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Breast Conserving Surgery: Has the Standard of Care Enhanced Outcomes for Patients?

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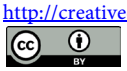

Abstract

Breast Conserving Surgery (BCS) is a rapidly emerging field increasingly adopted to facilitate breast conservation and preserve breast aesthetics. Since the publication of the Randomized Controlled Trials (RCTs) of Breast Conserving Surgery versus mastectomy in early breast cancer, the adoption of BCS for breast cancer patients' surgical management has been comprehensive. A computerized bibliographic search was performed on PubMed/MEDLINE, Embase, Google Scholar and Cochrane library databases. This article aims to perform a thorough review of new data regarding invasive cancer and margins while evaluating patient outcomes related to BCS after neoadjuvant chemotherapy focusing on margins, imaging evaluation, the extent of resection, and local regional recurrence outcomes. The growth pattern and biopsy of Ductal Carcinoma *In Situ* (DCIS) differ from invasive cancer, impacting margins. It is essential to understand how the Society of Surgical Oncology (SSO) DCIS margin guideline has influenced practice. Early breast cancer surgical management should be unique to each patient, driven by evidence-based medicine, and focused on specific clinical, histological, and molecular characteristics of the tumor. **Conclusion:** The current management for early breast cancer should be tailored and evidence-based to each patient based on the clinical, histological and molecular characteristics of the tumor. Presumably, the standard of care in BCS has enhanced the outcomes for this patient population. This review made by peers will help surgeons to stay up to date with the current literature and help them manage breast cancer while improving multiple clinical parameters such as Disease-Free Survival (DFS), Recurrence-Free Survival (RFS) and most importantly Overall Survival (OS).

Keywords

Breast Conserving Surgery (BCS), Disease-Free Survival (DFS), Recurrence-Free

Survival (RFS), Distant-Disease-Free Survival (DDFS), Overall Survival (OS), Ductal Carcinoma in Situ (DCIS), Neoadjuvant Chemotherapy (NAC)

1. Introduction

Mastectomy rates in the United States have been rising even though the only microscopic margin width in the Randomized Control Trials (RCTs) determining the safety of Breast Conserving Surgery (BCS) was "no ink on tumor". Re-excision rates to obtain wider negative margins are common among surgeons due to the false belief that a wider margin is better. An example of these RCTs was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B06 [1]. This has led to a collaboration between the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) to implement consensus guidelines on the appropriate margin width for invasive breast cancer [2].

The NSABP B06 trial was a RCT that was initiated in 1976 to determine whether lumpectomy with or without radiation therapy was as effective as total mastectomy for the treatment of invasive breast cancer [1]. A total of 1851 women were randomly assigned treatment consisting of total mastectomy, lumpectomy alone, or lumpectomy and breast irradiation. The cumulative incidence of tumor recurrence in the ipsilateral breast was 14.3% in women who underwent a lumpectomy and breast irradiation compared with 39.2% in women who underwent lumpectomy without irradiation ($P < 0.001$). No significant differences were observed among the three groups of women concerning Disease-Free Survival (DFS), Distant-Disease-Free Survival (DDFS), or Overall Survival (OS) [1]. This study validated that lumpectomy followed by breast irradiation was a satisfactory alternative to total mastectomy for the management of women with breast cancer, providing that the margins of the resected specimens are free of tumor ("no ink on tumor"), and a suitable cosmetic result can be obtained [1].

2. Discussion

A population-based study evaluating the outcomes of the initial BCS was reported by Morrow *et al.* [2], which included 800 patients who acknowledged that physicians are good at selecting who should undergo BCS versus mastectomy. In this study, 88% of the women who wanted BCS ended up with the procedure, but only 22% of the study participants had to have re-excision to obtain adequate margins, which meant that 34% of the women needed more than one surgery (this included the patients who had to be converted to mastectomy). The study evaluated the rates of re-excision based on stage (**Table 1**). Re-excision rates were highest among DCIS patients, which was not surprising because DCIS cannot be seen or palpated during surgery. Re-excision rates in stage 1 and 2 patients occurred in approximately a quarter of the patients [2].

During this same period, we saw rising rates of re-excision and mastectomies;

we identified a paradoxical improvement in breast cancer outcomes [2]. After BCS, local regional recurrences (LRR) were decreasing, and RCTs demonstrated the safety of treating subclinical disease in the axilla in a non-surgical approach [2] [3].

A study of over 86,598 women enrolled in phase 3 clinical trials by Bouganim *et al.* [4] showed that from 1985 to 2010 LRR, as a proportion of all recurrences, decreased from 30% to 15%, and this was true whether or not women were receiving chemotherapy or endocrine therapy. Physicians were also accepting the concept that microscopic disease could be left behind in the axillary lymph nodes. This was illustrated in the International Breast Cancer Study Group (IBCSG) 23-01 trial (micro-metastasis) and the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial (macro-metastasis) (**Table 2**) [3] [5] because they could depend on chemotherapy, endocrine therapy, and the edge of the radiation field to control this residual disease.

Patients with pathologically negative sentinel lymph nodes do not require completion Axillary Lymph Node Dissection (ALND); however, the management of patients with Isolated Tumor Cells (ITCs) and micro-metastatic disease in the sentinel lymph nodes has been extensively debated. The micro-metastatic disease is defined as tumor deposits spanning 0.2 mm to 2.0 mm within lymph nodes [6]. ITCs are groupings of cells not greater than 0.2 mm or 200 cells in a single lymph node cross-section [6]. According to the American Joint Committee on Cancer (AJCC) staging guidelines, patients with ITCs are N0(i+), whereas patients with micro-metastases in one to three axillary lymph nodes are N1mi [6].

The ACOSOG Z0010 trial is one of the leading trials to prospectively assess the importance of small metastases in sentinel lymph nodes. Hematoxylin and eosin (H&E) tumor-free sentinel nodes from patients with early breast cancer were evaluated in a central laboratory with immunohistochemistry (IHC) [7]. Micro-metastatic or ITC disease was found in 11% of the 3326 examined sentinel lymph nodes. With a median follow-up of 6.3 years, occult sentinel lymph

Table 1. Rates of re-excision by cancer stage [1].

No Additional Surgery	**62.1%**	
Re-excision:		
DCIS	30.7%	$p < 0.001$
Stage 1	23.7%	
Stage 2	24.0%	

Table 2. Non-surgical management of microscopic axillary nodal disease [2] [3].

	IBCST 23-01	**ACOSOG Z0011**
Positive Nodes after ALND	13%	27%
5-year Regional Recurrence	1%	0.9%
Disease Free Survival (DFS), Overall Survival (OS)	No change vs ALND	No change vs ALND

node metastases were not associated with differences in OS, DFS, or recurrence when compared with patients with IHC-negative lymph nodes [7].

A subset analysis of NSABP-B32 retrospectively examined patients with occult metastatic disease, including patients with micro-metastatic or ITCs [8]. Sixteen percent of sentinel node-negative patients had occult metastases detected on further evaluation. Eleven percent of occult metastases were ITC clusters, 4% were micro-metastases, and less than 1% of patients had macro-metastatic deposits seen on further sectioning of the lymph node. Log-rank tests showed that patients with occult metastasis had inferior OS (95% versus 96%), DSF (87% versus 89%), and DDFS (90% versus 93%) when compared with patients without occult metastases [8]. Even though these are statistically significant, these differences were not felt to be clinically relevant. There was no improvement in OS or DFS when patients with occult metastasis underwent completion ALND.

