Breast Cancer Research and Treatment (2024) 204:497–507
https://doi.org/10.1007/s10549-023-07192-8

CLINICAL TRIAL

Breast surgery after neoadjuvant chemotherapy in patients with lobular carcinoma: surgical and oncologic outcome

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Received: 11 July 2023 / Accepted: 19 November 2023 / Published online: 8 January 2024

Abstract

Introduction Breast cancer patients with invasive lobular carcinoma (ILC) have an increased risk of positive margins after surgery and often show little response to neoadjuvant chemotherapy (NAC). We aimed to investigate surgical outcomes in patients with ILC treated with NAC.

Methods In this retrospective cohort study, all breast cancer patients with ILC treated with NAC who underwent surgery at the Netherlands Cancer Institute from 2010 to 2019 were selected. Patients with mixed type ILC in pre-NAC biopsies were excluded if the lobular component was not confirmed in the surgical specimen. Main outcomes were tumor-positive margins and re-excision rate. Associations between baseline characteristics and tumor-positive margins were assessed, as were complications, locoregional recurrence rate (LRR), recurrence-free survival (RFS), and overall survival (OS).

Results We included 191 patients. After NAC, 107 (56%) patients had breast conserving surgery (BCS) and 84 (44%) patients underwent mastectomy. Tumor-positive margins were observed in 67 (35%) patients. Fifty five (51%) had BCS and 12 (14%) underwent mastectomy (p value < 0.001). Re-excision was performed in 35 (33%) patients with BCS and in 4 (5%) patients with mastectomy. Definitive surgery was mastectomy in 107 (56%) patients and BCS in 84 (44%) patients. Tumor-positive margins were associated with cT ≥ 3 status (OR 4.62, 95% CI 1.26–16.98, p value 0.021) in the BCS group. Five-year LRR (4.7%), RFS (81%), and OS (93%) were not affected by type of surgery after NAC.

Conclusion Although 33% of ILC breast cancer patients undergoing BCS after NAC required re-excision for positive resection margins, it is considered safe given that five-year RFS remained excellent and LRR and OS did not differ by extent of surgery.

Keywords Carcinoma · Lobular · Neoadjuvant systemic therapy · Breast conserving surgery · Mastectomy · Margins of excision · Recurrence · Overall survival

Abbreviations

ALND	Axillary lymph node dissection
BCS	Breast conserving surgery
BCT	Breast conserving therapy
CI	Confidence interval
DCIS	Ductal carcinoma in situ
HER2	Human Epidermal growth factor Receptor 2
HR	Hormone receptor
ILC	Invasive lobular carcinoma
LCIS	Lobular carcinoma in situ
LRR	Locoregional recurrence rate
MARI	Marked axillary lymph node
MRI	Magnetic resonance imaging
NKI-AVL	Netherlands Cancer Institute-Antoni van Leeuwenhoek
NAC	Neoadjuvant chemotherapy

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OR	Odds ratio
OS	Overall survival
pCR	Pathologic complete response
rCR	Radiologic complete response
RFS	Recurrence free survival
rPR	Radiologic partial response
TN	Triple negative

Introduction

The number of breast cancer patients receiving neoadjuvant chemotherapy (NAC) increased over the past two decades. One of the advantages of NAC is tumor downstaging, which enables breast conserving surgery (BCS) even in patients with initially large tumors [1]. BCS after NAC has proven to be safe, if resection margins are tumor free [2–5]. The extent of tumor downstaging is highly dependent on the breast cancer molecular subtype, with the highest pathologic complete response (pCR) rates for triple negative (TN, up to 60%) and Human Epidermal growth factor Receptor 2 positive (HER2+ , up to 89%) subtypes [6–8]. Invasive lobular carcinoma (ILC) accounts for 5–15% of breast tumor diagnoses worldwide and is the second most common histological type of breast cancer [9]. It shows mostly a diffuse growth pattern, and the majority of tumors are the HR+/HER2− subtype with a relatively low pCR rate (10%—15%) after NAC [10, 11].

Magnetic resonance imaging (MRI) is the most specific imaging tool to assess the efficacy of NAC and the extent of tumor downsizing [12]. Response monitoring with MRI seems especially accurate for HR-/HER2+ and TN breast cancer [13]. In case of a complete radiological response (rCR) on MRI, the pathology results after surgery correspond up to 69% (positive predictive value, PPV, 95% CI 0.61–0.77) in HR-/HER2+ subtype and up to 75% (PPV, 95% CI 0.67–0.81) in TN subtype [14, 15]. For the HR+/HER2− and HR+/HER2+ subtype, the positive predictive value of an rCR on MRI for a (near) pCR is relatively low: up to 37% (95% CI 0.28–0.47) and 47% (95% CI 0.38–0.56), respectively [14, 15]. Clinical and radiological detection and response monitoring are more challenging in patients with ILC, mostly due to its growth pattern which is caused the loss of E-cadherin. ILC is characterized by single cell or single-cell file infiltration through the stroma with only limited disruption of the normal tissue architecture resulting in an attenuated stromal response which is less visible on imaging [16]. Residual lobular tumor size after NAC is often underestimated by MRI, resulting in more frequent tumor-positive resection margins [17].

