2 Milestone Studies in Breast Cancer Surgery

Anees B. Chagpar

2.1 Introduction

Significant advances have been made in nearly every aspect of the multidisciplinary management of breast cancer patients over the last several decades. Indeed, breast cancer surgery has been revolutionized by a number of key studies (Table 2.1) and continues to morph in an era of increasing collaboration between disciplines. This chapter will review the tremendous progress made in the field of breast cancer surgery and milestone studies that have paved the way for this. It should be noted that there have been many other studies that have also been critical to our progress, and all studies add to our knowledge and have been building blocks for progress; however, it is impossible to include all studies in a single chapter. Hence we have focused on large randomized controlled trials that have been practice-changing.

2.2 Transformation of Surgery for Tumor Extirpation

2.2.1 From Radical Mastectomy to Total Mastectomy

One of the first landmark trials that spurred on the modern era of breast cancer surgery was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 [1]. This study stratified patients into node-positive versus node-negative groups and randomized patients to undergo either *radical mastectomy*, which had theretofore been the staple of breast cancer surgery and involved removal of the breast, pectoral muscles, and axillary lymph nodes, or *total mastectomy* (with or without radiation) in which the muscle and lymph nodes were left intact (Fig. 2.1). With over 25 years of follow-up, no difference was found between the two groups in terms of either overall or disease-free survival. These data allowed for a dramatic shift in the surgical management of breast cancer, sparing patients from the disfiguring sequelae of removing the pectoral muscles. In addition, the finding that removing axillary lymph nodes did not affect survival laid the foundation for lymph node-sparing procedures to come.

2.2.2 From Total Mastectomy to Breast-Conserving Surgery

Perhaps one of the greatest advances in breast surgery came from the realization of the survival equivalence of breast-conserving surgery and mastectomy. In the NSABP B-06 [2] and Milan [3] trials, women were randomized to undergo either mastectomy or breast-conserving surgery. Both of these studies provided robust evidence that these two strategies were

A. B. Chagpar (✉)
Yale University School of Medicine,
New Haven, CT, USA
e-mail: Anees.chagpar@yale.edu

M. Rezai et al. (eds.), *Breast Cancer Essentials*, https://doi.org/10.1007/978-3-030-73147-2_2

Table 2.1 Landmark trials

Study	Design	Years	Arms (*n*)	Key findings
NSABP B-04	RCT	1971–1974	Radical mastectomy[a] Total mastectomy Total mastectomy + XRT	No difference in OS, RFS, DDFS
NSABP B-06	RCT	1976–1984	Total mastectomy (*n* = 713) Lumpectomy alone (*n* = 719) Lumpectomy + XRT (*n* = 731)	No difference in OS, DFS, DDFS IBTR at 20 years. lower with XRT than lumpectomy alone (14.3% vs. 39.2%, p < 0.001)
Milan	RCT	1973–1980	Radical mastectomy (*n* = 349) Quadrantectomy + XRT (*n* = 352)	No difference in rates of distant metastases or death IBTR at 20 years higher in BCT group (8.8% vs. 2.3%, p < 0.001)
NSABP B-18	RCT	1988–1993	Preoperative chemotherapy (*n* = 763) Postoperative chemotherapy (*n* = 760)	No difference in DFS or OS Lumpectomy more likely with neoadjuvant chemotherapy (67% vs. 60%, *p* = 0.002)
INT 09/98	RCT	1998–2003	Quadrantectomy (*n* = 245) Quadrantectomy + ALND (*n* = 272)	At median follow-up of 10 years, no difference in DFS or OS
NSABP B-32	RCT	1999–2004	SLNB with routine ALND (*n* = 2807) SLNB with ALND only if SLN+ (*n* = 2804)	No difference in OS, DFS, regional node recurrence
ACOSOG Z-1071	Cohort	2009–2011	Neoadjuvant chemotherapy followed by SLNB and routine ALND (*n* = 649)	SLN identification rate = 92.7% FNR overall = 21.5%; FNR if >2 SLNs removed = 12.6%
SENTINA	RCT	2009–2012	See Fig. 2.2	See Fig. 2.2
AMAROS	RCT	2001–2010	SLNB+ → ALND (*n* = 744) SLNB+ → axillary XRT (*n* = 681)	At median follow-up of 6.1 years, no difference in DFS and OS 5-year axillary recurrence 0.43% in ALND vs. 1.19% in axillary XRT group
IBCSG 23-01	RCT	2001–2010	SLNB+ → ALND (*n* = 464) SLNB+ → no further tx (*n* = 467)	At median follow-up of 5 years, no difference in OS or DFS 5-yr axillary recurrence 0.2% in ALND vs. 0.9% in SLNB
ACOSOG Z-0011	RCT	1999–2004	SLNB+ → ALND (*n* = 420) SLNB+ → whole breast XRT (n = 436)	At median follow-up of 6.3 yrs., no difference in OS or DFS Axillary recurrence 0.5% in ALND vs. 0.9% in SLNB group

