The Egyptian Journal of Hospital Medicine (January 2019) Vol. 74 (5), Page 1186-1196

Breast-Conserving Surgery after Neoadjuvant Chemotherapy for Locally Advanced Breast Cancer: Single Institute Experience

Mohamed Esmat[1*] and Wael El-Sheshtawy[2]

Department of [1]General Surgery (Surgery Oncology Unit) and [2]Clinical Oncology

Faculty of Medicine, Al-Azhar University, Cairo, Egypt

***Corresponding author:** Mohamed Esmat, **E-Mail:** Prof.mohamed.esmat@gmail.com

Abstract

Background: from clinical and pathologic aspects, locally advanced breast cancer (LABC) can be considered a relatively heterogeneous group of tumors.

Objective: we aimed to evaluate local control after breast-conserving surgery in patients with locally advanced breast cancer who received neoadjuvant chemotherapy for down staging.

Patients and Methods: a retrospective study was performed to include patients with locally advanced breast cancer who underwent breast-conserving surgery after neoadjuvant chemotherapy (anthracylcine based regimen followed by taxans). The clinical, pathologic, and surgical factors that could contribute to locoregional recurrence were evaluated.

Results: after neoadjuvant chemotherapy, 49 patients underwent breast-conserving surgery. The average tumor diameter was 5.3 cm, and 87.8% of patients achieved a size of up to 3 cm. Furthermore, 85.7% were at clinical stage III, 75.5% had T3-T4 tumors, 81.6% had N1-N2 axilla, and 89.8% had invasive ductal carcinoma. A pathologic optimal response was achieved in 26.5% of the tumors, and all the samples had free margins. The 5-year overall survival rate was 81.6%, and the mean follow-up duration was 39.1 months. The rate of ipsilateral breast tumor recurrence was 10.2%, while the rate of locoregional recurrence was 16.3%. The regression analysis showed that multifocal morphology response was the only factor associated with ipsilateral breast tumor recurrence (p=0.04). The pathologic response evaluation criteria in solid tumors (RECIST) breast cutoff was the only factor associated with locoregional recurrence (p=0.01).

Conclusion: breast-conserving surgery is a safe and effective therapeutic option for selected locally advanced breast tumors after receiving neoadjuvant chemotherapy.

Keywords: Breast Neoplasms; Neoadjuvant Therapy; Drug Therapy Combination; Breast-Conserving Surgery; Recurrence; Disease-Free Survival.

Introduction

Breast cancer is the most prevalent cancer among women. Worldwide, 1.7 million new cases are estimated to occur each year and mortality rate is increasing in developing countries. This may be owed to the delay in the diagnosis until the disease is in an advanced stage [(1)]. During the past decade, advanced stage III and IV carcinomas represented 8.5% of all tumors in United States and 44.7% of all tumors in Brazil, making advanced breast carcinoma a public health problem in Brazil [(2)].

From clinical and pathologic aspects, locally advanced breast cancer (LABC) can be considered a relatively heterogeneous group of tumors. Despite neoadjuvant chemotherapy (NC) does not increase the survival rates, it is used to improve the outcome of tumor resection, increase the breast-conservative surgery (BCS) rates [(3,4)], and determine patients with better prognoses, those who showed a pathologic complete response (pCR) [(5)].

The conservative surgery rate after NC varies from 37% to 82% [(6, 7)]; however, only 1.7% to 28% of these patients are classified as LABC [(7, 8)]. The role of conservative surgery in the management of breast cancer is well known if the surgery is combined with radiotherapy [(5, 9)]. There is a limited number of studies of large cohorts of patients with LABC who underwent NC and conservative surgery [(10)]. The safety of

Received: 21/10/2018
Accepted: 10/11/2018

BCS may be assessed according to the rates of local and locoregional recurrence (LRR). The selection of patients for BCS relies on the tumor characteristics, chemotherapy type, pre- and post-chemotherapy clinical-radiologic correlation, the marking and resection of the tumor bed, the type of response to chemotherapy, excision margins, and the molecular sub-type [(11-14)]. Local recurrence and LRR are influenced by the tumor characteristics, the size of the initial or residual tumor, the rate of initial or residual lymph node metastatic disease, the type of response to NC, the duration of follow-up, the expression of markers measured by immunohistochemistry, and the molecular subtype [(11-15)]. However, studies of large cohorts are needed to assess the safety of BCS in patients with LABC subjected to the same chemotherapy regimen. Therefore, this study aims to evaluate the clinical, pathologic, and molecular factors associated with ipsilateral breast tumor recurrence (IBTR) and LRR after conservative surgery in patients submitted to NC.

Patients and Methods

We conducted this retrospective observational study to assess the local control among patients with non-metastatic LABC who managed with NC and BCS at our institute (Al Hussein and Bab-Elshaarya, Al-Azhar University Hospitals) between October 2010 and December 2015.

Ethical statements

This study was done under the declaration of Helsinki and the ethical approval was optained from the ethical committee of Faculty of Medicine, Al-Azhar University. All patients or their relatives were contacted to get their consent before using their data in the study.

Data collection

All medical charts of patients who received NC at the Clinical Oncology department, Al Hussein University Hospital and presented to the Surgical Oncology unit at Bab-Elshaarya University Hospital for surgical management were reviewed from the archive. Only patients who have LABC (clinical stage III disease at first presentation) were included in this study, i.e., tumors larger than 5 cm with positive Axilla, skin infiltration either localized or diffuse, or N2 disease.