A second operation often has a negative effect on cosmetic surgical outcome, especially when a primary oncoplastic reconstruction needs to be dismantled to allow re-excision [18–21]. It delays administration of adjuvant treatment and, consequently, may negatively affect the oncological outcome.

In this study, we aimed to assess surgical outcome in patients with ILC treated with NAC by analyzing tumor-positive margins and associative factors, the re-excision and complication rate. The oncological outcome was evaluated by the local recurrence and survival rates.

Methods

Design/participants

In this single-center cohort study, all women with ILC of the breast treated with NAC and subsequent surgery at the Netherlands Cancer Institute-Antoni van Leeuwenhoek (NKI-AVL) from January 2010 to December 2019 were retrospectively reviewed for eligibility. We excluded patients with mixed type ILC when the lobular component was not confirmed in the surgical specimen, patients without a pre-NAC MRI, patients who received less than 4 cycles of NAC and patients with recurrent ipsilateral ILC. In general, NAC was administered when there was a confirmed need for chemotherapy at the time of diagnosis. Also, when adjuvant systemic treatment depends on the response of the neoadjuvant systemic therapy, if BCS was expected to be possible after NAC or when better cosmetic outcome was expected due to smaller tumor volumes. Reasons for administration of NAC include node-positive disease (cN+), larger tumor volumes (> 3 cm), HER2+, and TN disease and multifocal disease. Concisely, HER2+ tumors were treated with nine cycles of paclitaxel, carboplatin, trastuzumab, and pertuzumab (PTC-Ptz) or three cycles of 5-fluorouracil, epirubicin, cyclophosphamide, trastuzumab, and pertuzumab (FEC-T-Ptz), followed by six cycles PTC-Ptz [8]. Patients with cT1N0 HER2+ disease received twelve weekly cycles of paclitaxel and trastuzumab [22]. Patients with HR+/HER2− tumors were treated with four cycles of two weekly (dose-dense) doxorubicin and cyclophosphamide followed by 12 weekly administrations of paclitaxel. Patients with TN disease were additionally treated with carboplatin concurrent with paclitaxel. Tumors were marked prior to NAC and response to systemic treatment was evaluated by dynamic contrast-enhanced (CE) 3T MRI followed by a multidisciplinary meeting where the surgical plan was discussed based on clinical and imaging findings. The aim was to strive for BCS when technically possible with or without the use of oncoplastic techniques. Alternatively a mastectomy was performed with or without direct implant breast reconstruction (IBR). Removal of the pectoral fascia was standard when performing a mastectomy. Among other things, the ratio between breast volume and (residual) tumor size, patient

preference, and the presence of gene mutations were considered in this decision. Axillary surgery consisted of a sentinel node procedure or marked axillary lymph node (MARI) procedure, and/or axillary lymph node dissection (ALND) [23]. In general, sentinel node procedure was performed in clinically node-negative patients and stadium I clinically node-positive patients. Patients with stadium II/III and cN + ILC were re-staged with the MARI procedure. Additional ALND followed if deemed necessary.

Adjuvant radiotherapy was standard treatment after BCS and given when indicated after mastectomy. Adjuvant endocrine therapy was given to all HR+patients according to institutional guidelines. This study was approved by the institutional review board of the Netherlands Cancer Institute.

Outcomes

Baseline patient and tumor characteristics were described by type of surgery performed after NAC. All patients underwent CE-MRI before the start of NAC to assess tumor size and multifocality. Histological subtype, Bloom-Richardson grade, HR status, and HER2 expression were determined by pre-NAC 14-gage core needle histological biopsies. The diagnosis of ILC was made based on the characteristic cytologic features and growth patterns: a proliferation of usually small cells lacking cohesion, distributed either in single-file linear cords or individual cells invading the stroma. E-cadherin staining was performed to support the diagnosis (showing absence of abnormal staining). Lymph node status was determined with axillary and if indicated peri-clavicular ultrasound with fine needle aspiration (FNA) and/or biopsy in case of suspicious nodes. Post-NAC CE-MRI was used to assess the response to NAC and residual tumor size. Definition of rCR was a complete absence of pathologic contrast enhancement in the original tumor area. Near rCR is used by our radiologists in daily practice to describe an outstanding response but not yet complete. Patients mostly have two to four remaining cycles after response MRI, and this is, therefore, considered a favorable subgroup and described separately. A radiologic partial response (rPR) was defined according the RECIST 1.1 criteria as ≥ 30% decrease in tumor size [24].