The IBCSG 23-01 trial randomized 934 patients with sentinel lymph nodes with micro-metastasis (2.0 mm or less in diameter) to ALND or no ALND [5]. Following a median follow-up of 60 months, there was no statistical difference in breast cancer–related events or DFS between the patients who underwent ALND (#464) and the patients who underwent sentinel lymph node biopsy (SLNB) alone (#467). The number of regional axillary events was low: one in 464 patients (less than 1%) in the ALND group and five in 467 patients (1%) in the no-ALND group. The 5-year OS was 84% for the group with ALND and 88% for the group without ALND, and the SLNB alone group was found to be non-inferior to ALND in this study [5].

These three studies prospectively collected data that indicate that ALND does not improve OS or DFS for patients with occult lymph node metastasis and is not recommended for these patients [5] [7] [8]. The College of American Pathologists (CAP) also advises against the routine use of IHC on sentinel lymph nodes [9].

It did not appear to make sense that if the same microscopic residual disease is located in the center of the radiation field in an intact breast, more surgery to obtain wider margins to achieve better local control would be appropriate. In 2014 the SSO and ASTRO conducted an evidence-based consensus by reviewing 33 studies (870 abstracts screened) with 28,162 patients (1506 local recurrences) and performed a metanalysis with whole breast radiation and a minimum of 4 years follow-up (mean/median) as eligibility criteria [10]. The crude local recurrence rate was very low at 5.3% (range: 2.3% to 7.6%), with the key finding was that the outcomes based on the different margin thresholds showed no evidence that a wider margin decreased local recurrences (**Table 3**).

The consensus statement published by the SSO and ASTRO mentioned that negative margins (no ink on tumor) optimize local control, wider margins do not significantly improve local control, and the routine/standard practice of obtaining wider margins than no ink on tumor is not indicated [11]. They also commented that wider margins might have suggested a small benefit in the past, but today's multidisciplinary systemic therapies obviate the need for wider

margins and that avoidance of routine re-excision benefits patients and decrease healthcare costs [11]. The essential point is that the consensus guidelines do not say re-excision to obtain wider margins is always inappropriate and recognizes that multiple factors beyond tumor burden influence local recurrence.

When performing clinical research, one important question to ask is if the guidelines have changed the clinical practice? Three studies performed before developing the SSO/ASTRO guidelines surveyed surgeons on what margins they use. As demonstrated in **Table 4**, no ink on tumor was not very popular, with fewer than 20% of physicians using these criteria [12] [13] [14].

Two studies evaluated the trends on margins after the SSO/ASTRO guideline was published in 2014 (**Table 5**) [15] [16]. The first study was a survey of members of the American Society of Breast Surgeons (ASBrS), which showed that 99% of them endorsed the margin guideline [15]. The second study was a population-based study using the Los Angeles and Georgia Surveillance, Epidemiology, and End Results (SEER) registries, where 69% of surgeons endorsed the margin guideline [16].

These studies showed us that surgeons were at least endorsing the new margin guideline but did this change the outcomes? A National Cancer Data Base (NCDB) study between 2004 and 2010 revealed that the rates of re-excision were stable, around 23% (62% re-excision, 38% mastectomy), with only a 2.9% change (**Table 6**) [17]. This exemplifies that during this time frame, no slow trend toward

Table 3. Local recurrence and threshold margin distance [4].

Threshold Distance (mm)	Odds Ratio (OR)	95% CI
1 mm Margin	1.0	
2 mm Margin	0.91	0.46 - 1.80
5 mm Margin	0.77	0.37 - 1.88
	p association 0.90 p trend 0.58	

Table 4. Studies showing surgeons pre-guideline margin preference [5] [6] [7].

Number of Surgeons, Year	Blair *et al.* N = 351, 2009	Parvez *et al.* N = 1447, 2009	Azu *et al.* N = 318, 2005 to 2007
% No Ink on Tumor	15%	18%	11%

Table 5. Studies showing surgeons post-guideline margin preference [8] [9].

Number of Surgeons, Year	De Snyder *et al.* N = 777, 2014	Morrow *et al.* N = 342, 2014 to 2015
% No Ink on Tumor	99%	69%

Table 6. Rates of Re-Excision Based on the NCDB [10].

	2004	2010
Rate of Re-Excision (%)	25.4%	22.5%

smaller margins was occurring.

In a study of 1205 women performed at the Memorial Sloan Kettering Cancer Center (MSKCC), the number of women that did not undergo re-excision increased from 79% to 85% within the first six-months of guideline acceptance (**Table 7**) [18], which was statistically significant (p = 0.017). This was not due to an increase in the mastectomy rate, which remained stable pre- and post-guideline adoption (0.4% vs. 0.9%).

Mamtani *et al.* showed that the rates of re-excision in invasive lobular carcinoma (ILC) after the implementation of the SSO/ASTRO margin guideline decreased from 31% to 23%, which was statistically significant (p = 0.01) [19]. Another study evaluating the trend of decrease margin re-excision was performed by Morrow *et al.* [16]. Using the Los Angeles and Georgia SEER registries, they evaluated women between 20 and 79 years of age diagnosed with stage I and II breast cancer between April 2013 and April 2015 (the period that expands the guideline dissemination). The results showed that the initial lumpectomy rate remained constant (68%) during the study period and that the overall lumpectomy rate continued to be stable at 63%, while the unilateral and bilateral mastectomy rates decreased [16]. This was due to a significant decrease in the re-excision rates and decreased conversion from BCS to mastectomy rates (**Table 8**) [16].

The net effect of the implementation of the SSO/ASTRO margin guidelines was that women who started by being candidates for BCS increased their likelihood of ending up with BCS (52% vs. 65%) and a substantial decrease in unilateral and bilateral mastectomy (**Table 9**) [16].

Multiple studies have been published that looked at the changes in the re-excision rates pre and post SSO/ASTRO margin guideline implementation [11]. The vast majority of these studies show a statistically substantial decline in re-excision use [20] (**Table 10**). One of the publications that did not reveal a statistically

Table 7. Impact of margin guidelines on re-excision at the MSKCC [11].

Number of Re-Excisions	Pre-Guideline N = 504	Post-Guideline N = 701	p-Value
0	78.6%	84.9%	0.017
1	19.2%	14%	
2	2.0%	0.9%	
≥3	0.2%	0.3%	
Mastectomy after BCS	0.4%	0.9%	0.480

Table 8. Summary results of the study period [9].

	April 2013	April 2015
Re-Excision Rates	21%	14%
Conversion to Mastectomy Rates	13% p < 0.001	4%

significant decrease in the re-excision rates was published by Heelan *et al.* [21], which did not have very high re-excision rates before the release of the guidelines suggesting that they might have been using the guideline before its implementation.

A recent metanalysis that evaluated seven studies with 16,282 patients pre-guidelines and 15,900 patients post-guidelines identified a reduction in the re-excision rates from 22% to 14%, with and odds ratio (OR) of 0.65 (0.54 to 0.78), which was statistically significant ($p < 0.0001$) [20].

In summary, the SSO/ASTRO margin guidelines resulted in a relatively quick change in surgeon's attitudes, which translated into an eight percent decrease in the re-excision rates in the early post-guideline period, which led to the decline in the mastectomy rates. This number might continue to decrease with further follow-up as more surgeons continue to adopt the guideline.

BCS after Neoadjuvant Chemotherapy

Neoadjuvant Chemotherapy (NAC) has usually been administered in cases of inoperable or locally advanced breast cancer to downsize the primary tumor and nodal disease to facilitate local-regional therapy with surgery and/or radiation [26]. Given this approach's success in locally advanced disease, combined with adjuvant systemic therapy's known benefits, neoadjuvant chemotherapy has also been assessed to manage patients with operable breast cancer.