All personal, diagnostic, treatment related and follow up data for the included patients (including details of locoregional recurrence if exist) were retrieved from their medical files and collected.

Statistical analysis

The data were standardized and analyzed using the SPSS 23.0 software for Windows (Armonk, New York, NY). The Kaplan-Meier method was used in the univariate analyses of the categorical variables related to locoregional DFS. The log-rank method was used to assess the difference between the curves. Variables independently associated with locoregional DFS were identified using the Cox model. We evaluated continuous variables without dichotomization. For Cox modeling, categorical interest variables and variables exhibiting $p < 0.10$ were evaluated in the univariate analysis. The significance level was identified when $p < 0.05$.

Results

Out of 136 patients who received NC, we included 49 patients with LABC who had undergone NC and BCS. Tumor size, TNM stage, pT-TNM, and pN-TNM were relatively low, while the incidence of triple-negative tumors was relatively high **(Table 1)**. The average age of patients who were subjected to BCS was 48.5 years old, and the mean duration of complaint was 8 months. Bilateral tumor was identified in 2% of patients. The mean diameter of the tumors was 5.3 cm (range: 2-8.5 cm). Clinical-radiologic staging was done for all patients, but two patients (4.2%) were identified as stage IIa (T2N0) after initial radiologic examination and were subsequently analyzed. In 59.2% of patients, staging was based on chest radiographs and abdominal ultrasound, while it was based on thoracic and abdominal computed tomography (CT) in the remaining patients. All patients underwent mammography with breast ultrasonography (75.5%) or ultrasonography and magnetic resonance imaging (24.5%). Skin lesions were preoperatively marked in 24.5% patients. The characteristics related to tumor staging and treatment is mentioned in Table 2.

Table (1): Main characteristics of the patients submitted to NC.

Variable	Category	Measurement
Number		49 (100%)
Tumor size	cm	5.23 ± DP 1.64
Age at diagnosis	years	48.48 ± DP 11.38
EC TNM	II	6(12.2%)
	III	43(87.8%)
EC-T TNM	T2	13(26.5%)
	T3	26(53.1%)
	T4	10(20.4%)
EC-N TNM	N0	8(16.3%)
	N1	28(57.1%)
	N2	11(22.4%)
	N3	2(4.1%)
Molecular Subtype*	Luminal/ Her-	22(44.9%)
	Luminal B/Her +	6(12.2%)
	Her 2+	6(12.2%)
	Triple negative	15(30.6%)
NC response	Non pCR	35(71.4%)
	pCR	14(28.6%)

*Cases with missing data. Abbreviations; neoadjuvant chemotherapy (NC), pathologic complete response (pCR)

Table (2): Univariate analysis of factors related to local and locoregional recurrence -free survival.

Category	Variable	N (%) (Total N= 49)	Local 60 months DFS	P-value	Locoregional 60 months DFS	P-value
Pre-operative						
EC TNM	II	6(12.2)	38.6	0.54	33.8	0.37
	III	43(87.8)	44.7		41.4	
ECT - TNM	T2	13(26.5)	39.6	0.53	33.4	0.23
	T3	26(53.1)	44.7		43.2	
	T4	10(20.4)	48.2		47.5	
ECN - TNM	N0	8(16.3)	50	0.71	50	0.40
	N1	28(57.1)	42.6		40.5	
	N2-3	13(26.5)	43.6		38.9	
Tumor marking	Absent	38(77.6)	43.0	0.68	40.0	0.37
	Present	11(22.4)	47.5		47.5	
Histologic type	CDI	45(91.8)	44.8	0.13	42.1	0.31
	CLI+ other	4(8.2)	35.0		35.0	
Nottinghan grade*	G1+2	28(57.1)	42.6	0.29	38.2	0.07
	G3	20(40.8)	45.6		45.6	
Necrosis*	Absent	30(61.2)	41.0	0.039	36.9	0.008
	Present	18(36.7)	48.6		48.6	
PeritumoralInfiltration*	Slight	28(57.1)	45.0	0.80	42.6	0.68
	Moderate/intense	20(40.8)	42.5		39.7	
Lymphaticembolization *	Absent	43(87.8)	43.3	0.29	41.1	0.75
	Present	5(10.2)	50.0		45.5	
ER	Negative	22(44.9)	43.5	0.50	41.4	0.90
	Positive	27(55.1)	44.5		41.7	
PR	Negative	26(53.1)	44.3	0.80	43.4	0.49
	Positive	23(46.9)	43.5		39.4	
Her2	Positive	11(22.4)	43.1	0.79	40.0	0.41
	Negative	38(77.6)	44.4		44.5	
Molecular Subtype	Luminal / Her -	22(44.9)	42.8	0.63	39.5	0.40
	Luminal B Her+	6(12.2)	45.9		45.9	
	Her2	6(12.2)	39.4		39.5	
	Triple negative	15(30.6)	46.6		44.9	
Postoperative						
Oncoplastic surgery	Absent	36(73.5)	42.5	0.50	39.9	0.52
	Present	13(26.5)	48.0		46.0	
RECIST-B	Complete response	15(30.6)	46.3	0.16	46.4	0.003
	Partial response	32(65.3)	43.5		40.3	
	Stable disease	2(4.1)	33.4		16.7	
Morphology MDA (11)	Solid mass	25(51.0)	45.0	0.04	41.4	0.03
	Multifocal disease	7(14.3)	38.7		34.8	
	Without disease	15(30.6)	46.0		46.1	
	Stable disease	2(4.1)	37.5		25.0	
pCR/ NSABP	Absent	36(73.5)	43.7	0.58	40.3	0.28
	Present	13(27.5)	45.2		45.2	