The surgical specimens were analyzed by specialized breast pathologists. Main outcomes for the current study were the rate of tumor-positive resection margins and the percentage of patients requiring re-excision. Margins were considered tumor-positive when tumor cells (invasive or DCIS) were found in the surgical margin (ink on tumor). In addition, the rate of focally involved margins was reported, defined as tumor cells in the surgical margins over a distance of maximal 4 mm [25]. Pathologic complete response is defined as follows: the absence of invasive and in situ carcinoma in the surgical specimen, irrespective of nodal status (ypT0Nany). Pathology results and indication for re-excision of all patients were discussed in a multidisciplinary breast tumor meeting. Re-excision (BCS or mastectomy) was performed in case of more than focally (> 4 mm) involved margins [26], presence of DCIS at the margin or multifocality in patients with diagnostic BCS (in case of residual disease of the index tumor indicating that the other tumor deposits are persistent as well, additional surgery was performed).

Secondary outcomes were associations between baseline characteristics and tumor-positive margins in patients treated with BCS after NAC. Short-term postoperative complications in all patients were assessed, defined as a 'minor' (i.e., Clavien-Dindo grade I–II) or 'major' (i.e., Clavien-Dindo grade ≥ III) complication occurring within 30 days after surgery [27]. Furthermore, locoregional recurrence rates (LRR), recurrence-free survival (RFS), and overall survival (OS) were analyzed.

Statistical analysis

Groups for comparisons were defined by initial surgery type: BCS or mastectomy. Comparisons were made using the Chi-square test and Fisher's exact test for categorical variables and with the independent-samples *t*-test or Mann–Whitney *U* test for continuous variables, as deemed appropriate. To evaluate associations between baseline characteristic and tumor-positive margins, univariate and multivariate logistic regression models with backward elimination were used. Variables were included in the multivariate model if considered clinically significant and/or were associated with $p < 0.100$ at univariate analysis. Statistical significance for comparisons between groups was defined as $p < 0.05$. RFS and OS of the two treatment groups were estimated by the Kaplan–Meier method and compared with the log-rank test. All statistical analyses were performed in IBM SPSS Statistics, version 27.0.

Results

Baseline characteristics

A total of 244 breast cancer patients with ILC treated with NAC followed by surgery between 2010 and 2019 were reviewed for eligibility, 191 of whom were included in the analysis (Table 1). Median age was 52 years (IQR 47–61 mm). MRI imaging depicted multifocal disease in 46% of all patients ($n = 88$). Histology showed that the majority of patients had solely ILC ($n = 177$, 93%), grade 2 breast cancer ($n = 117$, 82%), and HR+/HER2− breast cancer ($n = 162$, 85%).

Table 1 Patient characteristics and treatment by initial surgery

	BCS ($n=107$, 56%)		Mastectomy ($n=84$, 44%)		Total ($n=191$)	
Age (years)	55	(48–63)	50	(46–57)	52	(47–61)
MRI pre-NAC						
Tumor size (mm)	37	(24–54)	52	(29–76)	40	(27–63)
Multifocal	43	(40%)	45	(54%)	88	(46%)
Histology						
ILC	97	(91%)	80	(95%)	177	(93%)
ILC and other type	10	(9%)	4	(5%)	14	(7%)
Tumor grade biopsy						
Grade 1	6	(7%)	6	(11%)	12	(8%)
Grade 2	71	(79%)	46	(87%)	117	(82%)
Grade 3	13	(14%)	1	(2%)	14	(10%)
Unknown	17	–	31	–	48	–
Clinical tumor stage						
cT1	19	(18%)	11	(13%)	30	(16%)
cT2	55	(53%)	29	(35%)	84	(45%)
cT3	27	(26%)	40	(48%)	67	(36%)
cT4	3	(3%)	4	(5%)	7	(4%)
Clinical N-stage						
cN0	45	(42%)	36	(43%)	81	(43%)
cN+	62	(58%)	48	(57%)	110	(57%)
Tumor subtype						
HR+/HER2 -	86	(80%)	76	(91%)	162	(85%)
HR+/HER2+	16	(15%)	6	(7%)	22	(11%)
HR—/HER2+	2	(2%)	0	(0%)	2	(1%)
Triple-negative	3	(3%)	2	(2%)	5	(3%)
LCIS	14	(13%)	12	(14%)	26	(14%)
MRI post-NAC						
Complete response	43	(40%)	20	(24%)	63	(33%)
Near complete response	16	(15%)	13	(16%)	29	(15%)
Partial response	42	(39%)	45	(54%)	87	(46%)
No response	3	(3%)	3	(4%)	6	(3%)
Unknown	3	(3%)	3	(4%)	3	(3%)
Tumor size (mm)	5	(0–18)	15	(0–35)	7	(0–24)
Axillary surgery						
Sentinel node	51	(48%)	39	(46%)	90	(47%)
Marked axillary lymph node*	30	(28%)	15	(18%)	45	(24%)
Axillary lymph node dissection	26	(24%)	30	(36%)	56	(29%)
Follow up time (years)	5	(3–7)	6	(3–8)	5	(3–7)

