIG. 2 Local recurrence-free survival over time, comparing lobular- with ductal-type breast cancer patients after neoadjuvant chemotherapy and breast-conservative treatment as well as radiotherapy

TABLE 3 Prognostic factors for local recurrence

	Univariate	Multivariate	HR (95% CI)
Tumor size			
T3/4 vs. others	0.524	0.306	1.93 (0.26–14.6)
Grading			
G3 vs. G1/G2	0.589	0.854	1.30 (0.50–3.37)
Lymph node status			
N1 vs. N0	0.883	0.955	0.93 (0.35–2.44)
Age			
>40 vs. ≤40 years	0.423	0.415	2.28 (0.30–17.2)
Endocrine receptor			
ER−/PgR− vs. any positive	0.085	0.245	2.34 (0.89–6.15)
HER-2/neu			
+++/FISH positive vs. +/++/neg	0.413	0.465	0.43 (0.06–3.25)
Tumor type			
Ductal vs. lobular	0.169	0.192	4.13 (0.55–31.1)

FISH fluorescence in situ hybridization

Increase in Re-resection after nCT in Lobular Cancer

Data have been published demonstrating that nCT may increase the re-resection rate in cases of positive resection margin due to a higher false-negative rate of frozen-section analyses.[15] This effect seems to be even higher in lobular-type breast cancer.[23] Wagner et al. analyzed 311 patients with lobular-type breast cancer. Eighteen percent positive resection margins (<1 mm) were seen in lobular-type breast cancer patients after BCT and nCT, while this was found in only 8% of patients without nCT (nonsignificant trend). Compared with other parameters, lobular-type breast cancer may be an independent predictor of positive margins after nCT.[10] Our data confirm the latter result. Out of 67 lobular breast cancer patients, 12% had positive resection margin (<1 mm or tumor at ink), while this was only seen in 2% of ductal-type cancer patients after the first surgical attempt. The number of additional MX after R1 resection was nonsignificantly higher in lobular-type breast cancer patients as compared with ductal type (10% versus 2%). The number of patients within our cohort is small. In this respect we suggest that there may be a chance of significant comparability with more patients. Straver et al. showed a secondary MX rate of 50% in lobular-type breast cancer.[19] In this respect, it is crucial to maintain a good pretherapeutic diagnostic setting. Our institution always applies MRI to finally rule out multicentricity before and after nCT, especially in lobular-type breast cancer. This may serve to reduce the rate of secondary MX.

pCR rate in Lobular Cancer

Several publications have clearly shown that lobular breast cancer has significantly lower pCR rates as compared with ductal-type cancer.[9,24] Our results are in line with these data. Only one lobular-type cancer patient (endocrine negative and HER-2/neu positive) had pCR. Lobular-type cancer was an independent predictor for not developing pCR. However, it is not necessary to have pCR in order to downsize the tumor in an attempt to convert MX into BCT. Thus, we believe that not reaching pCR is not an exclusion criteria for use of nCT in patients primarily scheduled for MX.

Oncologic Outcome after nCT in Lobular Cancer

Prospective trials have demonstrated that nCT has equal efficacy regarding overall and distant recurrence-free survival as compared with adjuvant therapy.[4,25] Patients with lobular-type breast cancer showed even better outcome after nCT in comparison with those with ductal-type breast cancer.[24,26] Our study showed that 5-year local recurrence rates were insignificantly lower in lobular- compared with ductal-type breast cancer (2.7% versus 10%) after BCT. Moreover, overall as well as distant recurrence-free survival did not differ between the two groups, suggesting a similar oncologic outcome in lobular- and ductal-type breast cancers. However, further prospective evaluation is warranted due to the small number of patients, short follow-up period, single-center evaluation, and retrospective analyses within our trial.

CONCLUSIONS

Lobular-type breast cancer responds poorly to nCT (yielding a reduced pCR rate, increased R1 resection rate, and increased secondary mastectomy rate as compared with ductal-type breast cancer). However, as long as nET is only accessible in clinical trials, nCT should not be completely excluded for lobular-type breast cancer patients primarily scheduled for mastectomy, as every second patient may finally undergo BCT without compromising the oncologic outcome.[27]

ACKNOWLEDGMENT The authors are grateful to Natalija Frank for her dedicated work on patients and building up the database, and to Karl Thomanek for language improvement.

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