* One case missing data. Abbreviations; Disease free survival (DFS), Estrogen receptors (ER), Progesterone receptor (PR), Response Evaluation Criteria in Solid Tumors *(*RECIST*), pathologic complete response (pCR),* National Surgical Adjuvant Breast and Bowel Project (NSABP*).*

Surgery

On average, surgery was performed 43 days after the end of chemotherapy. The mean duration from the first visit to surgery was 8.3 months. All patients subjected to a quadrantectomy, and oncoplastic surgery was performed in 26.5% of patients. These surgeries distributed as; central quadrantectomy (8.2%), rotation flap (8.2%), periareolar (4.1%), inferior pedicle (4.1%), and superior pedicle (2.0%). Level III axillary lymph node dissection was done in 96.0% of patients, the sentinel lymph node was examined in 2.0% of patients, and no axillary approach was performed in 2.0% of patients.

The margins were tumor-free in all patients, and 81.6% of patients harbored tumors measuring average of 12.3 mm (range: 1-40 mm). Furthermore, 12.2% of patients had pCR, and the margins were not evaluated. In 4.1% of patients (2 patients), the margins were considered free, and the distance measurement was not assessed. The average weight of the surgical specimens was 233 g (range: 41.5-980 g). Moreover, the average number of dissected lymph nodes reported during pathologic evaluation was 18.5 (range: 4 -42); Table 3 shows the response to NC.

Table (3): Cox analysis of factors related to local and locoregional recurrence-free survival (Total number =49).

Variable	Category	OR	CI	p factor	p general
Local recurrence (IBTR)					
Necrosis	Present	1.00	Ref		0.07
	Absent	7.00	0.85-57.19	-	
Morphology MDA (11)	Without disease	1.00	Ref.		0.08
	Solid mass	1.28	0.23-6.98	0.78	
	Stable disease	4.60	0.42-50.79	0.21	
	Multifocal disease	5.97	1.09-32.70	0.04	
Locoregional recurrence (LRR)					
RECIST-B	Complete response	1.00	Ref.		0.01
	Partial response	2.85	0.63-12.85	0.17	
	Stable disease	16.93	2.37-120.84	0.005	
Necrosis	Present	1.00	Ref.		0.03
	Absent	9.33	1.23-71.03		
Morphology MDA (11)	Without disease	1.00	Ref.		0.06
	Solid mass	2.25	0.47-10.86	0.31	
	Multifocal disease	6.09	1.11-33.40	0.04	
	Stable disease	9.08	1.28-64.51	0.03	
Nottinghan grade	G1+2	1.00	Ref.		0.08
	G3	0.33	0.09-1.16		-

Abbreviation; Evaluation Criteria in Solid Tumors *(*RECIST*).*

Adjuvant treatment

Having the adjuvant therapy, 98% of patients received radiotherapy to the chest wall (5040 cGy) and a boost to the breast (1000 cGy) approximate to the incision. Radiotherapy to the supraclavicular fossa was done in 88.4% of patients. One patient did not receive radiotherapy because of rapid disease progression. Hormonal therapy was recommended to 58.3% of patients and consisted of tamoxifen alone, anastrozole alone, or a combination regimen in 36.2%, 4%, and 18.1% of patients, respectively. Adjuvant trastuzumab was prescribed to 2.0% of patients.

Follow-up

The average duration of follow-up was 39.1 months (range: 13.4-72.8 months), with the follow-up period decreasing to 33.8 months (range: 3.6-65.7 months) after surgery. Furthermore, 6.1% of patients (three patients) were considered as lost of follow-up, and two of these three patients exhibited DFS with a mean time of 29.4 months (range: 16.3-38.6).

By the end of the follow-up, 20.4% of the patients had died from breast cancer, 4.1% had died from other causes, 8.2% were living with

cancer, and 67.3% were alive and free of cancer. The main metastases sites were in the bones (16.3%), lungs (12.2%), liver (8.2%), and brain (4.1%). The overall survival (OS) rates at 18, 30, and 49 months were 87.7%, 81.2%, and 71.4%, respectively **(Figure 1).**

Recurrence

The average months after surgery for recurrence ranged from 1.1 to 40.8 months and was 13.4, 13.8 and 14.1 months in general, IBTR and LRR, respectively. At 18 months of follow up, 72.4% of the general recurrence, 83.3% of the IBTR and 76.5% of the LRR occurred. The overall DFS rates at 18, 30 and 49 months of follow up were 77.9%, 68.9% and 67.0%, respectively **(Figure 1).**

The rate of IBTR was 11.2%. IBTR was categorised as local recurrence associated with systemic disease (3.1%), breast recurrence alone (3.1%), local plus LRR (3.1%), and secondary breast invasion from sternal recurrence (2.0%). When assessing disease progression, some patients showed rapidly progressive disease with early local recurrence plus sternal recurrence extending to the breast (2.0%), LRR (2.0%), breast recurrence alone (3.1%), and multiple local recurrence plus LRR (4.1%). Excluding the instance of local sternal recurrence that infiltrated the breast, the primary rate of recurrence was 9.3%.

A univariate analysis of local DFS relative to the categorical variables **(Table 3)** revealed that the absence of necrosis (p=0.04) and the morphologic response to chemotherapy characterized by multifocal disease and stable disease were correlated with poorer survival (p=0.04). Neither age (risk ratio (RR) 1.01, confidence interval (CI) 0.99-1.03, p=0.33) nor initial tumor size (RR 1.06, CI 0.93-1.20, p=0.35) influenced IBTR DFS. The Cox univariate analysis showed that multifocal morphology was the only factor correlated with IBTR because it raised the IBTR 5.97 folds (p=0.04). Figure 1 illustrates the overall and morphology factor risk curves related to the hazard risk of local DFS.