A well-recognized role of neoadjuvant chemotherapy is the ability to improve surgical options for patients by downsizing tumors and increasing the chances for breast conservation [27] [28] [29] [30] [31]. In the landmark National Surgical

Table 9. Final surgical treatment [9].

	April 2013	April 2015
Breast Conserving Surgery	52%	65%
Unilateral Mastectomy	27%	18%
Bilateral Mastectomy	21% p = 0.002	16%

Table 10. Studies of re-excision rates pre- and post SSO/ASTRO guideline publication [12].

Author		#Patients	Re-excision Rate Pre	Re-excision Rate Post	Delta	p-value
Schulman [13]	ASBS Mastery	26, 102	20.2%	16.5%	3.7%	<0.005
Morrow [9]	SEER	1976	27.3%	18.2%	9.1%	<0.001
Rosenberger [11]	MSKCC	1205	21.4%	15.1%	6.3%	0.006
Patten [14]	Carolinas	954	20.4%	16.3%	4.1%	0.1
Heelan [15]	U Col	863	11.9%	10.9%	1%	0.65
Chung [16]	Cedars Sinai	845	19.3%	12.9%	6.4%	0.03
Bhutiani [17]	Louisville	237	36.5%	9.0%	27.5%	<0.001

Adjuvant Breast and Bowel Project (NSABP) B-18 trial [28], 1523 patients with primary operable breast cancer were randomized to either preoperative or post-operative systemic therapy with four cycles of standard doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2) (AC) given every three weeks. In this trial, preoperative therapy's administration increased the proportion of patients who received breast conservation surgery by 12% (the breast conservation therapy rate increased from 60% to 68%) [28]. This result has been confirmed in other studies, suggesting that neoadjuvant chemotherapy can enable the downsizing of tumors and reduce mastectomy rates in favor of breast conservation therapy. Critical to this approach's success and widespread adoption demonstrated comparable distant disease control with neoadjuvant chemotherapy versus adjuvant chemotherapy. In the NSABP B-18 trial, at a mean of 9.5 years of follow-up, no significant differences were seen in disease-free and overall survival rates between the two randomized groups (69% vs 70%, P = 0.80; 55% vs 53%, P = 0.50, respectively) [28] [31]. Similar results have been observed in other randomized studies, and a recent pooled meta-analysis demonstrated that both approaches provide equivalent survival outcomes for patients [32]. Consequently, neoadjuvant chemotherapy is a safe alternative to adjuvant therapy, especially in patients in whom breast conservation therapy is desired.

Data from multiple studies have shown that when the same regimens are utilized, no survival advantage has been identified between neoadjuvant and adjuvant chemotherapy [27] [28] [29] [30] [31]. The two landmark trials that established that there is no survival advantage between neoadjuvant and adjuvant chemotherapy were the NSABP B-18 (roughly 1500 patients treated with adriamycin and cyclophosphamide, 16 years follow-up) [28], and the NSABP B-27 (approximately 2300 patients treated with adriamycin, cyclophosphamide, and taxanes, 8.5 years follow-up) [33].

Evolving evidence is demonstrating that the degree of pathologic response correlates with both disease-free survival (DFS) and overall survival (OS) outcomes [34]. These are breast cancer subtype dependent with the more aggressive subtypes, like triple-negative breast cancers (TNBC) and HER2 positive breast cancers, having much higher pathologic response rates than hormone receptor-positive cancers [34]. TNBC have a pathologic complete response (pCR) rate of 34%, HER2 positive hormone receptor-negative cancers have a pCR rate of 50%, HER2 positive hormone receptor-positive cancers have a pCR rate of 30%, and hormone receptor-positive cancers have a pCR rate of 7% to 16% [34]. This data will help refine adjuvant therapy options in patients with TNBC and HER2 positive breast cancers.

An advantage of neoadjuvant chemotherapy is that it allows for down-staging of the disease, making breast conservation surgery (BCS) a possible option in patients with large tumors, and it reduces the need for axillary node dissection (**Table 11**). In these trials, tumor shrinkage was seen in 79% of patients, 36% had a clinical complete response rate (cCR), and 43% had a clinical partial response

rate (cPR). The NSABP B-18 identified that the patients with the most extensive tumors (5 cm or greater) had the best benefit of neoadjuvant therapy in terms of BCS [28] (**Table 12**). Multiple studies have shown that BCS after neoadjuvant chemotherapy is safe and did not result in higher local or regional recurrence [27] [28] [29] [30] [31]. The long-term results of NSABP B-18 and B-27 showed no difference in local and regional recurrence after neoadjuvant chemotherapy by surgery type (**Table 13**) [35]. More recent data from MD Anderson Cancer Center, in a series of 751 patients (between 2005 to 2012) in which all participants received appropriate preoperative taxane-based chemotherapy and appropriate HER2 targeted therapy [36]. All women undergoing BCT had excellent outcomes across all molecular subtypes with 5-year local and regional recurrence-free survival between 93% and 97% (**Table 14**). The highest pCR rate (72.4%) was seen in patients whose tumors were hormone receptor-negative/HER2 positive, and the lowest pCR (16.5%) was seen in patients whose tumors were hormone receptor-positive/HER2 negative. One important point to note from the study is that not achieving a pCR in the hormone receptor-positive/HER2 negative patients was not associated with an inferior outcome; however, in the high-risk hormone receptor-negative subtypes, not achieving a pCR does result in higher rates of local and regional failure (**Table 14**), something that would've occurred if patients would have undergone mastectomy instead of BCS.

A study from the National Cancer Data Base (NCDB) from 2006 to 2011 of 354,202 patients with stage I to stage III breast cancer (47.8% of the study population

Table 11. Neoadjuvant therapy and breast conserving surgery (BCS) [18].

Trial	% BCS Neoadjuvant Therapy	% BCS Surgery First
Royal Marsden [19]	89%	78%
Institut Curie [20]	82%	77%
NSABP B-18 [21]	67%	60%
EORTC [22]	37%	21%

Table 12. NSABP B-18 breast conserving surgery (BCS) in Neoadjuvant therapy.

Tumor Size	Planned Lumpectomy	Lumpectomy Performed
All Patients	65%	67%
Equal or Less than 2 cm	89%	81%
2.1 cm to 5 cm	68%	71%
Equal or Greater than 5 cm	3%	22%

Table 13. Combined analysis of the NSAB B-18/27 [23].

Surgery	10-Year Incidence of Local or Regional Recurrence	Local	Regional
Mastectomy	12.3%	8.9%	3.4%
Breast Conservation Surgery	10.3%	8.1%	2.2%

underwent BCS) shows that the use of neoadjuvant chemotherapy in patients undergoing BCS is gradually increasing, from approximately 14% in 2006 to about 20% in 2011 [37]. The use of neoadjuvant chemotherapy requires a multidisciplinary approach.

The barriers to increasing BCS rates after NAC are that patients nowadays are more likely to choose mastectomy over BCS and that some patients are not good candidates for BCS regardless of their treatment (extensive DCIS that require excision of residual calcifications or MRI enhancement). Once we rule out contraindications for downstaging chemotherapy to make patients eligible for BCS, patients should be selected, taking into account tumor size, nodal status, ER, PR, HER2, histology (ductal vs. lobular), tumor grade, and genomic assays [38]. As surgeons, we need to evaluate the benefit of administering adjuvant chemotherapy up-front. If a patient is not a candidate for adjuvant chemotherapy, there is no benefit for the surgeon to propose neoadjuvant chemotherapy [38] [39] [40].