Numbers are in *n* (%) or median (IQR)

BCS, breast conserving surgery; MRI, magnetic resonance imaging; NAC, neoadjuvant chemotherapy; ILC, invasive lobular carcinoma; HR, hormone receptor; HER2, Human Epidermal growth factor Receptor 2.

*MARI procedure

BCS was primarily performed in 107 patients (56%) and 84 patients underwent a mastectomy (44%). In the BCS group, cT2 breast cancer was the most common ($n=55$, 53%) followed by cT3 ($n=27$, 26%). Almost half of the patients treated with mastectomy were diagnosed with cT3 breast cancer ($n=40$, 48%) followed by 35% with cT2 tumors ($n=29$). Lymph nodes were involved in 57% of patients ($n=110$).

Radiological and pathological response

Median tumor size prior to NAC as assessed by MRI was 37 mm (IQR 24–54 mm) in BCS patients and 52 mm (IQR 29–76) in patients treated with mastectomy. Post-NAC MRI showed a radiologic complete response (rCR) in 33% ($n=63$) of all patients, with 68% ($n=43$) initially treated with BCS and 32% ($n=20$) with mastectomy. A near rCR on MRI was observed in 15% of all patients ($n=29$) equally divided between both surgical groups. Almost half of all patients (46%, $n=87$) had an rPR on MRI of which 54% of patients were treated with mastectomy (with or without IBR).

Median tumor size before NAC was 37 mm (IQR 22–52 mm) in patients with an rCR and pathology showed a median residual tumor size of 20 mm (IQR 5–44 mm). Only nine patients (14%) with an rCR also had a pCR. Five of them were diagnosed with HER2+ breast cancer, three with HR+/HER2− and one with TN disease.

In patients with a near rCR, only four patients (14%) had a pCR, three had HER2+ disease, and one patient had HR+/HER2− breast cancer.

Median tumor size before NAC of the 87 patients with an rPR on MRI was 38 mm (IQR 28–55 mm) and post-NAC 24 mm (IQR 15–35 mm). Pathology showed a median residual tumor size of 25 mm (IQR 15–50 mm). Two patients (2%) with rPR had a pCR, both were HR+/HER2− breast tumors (Table 2).

Six patients with stable disease had a median tumor size before NAC of 36 mm. Pathologic median tumor size was 28 mm (IQR 18–47), and two patients had a pCR.

Surgical treatment and margin involvement

The majority (56%) of the included study patients underwent BCS post-NAC ($n=107$). Axillary surgery consisted of a sentinel node procedure in 47% ($n=90$) of patients, MARI procedure in 24% ($n=45$), and ALND in 29% ($n=56$) of the patients (Table 1).

Table 3 shows the surgical outcome in patients treated with initial BCS or mastectomy. The overall rate of tumor-positive margins (i.e., ink on tumor) in our cohort was 35% ($n=67$) and differed significantly between patients that underwent BCS and patients that underwent mastectomy (respectively $n=55$, 51% vs $n=12$, 14%, p value <0.001). Resection margins were more than focally involved in 37 of the 55 (67%) BCS patients with tumor-positive margins. Re-excision due to tumor-positive margins was performed in 35 patients that initially underwent BCS (33%). Of these, 29 patients had more than focally involved margins and 6 patients had focally involved margins.