The LRR rate was 14.2% and was distributed as; ipsilateral supraclavicular fossa (4.1%), local and systemic recurrence (4.1%), ipsilateral axilla (2.0%), breast recurrence alone (2.0%), and breast associated with sternal recurrence (2.0%).

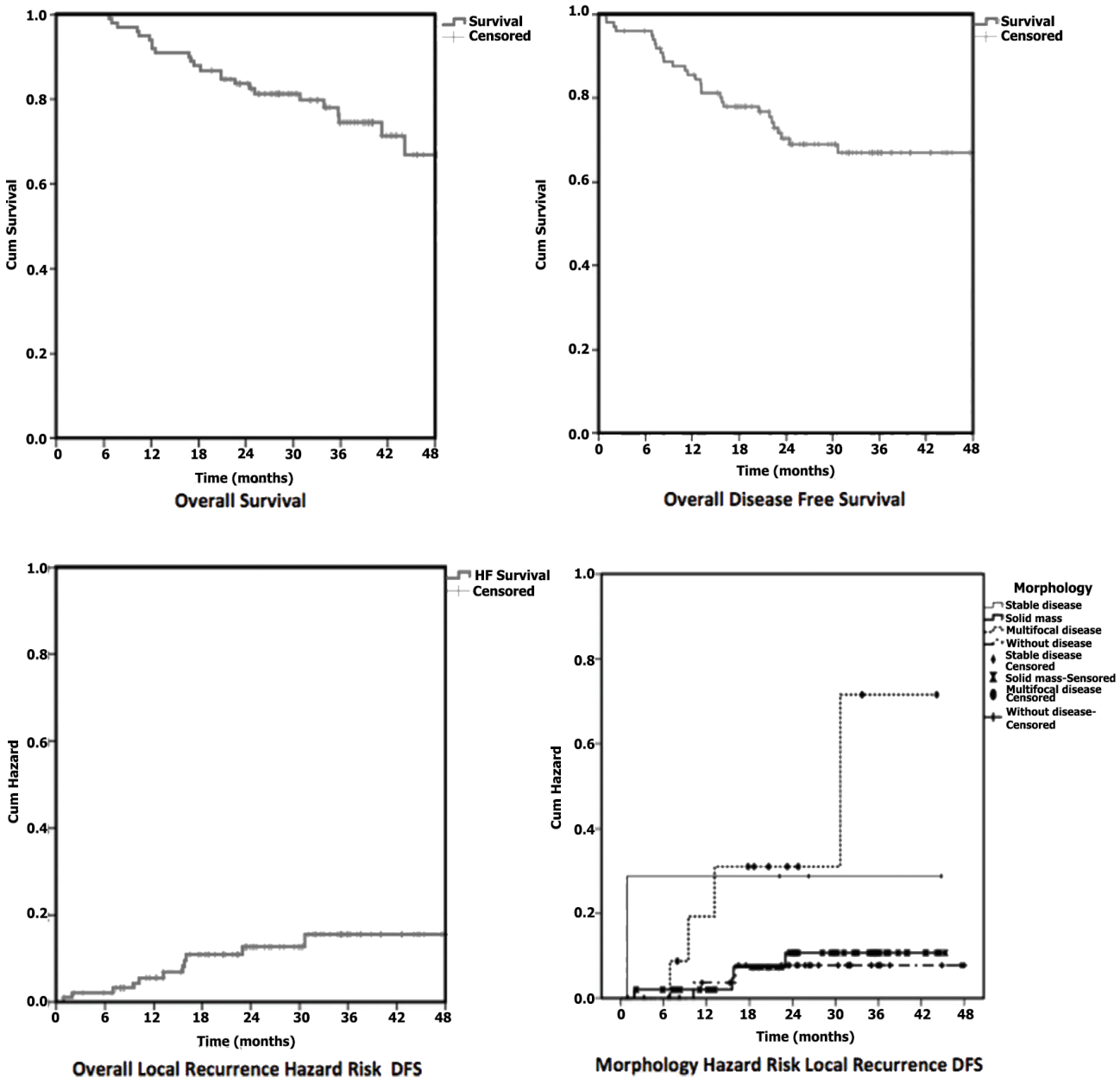
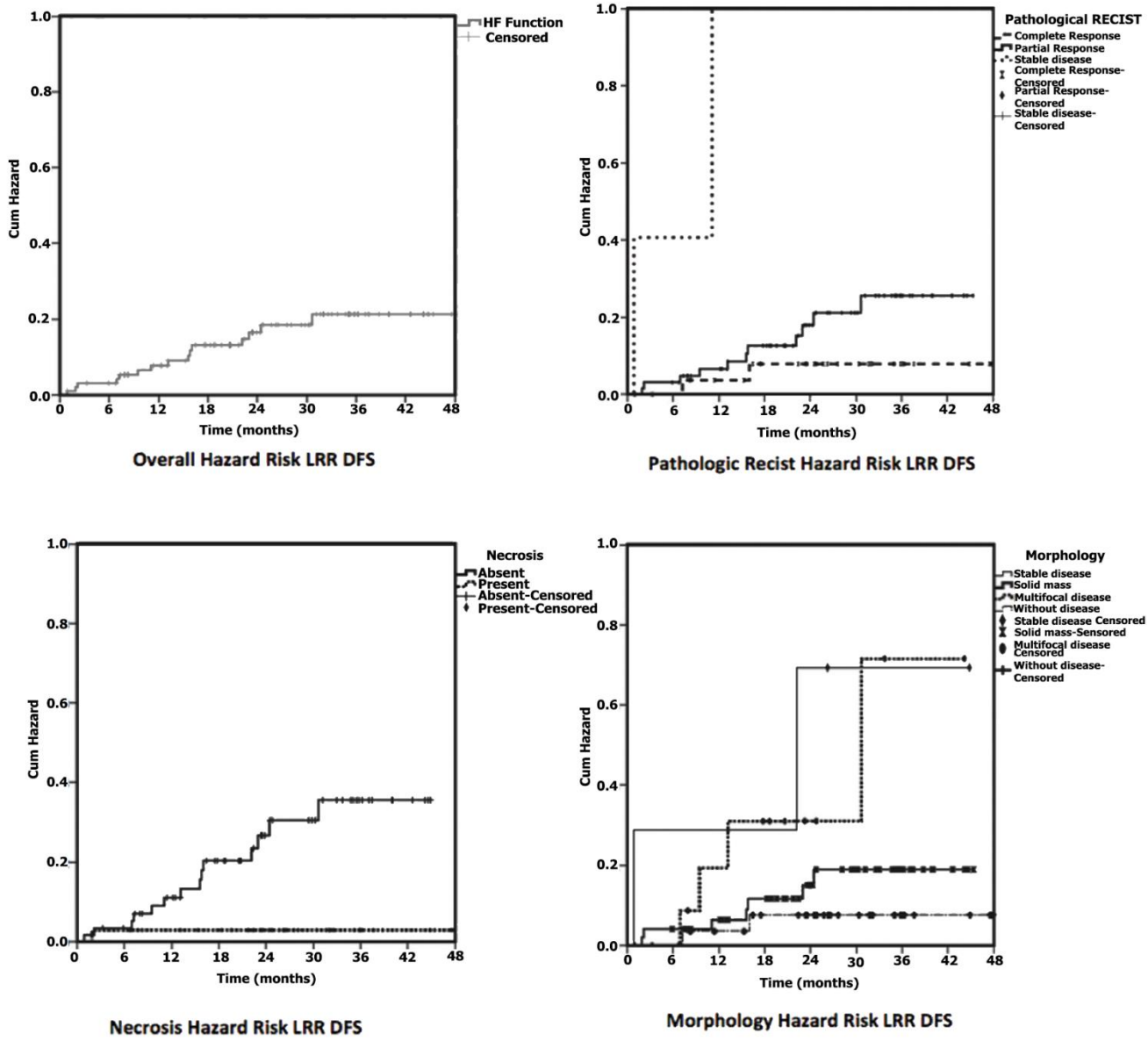