Over 6072 consecutive patients were treated at MSKCC for ten years. Among the HER2 positive breast cancer patients, 50% were likely to have positive lymph nodes, and roughly 20% to 25% had a higher disease burden with four or more positive lymph nodes. This group was also more prone to having a larger T stage and higher rates of pCR. We believe that this group of patients should be offered neoadjuvant chemotherapy. In contrast, in the HER2 negative breast cancer group, patients were less likely to have positive lymph nodes, they were the least likely to have a high disease burden of positive lymph nodes, with only about 10% with four or more positive nodes, and they were more likely to have smaller T stage and lower pCR rates. In this group, we should consider upfront surgery,

Table 14. Neoadjuvant Chemotherapy and BCS-pCR and LRR by Subtype.

Variable	HR+/HER2- (n = 369)	HR+/HER2+ (n = 105)	HR-/HER2+ (n = 58)	HR-/HER2- (n = 219)
pCR Rate	16.5%	45.7%	72.4%	42.0%
5-yr LRR-Free Survival				
pCR	100%	100%	97.4%	98.6%
No pCR	95.3%	94.6%	86.7%	89.9%
5-yr LRR-Free Survival	97.2%	96.1%	94.4%	93.4%

Table 15. Presenting features by molecular subtype [24].

	ER+/PR+/ HER2- 4311 (71%)	ER+/PR+/ HER2+ 486 (8%)	ER-/PR-/ HER2+ 364 (6%)	ER-/PR/ HER2- 911 (15%)	p value
Age (mean)	58 years	52 years	53 years	54 years	<0.0001
T size (cm)	1.68 cm	1.97 cm	2.22 cm	2.25 cm	<0.0001
Nodal involvement					
% positive	43	52	57	44	<0.0001
% ≥ 4 pos LN	11	20	28	14	<0.0001

especially if they are eligible for Z0011 or AMAROS trials. Finally, even though they have a highly aggressive disease in the triple-negative cohort, they are less likely to have high volume nodal disease or larger T stage, and they usually have excellent pCR rates. In this group of patients, we should consider neoadjuvant therapy, especially if the goal is to downstage the patient so we can offer BCS [41]

The ACOSOG Z1071 trial (**Table 16**) was designed to evaluate the regional lymph nodes' response to adjuvant chemotherapy. It enrolled 694 patients with stage II to stage III breast cancer. As expected, the investigators reported higher rates of pCR in HER2 positive and triple-negative breast cancer patients, with higher rates of BCT, although they are still below 50% [42]. As we know, pCR is not necessary for BCT, but there is a need for accurate imaging tools to quantify better the response (tumor shrinkage) to neoadjuvant therapy, and we should consider the differences in response based on histological subtypes as well as the patient desire for BCS.

There are some essential pre-treatment considerations when contemplating the use of neoadjuvant therapy. First of all, the diagnosis should be made by core needle biopsy with clip placement in the tumor bed to help the BCS surgical procedure and help the pathologist examine the specimen. It is also recommended to perform an FNA or preferably a core needle biopsy of palpable or radiographically suspicious lymph nodes. If the patient is a candidate for BCS without downstaging, the standard of care regarding staging imaging studies mammography and US are the preferred studies, and if the patient requires downstaging, an MRI should be performed before and after neoadjuvant therapy. It is important to have the same imaging studies both pre-treatment and posttreatment to facilitate the surgical treatment planning [42]

There is very little prospective data on what is the optimal imaging after NAC (**Table 17**). This study enrolled 31 patients with palpable tumors greater than 3 cm; they all had a physical examination, mammography, US, and MRI performed

Table 16. Subtype and rates of BCS after NAC [25].

Subtype	n	Breast pCR rate	BCS rate
HR+ HER2-	317	16%	35%
HER2+	207	50%	43%
TNBC	170	48%	47%

Table 17. What is the optimal imaging modality following NAC? [26]

Performance of Imaging technique	Pathology Results vs Imaging Modalities			
	Physical examination	Mammography	Sonography	MRI
Underestimate	17 (55)	16 (52)	16 (52)	7 (23)
Equal	6 (19)	8 (26)	11 (35)	22 (71)
Overestimate	8 (26)	7 (23)	4 (13)	2 (6)

before and after therapy [43]. MRI was the most accurate in predicting the pathologic size than the surgical specimen in 71% of the cases, whereas physical examination, mammography, and US only matched the pathology size of disease in up to 1/3 of the patients [43]. Even though there is not enough prospective data, some retrospective data compare contrast-enhanced MRI vs. other modalities [44]. Contrast-enhanced MRI has shown to outperform other imaging modalities, even though there is more work to be done with DM-MRI that might have higher sensitivity [44]

MRI's diagnostic performance depends not only on the patient's disease presentation but also on the pattern of response; some tumors shrink very concentrically, whereas others have a different shrinkage pattern with residual scattered cells. In these cases, there are higher rates of false-negative MRI when there are residual scattered cells [45]. There is emerging data about how these patterns of response vary by subtype, suggesting that triple-negative tumors are more prone to have a concentric shrinkage, whereas the HER2 positive and hormone receptor (HR) positive patients are more likely to have a scattered response [44].

De Los Santos *et al.* published a multicenter, retrospective study, where investigators from the TBCRC 017 study pooled data from eight National Cancer Institute (NCI) centers looking at the utility of using MRI as a predictor of pCR. The accuracy of MRI varies from 69% to 80% across the histologic subtypes (**Table 18**); notably, the negative predictive value (NPV) of MRI was highest in the HR negative/HER2 positive group and in the triple-negative (TN) group where if the MRI was negative, it was most likely to be negative in these subtypes. The MRI has the highest PPV in the HR-positive cases, so there is a higher possibility of having disease leftover in these patients. We can conclude that the performance of MRI varies between histologic subtypes, with HR-positive, low-grade tumors tending to have residual disease even if they look to have had a complete radiographic response. The HR negative/HER2 positive and TN tumors had the highest NPV. A complete clinical response (cCR) is insufficient to rule out residual disease in any subtype [45].

After neoadjuvant therapy, the goal of BCS is to remove any remaining suspicious clinical or radiographic abnormality. For instance, in a patient who seemed to have a cCR, we would still have to remove a sample of normal breast tissue around the localizing clip without needing to remove the entire volume of tissue

Table 18. MRI as a predictor of pCR [27].

	Negative Predictive Value (NPV)	Positive Predictive Value (PPV)	Accuracy ($p < 0.001$ and 0.01)
HR+/HER2-	33%	91%	80%
HR-/HER2+	62%	72%	69%
HR+/HER2+	42%	82%	70%
TN	60%	73%	69%
ALL	85/182 (47%)	470/564 (83%)	555/746 (74%)

that was initially occupied by the tumor, keeping with the idea of downstaging the patient [45] [46].

Table 19 shows an old series from the MD Anderson Cancer Center that reported the volume of breast tissue resected after NAC decreased in 150 patients who received NAC compared to 91 who received adjuvant chemotherapy [27]. The median pre-treatment tumor size was the same in both groups, the volume resected in the NAC group was about half the volume resected in the adjuvant chemotherapy group, and both the re-excision and local recurrence rates were the same in both groups [27].

There are some challenges regarding NAC, especially regarding the pattern of response. In some cases, the pathology reports might show negative margins even though some scattered cells might still be present. There are guidelines from the American College of Radiology, the American College of Surgeons, the College of American Pathology, and the Society of Surgical Oncology that state that in the setting of downstaging for BCS after neoadjuvant chemotherapy if viable tumor is present throughout the specimen, even if it doesn't extend to the margin, a further re-excision should be considered (Table 20).