Table 2 Correlation between radiological and pathological response

	Radiologic response									
	rCR ($n=63$)		near rCR ($n=29$)		rPR ($n=87$)		no response ($n=6$)		Unknown ($n=6$)	
Tumor size pre-NAC (cT in mm)	37	(22–52)	38	(27–69)	38	(28 -55)	36	-	40	–
Tumor size post-NAC (mm)	0	(0–0)	5	(5–5)	24	(15–35)	35	(20–60)		
Pathologic complete response	9	(14%)	4	(14%)	2	(2%)	2	(33%)	0	(0%)
Tumor size (ypT in mm)	20	(5–44)	22	(10–40)	25	(15–50)	28	(18–47)	70	(52–133)

Numbers are in n (%) or median (IQR)

rCR, radiologic complete response; rPR, radiologic partial response; NAC, neoadjuvant chemotherapy

Table 3 Surgical outcomes in patients treated with initial BCS or mastectomy

	BCS ($n=107$)		Mastectomy ($n=84$)		Total ($n=191$)	
Tumor-positive margins	55	(51%)	12	(14%)	67	(35%)
Focal	18	(17%)	5	(6%)	23	(12%)
> Focal	37	(35%)	7	(8%)	44	(23%)
Tumor-positive margins requiring re-excision	35	(33%)	4	(5%)	39	(20%)
Definitive surgery						
Breast conserving surgery	84	(79%)	–	–	84	(44%)
Mastectomy	23	(21%)	84	(100%)	107	(56%)
Tumor size (ypT in mm)[a]	20	(9–40)	37	(17–50)	25	(12–50)

Numbers are in n (%) or median (IQR)

BCS, breast conserving surgery

[a]Five missing values, three in the BSC group and two in the mastectomy group

BCS was preserved in 79% ($n=84$) of patients that initially underwent BCS, and in 21% ($n=23$), a mastectomy was deemed necessary.

In 84 patients (44%), mastectomy was the first surgical step post-NAC. A non-skin sparing mastectomy (NSSM) was performed in 36 patients (43%), 48 (57%) patients underwent a skin sparing mastectomy (SSM) in which in 21 patients the nipple was spared. Tumor-positive margins were seen in 14% ($n=12$) of whom seven with more than focal involvement. Of these 12 patients, eight were treated with SSM (of which six nipple sparing) and four with NSSM. Re-excision was performed in four (5%) patients. In four patients with more than focally involved margins, extensive resection had already been performed, and re-excision was not considered technically possible nor beneficial. These patients were treated with adjuvant local radiotherapy.

In total, 39 (20%) patients underwent re-excision due to tumor-positive margins. In 12 (31%) of these, BCS was sufficient, and in 27 (69%), a mastectomy was performed. In half ($n=6$) of the patients in which BCS was preserved, no residual disease was found after re-excision. When a mastectomy was performed, 21 (78%) patients had invasive residual disease. Margins after re-excision were tumor-negative in the majority (92%, $n=36$) of patients, and none had more than focal tumor-positive margins.

Short-term postoperative complications occurred in 24 (13%) patients (Supplementary Table 1). Re-excision due to tumor-positive margins was not significantly associated with a higher complication rate (p value 0.837).

Adjuvant radiotherapy

All of the patients in which BCS was preserved ($n=84$) received whole breast radiation and 53 (63%) patients also received regional radiation. Of patients who underwent mastectomy at final surgery, 85% ($n=91$) received chest wall radiation. Regional radiation was given in 56 (62%) of these patients.

Oncoplastic surgery

Oncoplastic BCS was performed in 22% ($n=24$) of which 15 patients underwent an immediate oncoplastic reduction and seven patients a direct autologous reconstruction. The most commonly used technique for autologous reconstruction was a reconstruction using a thoracodorsal flap and thoracoabdominal flap reconstruction was performed in one patient. The oncoplastic reconstruction had to be dismantled in six patients.

Of 84 patients that underwent a mastectomy, immediate IBR was performed in 46 patients and immediate autologous reconstruction in one patient. In six patients, IBR was performed in two stages, and five patients had secondary autologous reconstruction.

Almost a third ($n=26$, 31%) of the mastectomy patients withheld from reconstruction, reasons that have been reported are patients' preference or a recurrence had occurred before secondary reconstruction was performed.

Immediate IBR was performed in all four patients requiring re-excision after mastectomy. In only one patient, dismantling of the breast implant reconstruction was necessary.

Association baseline characteristics and tumor-positive margins

A cT ≥ 3 was associated with increased risk of tumor-positive margins (OR 4.62, 95% CI 1.26–16.98, p value <0.021) in patients who underwent BCS after NAC as shown by the multivariate analysis in Table 4.

Breast cancer recurrence and survival

Median follow-up was five years (IQR 3.2–7.2, range 0.1–11.5). In total, 38 (20%) patients developed one or more recurrences (local, regional, or distant). LRR was 4.7% ($n=9$) and was not significantly different between the surgical treatment groups (p value 0.977), 33 (17%) patients developed distant metastases (Table 5). RFS and OS per treatment group are shown in Fig. 1. RFS after five years was 81% and did not differ between the two surgical groups (p value 0.621). A total of 23 (12%) patients died, all due to breast cancer, resulting in a five-year OS of 93% in both groups (p value 0.308).