Figure 1. Overall survival of patients with NC and BCS (upper images) and hazard risk of local recurrence DFS (lower images).

A univariate analysis showed that the pathologic RECIST-B response (p=0.003), necrosis (p=0.008), and morphology were significantly associated with locoregional DFS. Neither age (RR 1.00, CI 0.98-1.03, p=0.41) nor initial tumor size (RR 1.08, CI 0.94-1.23, p=0.27) influenced LRR DFS. The Cox univariate analysis showed that the absence of tumor necrosis at diagnosis raised the LRR 9.33 folds (p=0.03), multifocal morphology raised the risk of LRR 6.09 folds (p=0.04), and stable disease raised the risk of LRR 9.08 folds (p=0.03). However, the RECIST-B pathologic response was the main factor related to locoregional DFS (p=0.01) because stable RECIST-B disease raised the risk of LRR 16.93 folds (p=0.005). The Cox multi-variate analysis model showed that RECIST-B pathologic response was the only factor associated with locoregional DFS. Figure 2



illustrate the curves related to the hazard risk of locoregional DFS.

Figure 2. Hazard risk curves of locoregional DFS

Discussion

NCT provides global survival like adjuvant chemotherapy, with the extra advantage of identifying patients with better prognoses, that is, patients who show pCR in addition to increasing the rates of BTC [16]. The primary indication for NC is larger tumors or tumors with higher rates of lymph node affection [17,18].

When comparing patients treated with NC and BCS with patients underwent mastectomy, the former has a lower T-TNM stage at diagnosis; higher rates of pCR; and higher rates of ER-negative, PR-negative, and triple-negative tumors, revealing bias in the analysis of this subgroups. This bias may affect the rates of recurrence and survival [19]. In our group of patients, patients who submitted to BCS exhibited better survival than the mastectomy group, which confirmed previous reports comparing mastectomy with BCS [9,19]. Selection bias likely occurred based on tumor size, breast-tumor relation, response to NC, and molecular subtype **(Table 1)** because BCS was done in patients with smaller tumors, lower clinical TNM stage, and a better response to NC. Because the characteristics changed between groups, we only evaluated patients who submitted to BCS.

Bleicher *et al.* [20] assessed Surveillance, Epidemiology, and End Results (SEER) data from a cohort of 5,685 patients with tumors <5 cm. Of these patients, 887 (15.6%) was submitted to BCS, and only 205 (3.6%) received NC. BCS group was associated

with a lower clinical stage and more NC, but only 101 patients subjected to both NC and BCS, and these patients were not evaluated separately. Our study represents one of the best institutional retrospective cohort studies of LABC treated with NC and BCS.