The definition of negative margin after NAC was studied by Choi J, *et al.* [47], where patients with stage I to stage III who completed NAC underwent BCS in 12 years and had a median follow-up of 57 months. The overall local recurrence rate was only 3.9%, and on multivariable analysis, the margin width was not associated with local recurrence-free survival (RFS), DFS, or OS and the results did not change when breast pCR patients were removed from the analysis [47].

In conclusion, for the surgical management of the breast after NAC, patient and tumor selection are critically important with increasing rates of pCR not translating into rising rates of BCS; thus, pCR is not required for BCS. If the patient is a candidate to receive NAC, it is important to ask ourselves if there's an

Table 19. Approach to lumpectomy after NAC complete clinical response [28].

Tumors T2 and T3	NAC n = 150	Adjuvant Chemotherapy n = 91	p Value
Median Pre-Tx T Size (cm)	3.45	3.0	0.13
Volume Resected (cm^3)	113	213	0.004
Re-Excision Rate	18 (14%)	3 (14%)	1
Local Recurrence*	1	1	

*Median follow-up 33 months.

Table 20. Margin width and outcomes NAC and BCS [47].

5-year Outcome Measures	% (95% CI)
Local Recurrence Free Survival	96.3% (94.0 - 98.6)
Disease Free Survival	85.5% (81.8 - 90.7)
Overall Survival	90.8% (87.4 - 94.2)

advantage to giving the chemotherapy before surgery. Evaluating the extent of the residual disease remains a problem, especially in HR-positive disease. After the operation, the pathology report is critical for assessing the pattern of response and the margin status, critically important in determining success. Although the data is limited, "no tumor on ink" is probably good enough. However, a persistent finding of scattered, viable tumor in the resection specimens should prompt consideration of re-excision.

Ductal Carcinoma In Situ (DCIS) accounts for roughly 20% of all newly diagnosed breast cancers, with most women with DCIS undergo BCS. DCIS's problem is that there are multiple management options, and regardless of what treatment the patient received, survival is excellent for most patients, but recurrence rates vary widely depending on treatment and clinical/pathologic characteristics. In general, the more aggressive the treatment is, the lower the local recurrence rate, but the quality of life tends to be poorer.

There have been four mature randomized controlled studies of radiation after BCS for DCIS (**Table 21**). These studies have at least 12.7 years of follow up showing that patients who did not have radiation therapy, the local recurrence rate ranged from 25% to 30%, and for patients who did undergo radiation therapy, the local recurrence rate went from 10% to 20%, with a risk reduction around 50% in all studies [48] [49] [50] [51].

There are two randomized studies for patients who were administered Tamoxifen (**Table 22**), the NSABP B24 study where all women got radiation and the UK/ANZ study where some women got radiation, and some did not. The risk reduction for these studies was 20% to 25% [50] [52].

Comparing women who underwent lumpectomy alone in the NSABP B17/B24 trials and UK/ANZ study comparing women receiving lumpectomy plus radiation and Tamoxifen, the groups receiving radiation therapy and Tamoxifen had

Table 21. Prospective randomized trials of radiation for DCIS [48] [49] [50] [51].

			Local Recurrence			
Trials	**N**	**Median Follow-Up (years)**	**No RT**	**RT**	**Risk Reduction**	**p**
NSABP B17	813	17.25	35%	20%	47% - 52%	<0.001
EORTC 10853	1010	15.8	31%	18%	48%	<0.001
UK, Aust, NZ	475	12.7	26%	9%	69%	<0.0001
SweDCIS	1046	17	32%	20%	37.5%	<0.001

Table 22. Lumpectomy alone vs dual adjuvant therapy (RT + TAM) Arms of NSABP B17/B24 and UK/ANZ [30] [31].

			Local Recurrence		
Trials	**N**	**F/U (years)**	**No RT/No TAM**	**RT + TAM**	**Risk Reduction**
NSABP B17/B24	403/899	15.0	35.1%	16.0%	54%
UK/ANZ	531/252	12.7	26.0%	8.7%	67%

an overall risk reduction of over 50% and probably close to 67% [48] [49] [50].

It is essential to mention that this was in the era before estrogen receptor testing of DCIS, so these risk reductions associated with Tamoxifen or the dual adjuvant therapy are underestimating the magnitude of risk reduction associated with Tamoxifen as we now only use it for women with ER-positive disease. In summary, radiation therapy reduces the risk by about 50%, and Tamoxifen reduces the risk by 25%. The therapies are additive: RT + Tamoxifen reduces the risk by 67% over someone with lumpectomy alone [48] [50].

Other factors that influence recurrence rates are the time period of treatment, margin status, margin width, and age. The question poses if DCIS recurrences decreased over time as we have seen in the recurrence rates for invasive cancer. A study conducted at MSKCC looked at around 3000 patients who underwent breast conservative surgery for DCIS from 1978-2010 with an average follow-up of 75 months, and over 700 women followed-up for at least ten years [52].

In **Table 23**, we can see that initially, the recurrence rates were roughly 10%, and in recent years, the recurrence rates were lower, around 7%.

Because of that apparent split between the early years and later years, they dichotomized the population between those earlier than 1998 and those after 1999, showing a 38% reduced risk in the recent years compared to the previous years. [52].

A multivariable model was created to adjust for all the possible factors responsible for this improvement over time; as a result, they found that there was no explanation since remains a 25% reduced risk in the later years compare to the earlier years, there was no explaining to the increasing use of radiation, the increase in negative margins, increase in the screen of DCIS. Stratification of women between those that did get radiation and women who did not get radiation to assess if radiation became more efficacious over time. Among those receiving radiation, the two curves overlap, but among those not receiving radiation, there

Table 23. Multivariable model: decreasing recurrence rates over time [32].

	Characteristic	HR	P Value
Age	Continuous, per year	0.977	<0.0001
Family History	Yes vs No	1.28	0.03
Presentation	Clinical vs Radiologic	1.40	0.03
Nuclear Grade	High vs Non-high	1.03	0.8
Necrosis	Present vs Absent	1.43	0.01
No. of Excisions	≥3 vs ≤2	1.56	0.03
Margin Status	Negative vs Positive/Close	0.72	0.02
Radiation	Yes vs No	0.40	<0.0001
Endocrine Treatment	Yes vs No	0.52	0.0002
Time Period	1999-2010 vs 1978-1998	0.74	0.02

was a significant improvement, highly statistically significant between earlier years and later years [52].

A multivariable model was created for those not receiving radiation and those receiving radiation to adjust to the other factors. As a result, among those not receiving radiation, the more recent years had a 38% reduction in risk than the earlier years; in those who did receive radiation, there was no significant difference over time (**Table 24**). The implication of this is that the recurrence rates now are lower than the historical rates from randomized studies that started in the late 1980', which is important when estimating the risk of recurrence for women with DCIS, especially in this era of rising mastectomies, giving an appropriate risk estimate for the patient can help her to appropriately weight in the pros and cons of the various options, and that can be incredibly important when counseling women regarding treatment options for DCIS [53].