Discussion

In this study, we investigated the surgical outcome after NAC in patients with ILC, a challenging type of breast cancer because of its diffuse growth pattern, lack of response to NAC, and difficulty of response monitoring. As expected, a high percentage of patients required re-excision due to tumor-positive margins: 33% of patients after BCS and 5% after mastectomy. A cT ≥ 3 tumor and, thus, larger (>5cm) tumor diameter was a significant higher risk for tumor-positive resection margins. Taking the additional surgery into account, 84 (44%) out of the 191 included patients underwent BCS. The oncologic outcome was good with a five-year LRR (4.7%), RFS (81%), and OS (93%) and was not different after BCS or mastectomy.

In our study, the majority (56%) of patients had undergone BCS as first surgical step. A recent meta-analysis reported that BCS was performed in 33.3% of patients with ILC after neoadjuvant therapy. The higher number of patients with cT3-4 (52%) included in this study may have

Table 4 Associations between baseline characteristics and tumor-positive margins in patients who underwent BCS after NAC

	Events		Univariate			Multivariate		
	N	(%)	OR	95% C.I	*p* value	OR	95% C.I	*p* value
Age	55	(51%)	0.96	0.92–1.00	0.061	**0.95**	**0.90–0.99**	**0.028**
MRI pre-NAC								
Tumor size (mm)	55	(51%)	1.02	1.00–1.04	0.108			
Multifocal								
No	34	(32%)	Ref					
Yes	21	(20%)	0.84	0.39–1.83	0.664			
LCIS								
No	50	(47%)	Ref					
Yes	5	(5%)	0.48	0.15–1.53	0.215			
Tumor grade								
Grade 1	3	(3%)	Ref					
Grade 2	40	(37%)	1.29	0.24–6.84	0.764			
Grade 3	4	(4%)	0.44	0.06–3.24	0.424			
Clinical tumor stage								
cT1	6	(6%)	Ref			Ref		
cT2	28	(26%)	2.25	0.75–6.77	0.150	1.79	0.56–5.78	0.329
cT ≥ 3	20	(19%)	4.33	1.27–14.82	0.019	**4.62**	**1.26–16.98**	**0.021**
Clinical N stage (cN+)								
No	25	(23%)	Ref					
Yes	30	(28%)	0.75	0.35–1.62	0.464			
MRI post-NAC								
Complete response	19	(18%)	Ref					
Near complete response	5	(5%)	0.57	0.17–1.93	0.371			
Partial response	27	(25%)	2.27	0.95–5.44	0.065			
No response	1	(1%)	0.63	0.05–7.50	0.716			
Tumor size (mm)	55	(51%)	1.03	1.00–1.07	0.060	**1.04**	**1.00–1.07**	**0.035**
Oncoplastic surgery								
No oncoplastic surgery	42	(39%)	Ref					
Oncoplastic BCS (one stage)	12	(11%)	1.04	0.41–2.62	0.935			
Oncoplastic BCS (two stages)	1	(9%)	0.95	0.06–15.74	0.973			

OR, Odds Ratio; CI, confidence interval; MRI, magnetic resonance imaging; NST, neoadjuvant chemotherapy; LCIS, lobular carcinoma in situ. Oncoplastic BCS one-stage: breast conserving surgery with oncoplastic recontruction performed in the same procedure Oncoplastic BCS two-stage: breast conserving surgery with delayed oncoplastic reconstruction

Table 5 Location of recurrences by type of initial surgery and cT status ($n = 38$)

	Breast conserving surgery					Mastectomy					Total
	cT1	cT2	cT3	cT4	Unknown	cT1	cT2	cT3	cT4	Unknown	
Local	2	1	–	-	-	-	1	1	-	-	5
Regional	-	-	-	-	-	-	-	-	-	-	0
Distant	2	8	7	-	-	-	5	5	2	-	29
Local + regional	-	-	-	-	-	-	-	-	-	-	0
Local + distant	-	1	-	-	-	-	1	-	-	-	2
Regional + distant	-	-	-	-	1	-	1	-	-	-	2
Total	4	10	7		1	0	8	8		0	38

Oncoplastic BCS two-stage: breast conserving surgery with delayed oncoplastic reconstruction