BCS is safe procedure provided that the excision margins are free of disease and this treatment is combined with adjuvant radiotherapy to the breast [21, 22]. Initially, BCS was used to treat tumors smaller than 3 cm associated with a 1-cm free margin. These criteria were changed, and smaller margins are currently accepted [23]. A meta-analysis of randomized controlled trials revealed that BCS is a safe treatment for patients with clinical stage I and II disease and tumors with diameter smaller than 5 cm [24]. SEER data evaluated for tumors 45 cm showed that breast cancer-specific survival did not differ between patients who underwent BCS and patients who received a mastectomy, but the women in this study were older, the IBTR and molecular subtype were not assessed, and few patients received NC [20].

The rate of conservative surgery after NC ranged from 37% to 82% [6, 7]; though, only 1.7%-28% of patients showed LABC [7, 8]. The LABC candidates who were initially selected were patients without skin or chest wall affection and who were free of multicentric disease or extensive microcalcifications. They harbored tumors smaller than 5 cm, showed favorable tumor localization, had no contraindications for radiotherapy, and had negative margins. Primary inflammatory carcinoma is not recommended for BCS [25]. Patients with N2-3 lymph nodes, residual multifocal components, residual tumors 42 cm, and the presence of lymphovascular embolization should be cautiously evaluated because of the higher risk of IBTR [11, 26]. Thus, the cutaneous infiltration criteria have become more flexible for localized cutaneous infiltration and the breast/tumor volume ratio, and the first indications for oncoplastic surgery have been expanded [17]. Although the average size of the initial tumors was 5.3 cm (range: 2-8.5 cm) in the present study, the margins were disease-free in 100% of cases, with a distance to the tumor of 12.3 mm. Moreover, oncoplastic techniques were used in 26.5% of patients, which augment the use of BCS in selected cases of LABC.

The preoperative planning was based on clinical-radiologic data and operative freezing. Two patients were excluded from the study because of positive surgical margins, which resulted in conversion to mastectomy.

Diagnostic imaging tests are essential to the therapeutic planning [3] and were done before and after the administration of NC in 100% and 87.7% of patients, respectively. Despite not shown numerically, a tendency toward the resection of the entire tumor bed before NC was observed in our study. Not all patients who exhibited a complete clinical response [21] reached pCR, and the anatomic-pathologic assessment was not always uniform. Therefore, the ‘‘Residual Cancer Burden’’ method affects the resection of the full area necessary prior to NC [27], but it is used in prospective studies. Pathologic sampling interferes with the pathologic results. In the present study, the average number of blocks per surgical specimen was 20, but a consensus for pathologic evaluation was obtained in 2015 [28].

On the assessment of patients subjected to BCS and radiotherapy, we should consider studies of patients who did not experience NC that ensure the long-term safety of BCS. **Veronesi** [9] assessed tumors smaller than 2 cm and identified a recurrence rate of 8% at 20 years, whereas Fisher reported recurrence rates at 20 years of 14.3% for patients who underwent lumpectomy and breast radiation and 39.2% for patients who did not receive radiation [21]. In patients subjected to NC and BCS, this rate was 14% at 5.8 years [29], 19% at 4.6 years [15], and 21.5% at 20 years [30]; though, the assessed tumors differed diagnostically and in their initial staging [19]. Thus, the possibility of new surgical margins remains open for discussion, but case-control studies assessing locally advanced tumors are lacking. National Surgical Adjuvant Breast and Bowel Project (NSABP B-27), that assessed patients with T1c-3N0 or T1-3N1M0 disease, was designed to investigate the addition of taxanes to anthracyclines and revealed an average tumor size of 4.4 cm and a 6% IBTR rate at 102 months; however, only 30% of patients exhibited lymph node involvement. In our study, the average tumor size was 5.3 cm, and 87.2% of tumors were larger than 3 cm; 88.9% of cases were diagnosed with stage III disease, 74.5% of cases harbored stage T3-4 disease, and 82.6% of cases had stage N1-3 disease. Although the IBTR rate is high, it is lower than the rate reported in a study by Fisher regarding patients subjected exclusively to lumpectomy without radiotherapy [21]. These findings show the effectiveness of BCS in patients with LABC subjected to NC and adjuvant radiotherapy.

In the evaluation of IBTR, we must discriminate true recurrence at the surgical site, ipsilateral second primary tumors, and ipsilateral thoracic wall tumors [31]. Despite ipsilateral thoracic wall events involving the sternal bone were defined as a distant event in 2014 [31], previous studies with long follow-up period did not distinguish this form of recurrence [32]. In our cohort, we observed two patients with simultaneous IBTR and

sternal infiltration, but one patient underwent local full-thickness chest wall resection. We opted to consider this patient as local recurrence to better compare our results to those of other studies with long follow-up periods. No pattern is correlated with the type of local recurrence, but many recurrences are defined as multiple recurrence. Alternatively, recurring tumors may be resulted as resistance to treatment and subsequent multiple recurrences. In our cohort, the LRR rate was 15.3% and consisted of all patients with local recurrence and the four patients with locoregional lymph node involve-ment. This finding corroborates the analysis of the DFS results.

The chi-squared test can be used to calculate recurrence, but we assessed DFS because recurrence depends on time. Better results were observed in patients who showed an early response to treatment [33] and were positive for hormonal receptors [12]; however, poorer outcomes were reported for patients with lymphovascularinvasion [11], residual tumors larger than 2 cm [11], no expression of hormonal receptors, multifocal disease after chemotherapy [11, 34], age p40 years old, excision margins p2 mm, stage III and N2-3 axillary nodal status [15], and S-phase fraction 44% [30].