Margin status and width of resection: from the early breast cancer trial collaborative meta-analysis of randomized studies of radiation vs. no radiation after BCS, we can see that women who had BCS and radiation who had negative margins had a lower risk of recurrence than those who had positive margins. In conjunction with ASTRO and ASCO, the SSO commissioned a systematic review and meta-analysis, and a consensus panel. The systematic review identified 20 studies included in the meta-analysis with 7883 patients [54] [55]. They categorized each study group according to the definition of "negative margins" used. The study groups were: >0 - 1 mm, 2 mm, 3 - 5 mm, 10 mm [54] [55]. They concluded that women receiving radiation who had negative margins reduced recurrence risk by nearly 50%. Margins of at least 2 mm were associated with a lower risk of recurrence than smaller margins, but a margin threshold of 3 to 5 mm or 10 mm was not significantly associated with lower odds of recurrence compared to a 2 mm margin. The consensus panel reviewed this meta-analysis and other data from the literature and published consensus guidelines in 2016, stating that the negative optimal margin width for women with DCIS receiving

Table 24. Recurrence rates over time, by radiation use: multivariable analysis [33].

		No RT (n = 1111)		RT (n = 1447)	
	Characteristic	**HR**	**p**	**HR**	**p**
Age	Continuous, per year	0.98	0.007	0.96	<0.0001
Family history	Yes vs No	1.31	0.08	1.28	0.2
Presentation	Clinical vs Radiologic	1.50	0.04	1.21	0.5
Nuclear grade	High vs Non-high	1.04	0.8	1.02	0.9
Necrosis	Present vs Absent	1.54	0.01	1.10	0.7
No. of excisions	≥3 vs ≤2	2.11	0.009	1.18	0.5
Margin status	Negative vs Positive/Close	0.58	0.001		
Endocrine Treatment	Yes vs No	0.57	0.02	0.45	0.002
Time period	1999-2010 vs 1978-1998	0.62	0.003	1.13	0.62

radiation is 2 mm.

They concluded that for women who received whole breast radiation therapy (WBRT), negative margins reduce the risk of recurrence by half and that the use of WBRT does not nullify the increased risk associated with positive margins. Margins of at least 2 mm are associated with a lower risk of recurrence than narrower margins, and that the routine practice of obtaining negative margins greater than 2 mm is not supported by the evidence [55]. For women treated with BCS without WBRT, the consensus states that excision alone is associated with higher recurrence rates, regardless of margin width and that the optimal margin width is unknown but should be at least 2 mm. Some evidence suggests lower recurrence rates with wider margins. A cohort was identified that did not receive radiation that included 1200 women, and almost 300 were followed for at least ten years. The 10-year recurrence rates by margin width in this population showed that the recurrence rate with wider margins was lower, which was highly statistically significant [56]. In conclusion, wider negative margins are associated with a lower risk of recurrence in women not undergoing radiation.

Age: has been recognized as a risk factor for recurrence after BCS for DCIS for more than 20 years, but the full relationship is unclear because most studies dichotomized at age 50, generally correlating with pre-menopause and post-menopause. Looking at the same population based on the decade of age, comparing the oldest population (over 80 years) with the youngest (under 40 years) identified that the 10-year recurrence rates were the lowest in the patient population over 80 years of age at 8% and the highest recurrence rates were seen in the patient population under 40 years, at 27% [57]. The multivariable analysis of the recurrence risk has to be adjusted for the other variables: presentation, family history, necrosis, number of excisions, margin status, adjuvant RT, adjuvant endocrine therapy, and treatment period [57]. The adjustment made helped determine the relationship between those women not receiving radiation and those receiving radiation. The lowest risk of recurrence was seen for women over 80 years (~0% recurrence), and the highest risk was for women under 50 years of age.

A competing risk analysis comparing the type of recurrence, invasive vs. DCIS by age group, identified that those under 40 years of age invasive recurrences were more frequent than DCIS recurrences; in the other age group, DCIS recurrences were more common than invasive recurrences [57]. After adjusting for the other variables, we can see a stronger relationship with women over 80 years, having an 86% lower chance of invasive recurrence than in women under 40 years of age. The ties for DCIS recurrence were not that strong. In summary, older age was associated with lower recurrence rates in cohorts who did and didn't receive radiation. Younger women were at higher risk of invasive recurrence than older women (women < 40 years had 7.1 – fold higher risk of invasive recurrence than those > 80 years); in women under 40 years, invasive recurrences were more common than DCIS recurrences; in women over 40 years old, DCIS recurrences were more common. In conclusion, age is an important factor

that should be considered in weighing the various treatment options, including surgical therapy, adjuvant radiation therapy, and endocrine therapy.

Several factors affect the risk of recurrence in DCIS after BCS, including treatment-related factors (adjuvant radiation and adjuvant endocrine therapy), both of which are effective; clinical pathologic factors (the period of treatment, margin status and width: with or without radiation, and age). It is challenging to incorporate all of these factors. Still, individualized risk factors can help a woman weighing the pros and cons of the various management options, all the way from lumpectomy alone, lumpectomy and radiation, endocrine therapy, mastectomy, or bilateral mastectomy. The MSKCC DCIS nomogram is a validated predictive tool that estimates recurrence risk by integrating ten different clinicopathologic and treatment factors [58]. The optimal treatment option for DCIS is the one that aligns with the woman's priorities and values in terms of local recurrence risk, preservation of the breast, quality of life, and the avoidance and use of adjuvant therapy. A thorough discussion between clinician and patient, including the pros and cons and estimated risk of recurrence of each management option, can help a woman make the best management option (individualized medicine).

3. Conclusion

Early breast cancer's current surgical management should be evidence-based and individualized to each patient based on the tumor's clinical, histological, and molecular characteristics. We feel that the standard of care in BCS has enhanced outcomes for patients with breast cancer. This review will help keep surgeons managing breast cancer up to date with the current literature, allowing them to improve on various clinical parameters like DFS, RFS, and most importantly, OS.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Fisher, B., *et al.* (2002) Twenty-Year Follow-Up of a Randomized Trial Comparing Total Mastectomy, Lumpectomy, and Lumpectomy plus Irradiation for the Treatment of Invasive Breast Cancer. *The New England Journal of Medicine*, **347**, 1233-1241. https://doi.org/10.1056/NEJMoa022152

[2] Morrow, M., *et al.* (2009) Surgeon Recommendations and Receipt of Mastectomy for Treatment of Breast Cancer. *JAMA*, **302**, 1551-1556. https://doi.org/10.1001/jama.2009.1450

[3] Giuliano, A.E., *et al.* (2011) Axillary Dissection vs No Axillary Dissection in Women with Invasive Breast Cancer and Sentinel Node Metastasis: A Randomized Clinical Trial. *JAMA*, **305**, 569-575. https://doi.org/10.1001/jama.2011.90

[4] Bouganim, N., *et al.* (2013) Evolution of Sites of Recurrence after Early Breast Can-

cer over the Last 20 Years: Implications for Patient Care and Future Research. *Breast Cancer Research and Treatment*, **139**, 603-606. https://doi.org/10.1007/s10549-013-2561-7

[5] Galimberti, V., *et al.* (2013) Axillary Dissection versus No Axillary Dissection in Patients with Sentinel-Node Micrometastases (IBCSG 23-01): A Phase 3 Randomised Controlled Trial. *The Lancet Oncology*, **14**, 297-305. https://doi.org/10.1016/S1470-2045(13)70035-4

[6] Hortobagyi, G.N., Edge, S.B., Mittendorf, E.A., *et al.* (2017) Breast. 8th Edition, AJCC Cancer Staging Manual. Vol. 1, Springer, Berlin.