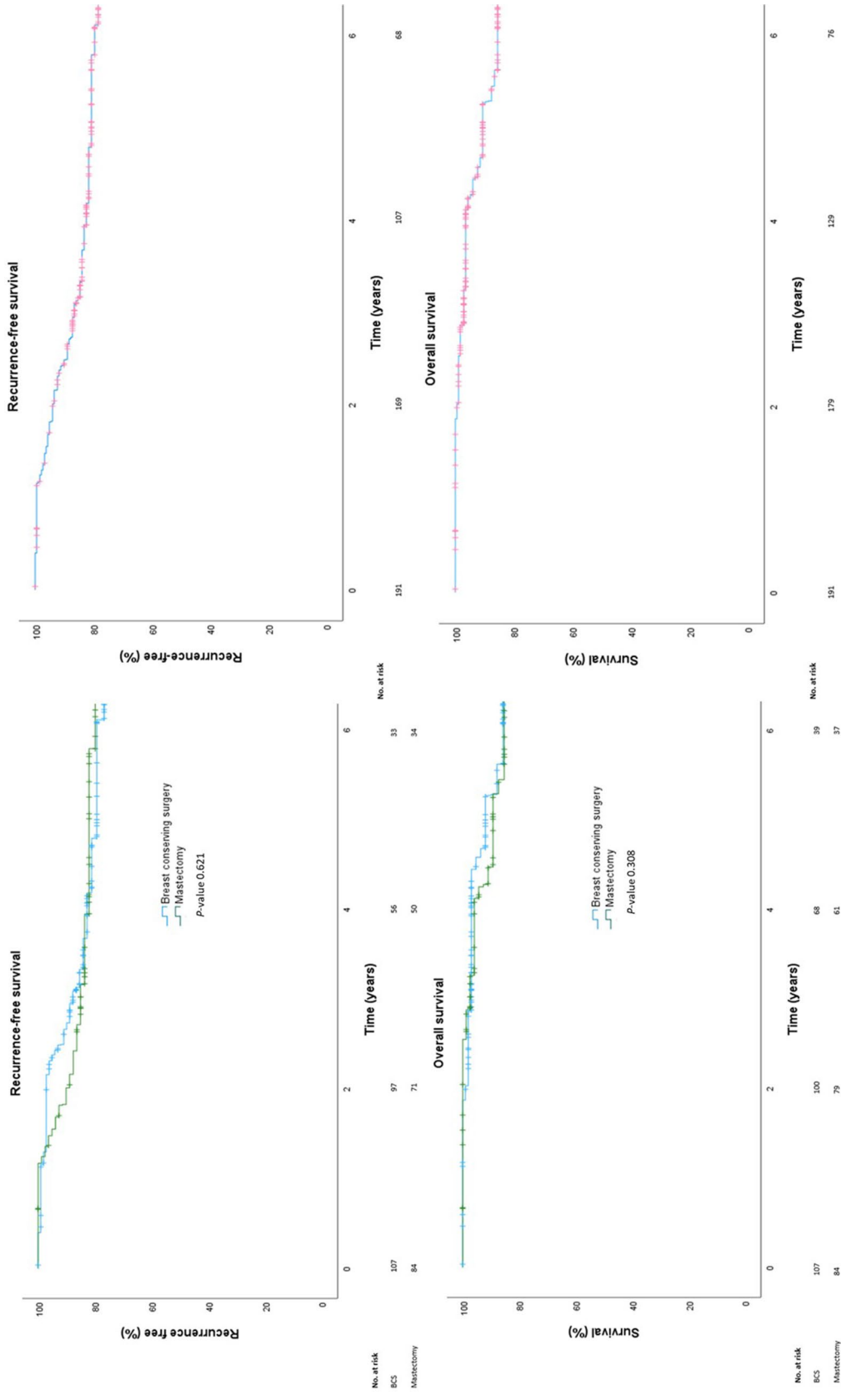

Fig. 1 Recurrence-free survival and overall survival

decreased the eligibility for BCS [10]. A relatively large number of patients underwent BCS in our cohort; however, the rate of tumor-positive margins and re-excision remained comparable with data in the literature [10, 28, 29][30, 31]. The large number of cT1-2 patients (60%) in a more contemporary cohort with more effective chemotherapy could be the reason for this higher percentage.

Another explanation for the relatively high number of patients undergoing BCS as the first surgical step post-NAC in our study may be that response was monitored by MRI. MRI is proven to be more accurate than conventional techniques [32, 33]. Based on our currently analyzed data, in case of a rPR, MRI reliably predicts the residual tumor size after NAC. However, in our study, pCR was found in only 14% of patients with rCR or near rCR, indicating underestimation of the actual residual tumor burden. This may be attributed to the predominance of HR+ILC in our cohort, which is associated with low positive predictive value of rCR on MRI for pCR, regardless of histological subtype. Patients with HER2+ subtype, where MRI is highly reliable (along with TN subtype), tended to achieve both rCR and pCR, which underlies that good correlation between radiological and pathological response is mainly determined by molecular subtype [13].