Few studies have examined a sufficient number of patients to evaluate the rates of recurrence in patients subjected to NC and BTC [11, 33, 34]. In our study, the morphologic response, however valid, was not significantly associated with recurrence, while the RECIST-B response was shown to have prognostic value in a multivariate analysis. The response to NC can be classified into several categories [35]. Chen et al. suggested a morphologic classification of the response, revealing that the response correlates with the occurrence of IBTR [11]. In our study, morphologic assessment showed an association, although a non-significant one, between the existence of multifocal disease/stable disease and higher rates of IBTR and LRR. The RECIST-B pathologic response (p=0.02) was the only variable retained in the multivariate model related to LRR: the risk was 2.85 times higher in patients with a partial response (p=0.17) and 16.93 times higher in patients with stable disease (p=0005).

In the present study, the absence of necrosis in the pretreatment biopsy sample was the only histological factor that was correlated with IBTR and LRR. This finding is supported by other studies, which detected association between complete response and the presence of necrosis. The absence of necrosis was correlated with a 7.00-fold higher rate of IBTR, but this increase was not significant (p=0.07). It was also correlated with a 9.33-fold higher LRR rate (p=0.03) in univariate analysis. The only factor related do LRR in multivariate analysis was the RECIST-B response.

In the investigation of IBTR, other variables, such as the type of tumor fragmentation and the presence of surgical margins, should also be considered. Therefore, the IBTR rates were reported to be 12.7% and 20.3% in the existence and absence of tumor-free margins, respectively [30]. In our study, all patients showed tumor-free margins. In a previous report, the presence of multifocal disease raised the risk of IBTR 3.3-fold [12], which is supported by our study: multifocal disease raised the rate of IBTR 5.97-fold (p=0.04). Moreover, the molecular subtypes are associated with the rate of recurrence in an adjuvant and neoadjuvant setting. Specifically, the rates of recurrence were 0.8% for luminal tumors (ER/PR-positive and HER2-negative), 1.5% for luminal B tumors (ER/PR-positive and HER2-positive), 8.4% for HER2 tumors (ER/PR-negative and HER2 positive), and 7.1% for triple-negative tumors.

A possible limitation of our study is the nonrandomized and retrospective design in which cases were selected in a continuous manner, that is, based on the feasibility of BCS. Therefore, multiple elements affected the selection of patients, including age, breast-volume ratio, comorbidities, and response to NC. Another limitation is the absence of NC correlation with trastuzumab, which may affect the pCR, OS, and DFS. Because HER2 tumors represent 23.5% [29] of cases, we observed only three incidences of local recurrence/LRR in this group and a 0.487-fold reduction in the recurrence rate. The addition of trastuzumab would slightly decrease the overall rate of recurrence.

Conclusion

The present study supports the fact that in patients selected by clinical and radiologic findings with a satisfactory response to NC, BCS is feasible and safe for the management of locally advanced tumors, provided that the tumor is completely resected, surgical margins are clear, and patients receive complementary multimodal treatment. This finding was supported by the occurrence of acceptable rates of local recurrence and LRR.

References

1. **Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015):** Global cancer statistics, 2012. CA Cancer J Clin., 65(2):87-108.

2. **Vieira RA, Uemura G, Zucca-Matthes G, Costa AM, Micheli RA, Oliveira CZ (2015):** Evaluating Breast Cancer Health System Between Countries: The

Use of USA/SEER and Brazilian Women as a Cohort Sample. Breast J., 21(3):322-3.

3. **Caudle AS, Kuerer HM (2014):** Breast conservation therapy after neoadjuvant chemotherapy: optimization of a multimodality approach. J Surg Oncol., 110(1):32-6.

4. **Mauri D, Pavlidis N, Ioannidis JP (2005):** Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst., 97(3):188-94.

5. **Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG *et al.* (1997):** Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol., 15(7):2483-93.

6. **Van der Hage JA, Van de Velde CJ, Julien JP, Tubiana-Hulin M, Vander-velden C, Duchateau L (2001):** Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol., 19(22):4224-37.

7. **Scholl SM, Asselain B, Palangie T, Dorval T, Jouve M, Garcia Giralt E *et al.* (1991):** Neoadjuvant chemotherapy in operable breast cancer. Eur J Cancer., 27(12):1668-71.

8. **Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B (2001):** Preoperative che-motherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr., (30):96-102.

9. **Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A *et al.* (2002):** Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med., 347(16):1227-32.

10. **Gianni L, Baselga J, Eiermann W, Guillem Porta V, Semiglazov V, Lluch A *et al.* (2005):** Feasibility and tolerability of sequential doxorubicin/paclitaxel fol-lowed by cyclophosphamide, methotrexate, and fluorouracil and its effects on tumor response as preoperative therapy. Clin Cancer Res., 11(24 Pt 1):8715-21.

11. **Chen AM, Meric-Bernstam F, Hunt KK, Thames HD, Oswald MJ, Outlaw ED *et al.* (2004):** Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience. J Clin Oncol., 22(12):2303-12.

12. **Ishitobi M, Ohsumi S, Inaji H, Ohno S, Shigematsu H, Akiyama F *et al.* (2012):** Ipsilateral breast tumor recurrence (IBTR) in patients with operable breast cancer who undergo breast-conserving treatment after receiving neoad-juvant chemotherapy: risk factors of IBTR and validation of the MD Anderson Prognostic Index. Cancer, 118(18):4395-93.