[7] Giuliano, A.E., Ballman, K.V., *et al.* (2011) Association of Occult Metastases in Sentinel Lymph Nodes and Bone Marrow with Survival among Women with Early-Stage Invasive Breast Cancer. *JAMA*, **306**, 385-393. https://doi.org/10.1001/jama.2011.1034

[8] Weaver, D.L., *et al.* (2011) Effect of Occult Metastases on Survival in Node-Negative Breast Cancer. *The New England Journal of Medicine,* **364**, 412-421. https://doi.org/10.1056/NEJMoa1008108

[9] Invasive Breast 3.3.0.0. Protocol for the Examination of Specimens from Patients with Invasive Carcinoma of the Breast 2016. https://documents.cap.org/protocols/cp-breast-invasive-2016-v3300.pdf

[10] Houssami, N., *et al.* (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. *Annals of Surgical Oncology*, **21**, 717-730. https://doi.org/10.1245/s10434-014-3480-5

[11] Moran, M.S., *et al.* (2014) Society of Surgical Oncology—American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer. *Annals of Surgical Oncology*, **21**, 704-716. https://doi.org/10.1245/s10434-014-3481-4

[12] Blair, S.L., *et al.* (2009) Attaining Negative Margins in Breast-Conservation Operations: Is There a Consensus among Breast Surgeons? *Journal of the American College of Surgeons*, **209**, 608-613. https://doi.org/10.1016/j.jamcollsurg.2009.07.026

[13] Parvez, E., *et al.* (2014) Survey of American and Canadian General Surgeons' Perceptions of Margin Status and Practice Patterns for Breast Conserving Surgery. *The Breast Journal*, **20**, 481-488. https://doi.org/10.1111/tbj.12299

[14] Azu, M., *et al.* (2010) What Is an Adequate Margin for Breast-Conserving Surgery? Surgeon Attitudes and Correlates. *Annals of Surgical Oncology*, **17**, 558-563. https://doi.org/10.1245/s10434-009-0765-1

[15] DeSnyder, S.M., *et al.* (2015) Assessment of Practice Patterns Following Publication of the SSO-ASTRO Consensus Guideline on Margins for Breast-Conserving Therapy in Stage I and II Invasive Breast Cancer. *Annals of Surgical Oncology*, **22**, 3250-3256. https://doi.org/10.1245/s10434-015-4666-1

[16] Morrow, M., *et al.* (2017) Trends in Reoperation after Initial Lumpectomy for Breast Cancer: Addressing Overtreatment in Surgical Management. *JAMA Oncology*, **3**, 1352-1357. https://doi.org/10.1001/jamaoncol.2017.0774

[17] Wilke, L.G., *et al.* (2014) Repeat Surgery after Breast Conservation for the Treatment of Stage 0 to II Breast Carcinoma: A Report from the National Cancer Data Base, 2004-2010. *JAMA Surgery*, **149**, 1296-1305. https://doi.org/10.1001/jamasurg.2014.926

[18] Rosenberger, L.H., *et al.* (2016) Early Adoption of the SSO-ASTRO Consensus

Guidelines on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Stage I and II Invasive Breast Cancer: Initial Experience from Memorial Sloan Kettering Cancer Center. *Annals of Surgical Oncology*, **23**, 3239-3246. https://doi.org/10.1245/s10434-016-5397-7

[19] Mamtani, A., *et al.* (2019) Was Re-Excision Less Frequent for Patients with Lobular Breast Cancer after Publication of the SSO-ASTRO Margin Guidelines? *Annals of Surgical Oncology*, **26**, 3856-3862. https://doi.org/10.1245/s10434-019-07751-8

[20] Havel, L., *et al.* (2019) Impact of the SSO-ASTRO Margin Guideline on Rates of Re-Excision after Lumpectomy for Breast Cancer: A Meta-Analysis. *Annals of Surgical Oncology*, **26**, 1238-1244. https://doi.org/10.1245/s10434-019-07247-5

[21] Heelan Gladden, A.A., *et al.* (2017) Re-Excision Rates after Breast Conserving Surgery Following the 2014 SSO-ASTRO Guidelines. *The American Journal of Surgery*, **214**, 1104-1109. https://doi.org/10.1016/j.amjsurg.2017.08.023

[22] Schulman, A.M., *et al.* (2017) Reexcision Surgery for Breast Cancer: An Analysis of the American Society of Breast Surgeons (ASBrS) Mastery (SM) Database Following the SSO-ASTRO "No Ink on Tumor" Guidelines. *Annals of Surgical Oncology*, **24**, 52-58. https://doi.org/10.1245/s10434-016-5516-5

[23] Patten, C.R., *et al.* (2017) Changes in Margin Re-Excision Rates: Experience Incorporating the "No Ink on Tumor" Guideline into Practice. *Journal of Surgical Oncology*, **116**, 1040-1045. https://doi.org/10.1002/jso.24770

[24] Chung, A., *et al.* (2015) Impact of Consensus Guidelines by the Society of Surgical Oncology and the American Society for Radiation Oncology on Margins for Breast-Conserving Surgery in Stages 1 and 2 Invasive Breast Cancer. *Annals of Surgical Oncology*, **22**, S422-S427. https://doi.org/10.1245/s10434-015-4829-0

[25] Bhutiani, N., *et al.* (2018) Evaluating the Effect of Margin Consensus Guideline Publication on Operative Patterns and Financial Impact of Breast Cancer Operation. *Journal of the American College of Surgeons*, **227**, 6-11. https://doi.org/10.1016/j.jamcollsurg.2018.01.050

[26] Chia, S., *et al.* (2008) Locally Advanced and Inflammatory Breast Cancer. *Journal of Clinical Oncology*, **26**, 786-790. https://doi.org/10.1200/JCO.2008.15.0243

[27] Boughey, J.C., *et al.* (2006) Impact of Preoperative versus Postoperative Chemotherapy on the Extent and Number of Surgical Procedures in Patients Treated in Randomized Clinical Trials for Breast Cancer. *Annals of Surgery*, **244**, 464-470. https://doi.org/10.1097/01.sla.0000234897.38950.5c

[28] Fisher, B., *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. *Journal of Clinical Oncology*, **15**, 2483-2493. https://doi.org/10.1200/JCO.1997.15.7.2483

[29] Mieog, J.S., van der Hage, J.A. and van de Velde, C.J. (2007) Neoadjuvant Chemotherapy for Operable Breast Cancer. *British Journal of Surgery*, **94**, 1189-1200. https://doi.org/10.1002/bjs.5894

[30] Guarneri, V., *et al.* (2006) Prognostic Value of Pathologic Complete Response after Primary Chemotherapy in Relation to Hormone Receptor Status and Other Factors. *Journal of Clinical Oncology*, **24**, 1037-1044. https://doi.org/10.1200/JCO.2005.02.6914

[31] Rastogi, P., *et al.* (2008) Preoperative Chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *Journal of Clinical Oncology*, **26**, 778-785. https://doi.org/10.1200/JCO.2007.15.0235

[32] Mauri, D., Pavlidis, N. and Ioannidis, J.P. (2005) Neoadjuvant versus Adjuvant Systemic Treatment in Breast Cancer: A Meta-Analysis. *Journal of the National Cancer Institute*, **97**, 188-194. https://doi.org/10.1093/jnci/dji021

[33] Mamounas, E.P. (1997) NSABP Protocol B-27. Preoperative Doxorubicin plus Cyclophosphamide Followed by Preoperative or Postoperative Docetaxel. *Oncology* (*Williston Park*), **11**, 37-40.