The definition of tumor-free surgical margin varies in literature; from clear tumor margins to involved tumor margins of > 2 mm [10]. The definition used in this study was no tumor cells (invasive or DCIS) found in the surgical margin (ink on tumor). Our percentage of tumor-positive margins ($n = 67$, 35%) was comparable with the literature [10].

The rate of tumor-positive margins requiring re-excision after BCS was 33% ($n = 35$) in our cohort. To our knowledge, there are only a few studies investigating margins and risk of re-excision in ILC after NAC and BCS, and most studies concern invasive breast cancer in which few patients with ILC are included. In a retrospective study by Straver et al., the type of surgery pre-NAC was compared with the actual performed surgery in 42 patients with ILC. Fourteen out of 35 patients with ILC converted from mastectomy to BCS after NAC, but in half of them, mastectomy had to be performed due to disappointing pathology results. In the seven patients who were feasible for BCS pre-NAC, no secondary surgery was indicated, resulting in an overall re-excision rate of 33% ($n = 7$) after BCS [28]. Three retrospective studies including ILC patients treated with NAC and BCS reported re-excision rates of 36% ($n = 20/55$) [29], 42% ($n = 32/77$) [31], and 44% ($n = 11/25$) [30]. However, in Dutch guidelines, re-excision is only required in more than focally involved margins and focally (4 mm) involved margins are, therefore, accepted [26]. This might explain the lower re-excision rate of our cohort.

Re-excisions as a result of tumor-positive margins may lead to complications such as surgical site infections and impaired cosmetic outcome delaying adjuvant treatment [18, 20, 21]. Especially in patients undergoing oncoplastic BCS, risk of complications following re-excision is increased and the oncoplastic reconstruction may have to be dismantled [19]. Although re-excision due to tumor-positive margins was not associated with a higher complication rate in our cohort (p value 0.837), dismantling of oncoplastic reconstructions should be avoided. For patients at significant risk of tumor-positive margins delayed oncoplastic reconstruction may be preferable. The aim of the first surgery is to strive for radical tumor excision, then closing the cavity without plastic surgery. The second surgery is already scheduled within a short period of time and by then possible re-excision based on the histology report is still feasible before plastic surgery (a so called two-step oncoplastic BCS). A retrospective study of 251 early breast cancer patients who received either immediate or delayed oncoplastic surgery indicated that secondary reconstruction allowed high breast conserving rates and facilitated re-excision without compromising complication rates [34].

Our analysis showed that clinical tumor stage ≥ 3 was significantly associated with tumor-positive margins after BCS. One previous study identified median tumor size > 1.5 cm on mammography and younger age as predictors for tumor-positive margins [31]. The limited association (OR 0.95, 95% CI 0.90–0.99, p value 0.028) between younger age and positive margins following BCS in our cohort may be attributed by efforts to preserve more breast tissue in younger women. Post-NAC tumor size on MRI appears to be unreliable, and the association with positive margins is, therefore, considered clinically less relevant.

Fodor et al. reported in 2011 that primary BCT is a safe alternative for mastectomy in patients with stage I or II ILC of the breast regarding local control, and that breast cancer specific survival did not differ between the two groups [35]. Our study provides five-year follow-up regarding recurrences and survival in ILC patients undergoing BCS or mastectomy after NAC, including cT ≥ 3. The five-year RFS (81%) did not significantly differ between BCS and mastectomy. More important, the majority of the detected recurrences were distant metastases and local recurrences were only detected in four patients with cT1-2 ILC after BCS and none in the cT ≥ 3 subgroup.

In conclusion: although we found that re-excision due to positive margins after BCS was required in 33% of ILC patients treated with NAC, five-year recurrence-free survival and overall survival were excellent and did not differ by type of surgery. Therefore, BCS after neoadjuvant chemotherapy is safe and may be considered in all ILC patients after shared decision making explaining the risk of tumor-positive margins and re-excision to the patient, especially in cT3 ILC.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-023-07192-8.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by AKEvanH and AAvanL. The first draft of the manuscript was written by AKEvanH and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability The data that support the findings of this study are available from the corresponding author, IVDP, upon reasonable request.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This study was approved by the institutional review board of the Netherlands Cancer Institute.

Consent to participate Informed consent was obtained from all individual participants by 'general hospital informed consent' from all individual participants included in the study.

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