13. **James T, McCahill L, Ratliff J, Ashikaga T, Single R, Sheehey-Jones J *et al.* (2009):** Quality assessment of neoadjuvant therapy use in breast conservation: barriers to implementation. Breast J., 15(5):524-6.

14. **Morrow M (2008):** Margins in breast-conserving therapy: have we lost sight of the big picture? Expert Rev Anticancer Ther., 8(8):1193-6.

16. **Min SY, Lee SJ, Shin KH, Park IH, Jung SY, Lee KS *et al.* (2011):** Locoregional recurrence of breast cancer in patients treated with breast conservation surgery and radiotherapy following neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys., 81(5):e697-705.

17. **Khokher S, Qureshi MU, Chaudhry NA (2012):** Comparison of WHO and RECIST criteria for evaluation of clinical response to chemotherapy in patients with advanced breast cancer. Asian Pac J Cancer Prev., 13(7):3213-8.

18. **ZuccaMatthes AG, Uemura G, Kerr L, Matthes AC, Michelli RA, Folgueira MA *et al.* (2012):** Feasibility of oncoplastic techniques in the surgical management of locally advanced breast cancer. Int J Surg., 10(9): 500-5.

19. **Hennequin C, Espie M, Misset JL, Maylin C (2004):** [Does primary chemotherapy really increase the rate of breast conserving treatments?]. Cancer Radio-ther., 8(1):48-53.

20. **Cho JH, Park JM, Park HS, Park S, Kim SI, Park BW (2013):** Oncologic safety of breast-conserving surgery compared to mastectomy in patients receiving neoadjuvant chemotherapy for locally advanced breast cancer. J Surg Oncol., 108(8):531-6.

21. **Bleicher RJ, Ruth K, Sigurdson ER, Daly JM, Boraas M, Anderson PR *et al.* (2016):** Breast conservation versus mastectomy for patients with T3 primary tumors (<5 cm): A review of 5685 medicare patients. Cancer, 122(1):42-9.

22. **Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER *et al.* (2002):** Twenty-year follow-up of a randomized trial comparing total mas-tectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med., 347(16):1233-41.

23. **Veronesi U, Saccozzi R, Del Vecchio M, Banfi A, Clemente C, De Lena M *et al.* (1981):** Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med., 305(1):6-11.

24. **Houssami N, Macaskill P, Marinovich ML, Morrow M (2014):** The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol., 21(3):717-30.

25. **Yang SH, Yang KH, Li YP, Zhang YC, He XD, Song AL *et al.* (2008):** Breast conservation therapy for stage I or stage II breast cancer: a meta-analysis of randomized controlled trials. Ann Oncol., 19(6):1039-44.

26. **Buchholz TA, Hunt KK, Whitman GJ, Sahin AA, Hortobagyi GN (2003):** Neoadjuvant chemotherapy for breast carcinoma: multidisciplinary con-siderations of benefits and risks. Cancer, 98(6):1150-60.

27. **Singletary SE, McNeese MD, Hortobagyi GN (1992):** Feasibility of breast-con-servation surgery after induction chemotherapy for locally advanced breast carcinoma. Cancer, 69(11):2849-52.

28. **Symmans WF, Peintinger F, Hatzis C, Rajan R, Kuerer H, Valero V *et al.* (2007):** Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol., 25(28):4414-22.

29. **Provenzano E, Bossuyt V, Viale G, Cameron D, Badve S, Denkert C *et al.* (2015):** Standardization of pathologic evaluation and reporting of post-neoadjuvant specimens in clinical trials of breast cancer: recommenda-tions from an international working group. Mod Pathol., 28(9):1185-201.

30. **Cance WG, Carey LA, Calvo BF, Sartor C, Sawyer L, Moore DT *et al.* (2002):** Long-term outcome of neoadjuvant therapy for locally advanced breast carcinoma: effective clinical downstaging allows breast preservation and predicts outstanding local control and survival. Ann Surg., 236(3): 295-302.

31. **Rouzier R, Extra JM, Carton M, Falcou MC, Vincent-Salomon A, Fourquet A *et al.* (2001):** Primary chemotherapy for operable breast cancer: incidence and prognostic significance of ipsilateral breast tumor recurrence after breast-conserving surgery. J Clin Oncol., 19(18):3828-35.

32. **Moossdorff M, van Roozendaal LM, Strobbe LJ, Aebi S, Cameron DA, Dixon JM *et al.* (2014):** Maastricht Delphi consensus on event definitions for classification of recurrence in breast cancer research. J Natl Cancer Inst., 106(12).

33. Cebrecos I, Cordoba O, Deu J, Xercavins J, Rubio IT (2010): Can we predict local recurrence in breast conserving surgery after neoadjuvant chemotherapy? Eur J Surg Oncol., 36(6):528-34.

34. **Ishitobi M, Komoike Y, Motomura K, Koyama H, Inaji H (2010):** Early response to neo-adjuvant chemotherapy in carcinoma of the breast predicts both successful breast-conserving surgery and decreased risk of ipsilateral breast tumor recurrence. Breast J., 16(1):9-13.

35. **Ishitobi M, Ohsumi S, Inaji H, Ohno S, Shigematsu H, Akiyama F *et al.* (2012):** Ipsilateral breast tumor recurrence (IBTR) in patients with operable breast cancer who undergo breast-conserving treatment after receiving neoad-juvant chemotherapy: Risk factors of IBTR and validation of the M. D. Anderson Prognostic Index. Cancer, 118(18):4385-93.