[34] Cortazar, P., *et al.* (2014) Pathological Complete Response and Long-Term Clinical Benefit in Breast Cancer: The CTNeoBC Pooled Analysis. *The Lancet*, **384**, 164-172. https://doi.org/10.1016/S0140-6736(13)62422-8

[35] Mamounas, E.P., *et al.* (2012) Predictors of Locoregional Recurrence after Neoadjuvant Chemotherapy: Results from Combined Analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. *Journal of Clinical Oncology*, **30**, 3960-3966. https://doi.org/10.1200/JCO.2011.40.8369

[36] Swisher, S.K., *et al.* (2016) Locoregional Control According to Breast Cancer Subtype and Response to Neoadjuvant Chemotherapy in Breast Cancer Patients Undergoing Breast-Conserving Therapy. *Annals of Surgical Oncology*, **23**, 749-756. https://doi.org/10.1245/s10434-015-4921-5

[37] Killelea, B.K., *et al.* (2015) Neoadjuvant Chemotherapy for Breast Cancer Increases the Rate of Breast Conservation: Results from the National Cancer Database. *Journal of the American College of Surgeons*, **220**, 1063-1069. https://doi.org/10.1016/j.jamcollsurg.2015.02.011

[38] Battisti, N.M.L., *et al.* (2020) Pathological Complete Response to Neoadjuvant Systemic Therapy in 789 Early and Locally Advanced Breast Cancer Patients: The Royal Marsden Experience. *Breast Cancer Research and Treatment*, **179**, 101-111. https://doi.org/10.1007/s10549-019-05444-0

[39] Broet, P., *et al.* (1999) Short and Long-Term Effects on Survival in Breast Cancer Patients Treated by Primary Chemotherapy: An Updated Analysis of a Randomized Trial. *Breast Cancer Research and Treatment*, **58**, 151-156. https://doi.org/10.1023/A:1006339918798

[40] Bonnefoi, H., *et al.* (2014) Pathological Complete Response after Neoadjuvant Chemotherapy Is an Independent Predictive Factor Irrespective of Simplified Breast Cancer Intrinsic Subtypes: A Landmark and Two-Step Approach Analyses from the EORTC 10994/BIG 1-00 Phase III Trial. *Annals of Oncology*, **25**, 1128-1136. https://doi.org/10.1093/annonc/mdu118

[41] Wiechmann, L., *et al.* (2009) Presenting Features of Breast Cancer Differ by Molecular Subtype. *Annals of Surgical Oncology*, **16**, 2705-2710. https://doi.org/10.1245/s10434-009-0606-2

[42] Boughey, J.C., *et al.* (2014) Tumor Biology Correlates with Rates of Breast-Conserving Surgery and Pathologic Complete Response after Neoadjuvant Chemotherapy for Breast Cancer: Findings from the ACOSOG Z1071 (Alliance) Prospective Multicenter Clinical Trial. *Annals of Surgery*, **260**, 608-614.

[43] Yeh, E., *et al.* (2005) Prospective Comparison of Mammography, Sonography, and MRI in Patients Undergoing Neoadjuvant Chemotherapy for Palpable Breast Cancer. *American Journal of Roentgenology*, **184**, 868-877. https://doi.org/10.2214/ajr.184.3.01840868

[44] Gu, Y.L., *et al.* (2017) Role of Magnetic Resonance Imaging in Detection of Pathologic Complete Remission in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy: A Meta-Analysis. *Clinical Breast Cancer*, **17**, 245-255. https://doi.org/10.1016/j.clbc.2016.12.010

[45] Pastorello, R.G., *et al.* (2020) Clinico-Pathologic Predictors of Patterns of Residual Disease Following Neoadjuvant Chemotherapy for Breast Cancer. *Modern Pathology*. https://doi.org/10.1038/s41379-020-00714-5

[46] Sun, S.X. and Kuerer, H.M. (2019) ASO Author Reflections: Selecting Patients for Elimination of Surgery Trials-Predicting Residual Invasive and In Situ Disease in Patients with HER2-Positive Breast Cancer after Neoadjuvant Systemic Therapy. *Annals of Surgical Oncology*, **26**, 804-805. https://doi.org/10.1245/s10434-019-07943-2

[47] Choi, J., *et al.* (2018) Correction to: Margins in Breast-Conserving Surgery after Neoadjuvant Therapy. *Annals of Surgical Oncology*, **25**, 995. https://doi.org/10.1245/s10434-018-6721-1

[48] Wapnir, I.L., *et al.* (2011) Long-Term Outcomes of Invasive Ipsilateral Breast Tumor Recurrences after Lumpectomy in NSABP B-17 and B-24 Randomized Clinical Trials for DCIS. *Journal of the National Cancer Institute*, **103**, 478-488. https://doi.org/10.1093/jnci/djr027

[49] Donker, M., *et al.* (2013) Breast-Conserving Treatment with or without Radiotherapy in Ductal Carcinoma *in Situ*: 15-Year Recurrence Rates and Outcome after a Recurrence, from the EORTC 10853 Randomized Phase III Trial. *Journal of Clinical Oncology*, **31**, 4054-4059. https://doi.org/10.1200/JCO.2013.49.5077

[50] Cuzick, J., *et al.* (2011) Effect of Tamoxifen and Radiotherapy in Women with Locally Excised Ductal Carcinoma *in Situ*: Long-Term Results from the UK/ANZ DCIS Trial. *The Lancet Oncology*, **12**, 21-29. https://doi.org/10.1016/S1470-2045(10)70266-7

[51] Warnberg, F., *et al.* (2014) Effect of Radiotherapy after Breast-Conserving Surgery for Ductal Carcinoma *in Situ*: 20 Years Follow-Up in the Randomized SweDCIS Trial. *Journal of Clinical Oncology*, **32**, 3613-3618. https://doi.org/10.1200/JCO.2014.56.2595

[52] Early Breast Cancer Trialists' Collaborative G., *et al.* (2010) Overview of the Randomized Trials of Radiotherapy in Ductal Carcinoma *in Situ* of the Breast. *Journal of the National Cancer Institute Monographs*, **2010**, 162-177. https://doi.org/10.1093/jncimonographs/lgq039

[53] Marinovich, M.L., *et al.* (2016) The Association of Surgical Margins and Local Recurrence in Women with Ductal Carcinoma *in Situ* Treated with Breast-Conserving Therapy: A Meta-Analysis. *Annals of Surgical Oncology*, **23**, 3811-3821. https://doi.org/10.1245/s10434-016-5446-2

[54] Morrow, M., *et al.* (2016) Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Ductal Carcinoma *in Situ*. *Practical Radiation Oncology*, **6**, 287-295. https://doi.org/10.1016/j.prro.2016.06.011

[55] Van Zee, K.J., *et al.* (2015) Relationship between Margin Width and Recurrence of Ductal Carcinoma *in Situ*: Analysis of 2996 Women Treated with Breast-conserving Surgery for 30 Years. *Annals of Surgery*, **262**, 623-631. https://doi.org/10.1097/SLA.0000000000001454

[56] Cronin, P.A., *et al.* (2016) Impact of Age on Risk of Recurrence of Ductal Carcinoma *in Situ*: Outcomes of 2996 Women Treated with Breast-Conserving Surgery over 30 Years. *Annals of Surgical Oncology*, **23**, 2816-2824. https://doi.org/10.1245/s10434-016-5249-5

[57] Rudloff, U., *et al.* (2010) Nomogram for Predicting the Risk of Local Recurrence af-

ter Breast-Conserving Surgery for Ductal Carcinoma *in Situ*. *Journal of Clinical Oncology*, **28**, 3762-3769. https://doi.org/10.1200/JCO.2009.26.8847

[58] Van Zee, K.J., *et al.* (2019) Comparison of Local Recurrence Risk Estimates after Breast-Conserving Surgery for DCIS: DCIS Nomogram versus Refined Oncotype DX Breast DCIS Score. *Annals of Surgical Oncology*, **26**, 3282-3288. https://doi.org/10.1245/s10434-019-07537-y