RCT randomized controlled trial; *XRT* radiation therapy; *OS* overall survival; *RFS* relapse-free survival; *DDFS* distant disease free survival; *DFS* disease-free survival; *IBTR* ipsilateral breast tumor recurrence; *BCT* breast-conserving therapy; *SLNB* sentinel node biopsy; *ALND* axillary lymph node dissection; *SLN* sentinel lymph node; *FNR* false-negative rate

[a]See Fig. 2.1 for schema

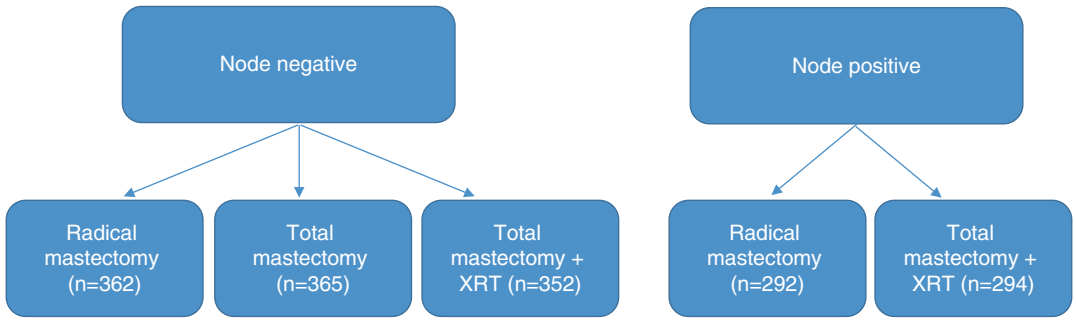


Fig. 2.1 Schema of NSABP B-04

equivalent in terms of survival. Furthermore, the NSABP B-06 trial, which randomized patients having breast-conserving surgery to undergo either adjuvant radiation therapy or not, also defined the need for radiation therapy to improve local control. These trials were paradigm shifting as they provided level 1 evidence to allow surgeons to preserve the breast and further highlighted the need for multidisciplinary collaboration. With advances in screening and early detection, breast-conserving surgery has become the mainstay of surgical management.

2.2.3 Making More Patients Candidates for Breast-Conserving Surgery

With increasing collaboration between surgery and medical oncology, the question of timing of surgery vis-à-vis chemotherapy was raised. Some argued that giving neoadjuvant chemotherapy followed by surgery would be an optimal strategy, as this would prioritize the reduction of the systemic burden of disease. Others argued that primary surgery would be better as this would remove the bulk of the cancer. The NSABP B-18 trial [4] randomized patients with operable breast cancer to either receive four cycles of doxorubicin-cyclophosphamide followed by surgery or surgery followed by the same chemotherapy regimen. With an endpoint of survival, this trial found no significant difference between the two arms. In addition, it was found that the degree of response to neoadjuvant chemotherapy could predict overall survival and further that neoadjuvant chemotherapy rendered more patients eligible for breast-conserving surgery [5]. As a result, the approach of treating patients with neoadjuvant therapy has become a mainstay in the surgeon's arsenal for converting patients with large tumors who are only candidates for mastectomy into patients with smaller tumors who may then become candidates for breast-conserving surgery.

2.2.4 Improving Techniques to Reduce Margin Positivity

A critical element of breast-conserving surgery is attainment of a negative margin, as positive margins have been associated with higher locoregional recurrence rates [6]. While there has been much debate over what constitutes a clear margin, a recent consensus statement [7] concluded that the definition of "no tumor at ink," which was used in the NSABP B-06 trial, should be used as the benchmark. Despite surgeons' best efforts, the rate of positive margins after breast-conserving surgery has been reported to be 20–40%. A number of techniques have been evaluated to lower this rate; randomized trials, however, have been few (Table 2.2).

Surgeons rely on preoperative imaging in their surgical planning, but the value of magnetic resonance imaging (MRI) in improving margin clearance had been contested. There have been two randomized controlled trials that have evaluated the impact of this technology in reducing positive margin rates. While the COMICE trial [8] found no difference between the two arms, the MONET trial [9] paradoxically demonstrated an increase in positive margins associated with the use of preoperative MRI. An ongoing American College of Surgeons Oncology Group (ACOSOG)/American College of Radiology Imaging Network trial seeks to further evaluate the impact of MRI on surgical outcomes.

Other studies have evaluated the impact of intraoperative imaging, frozen section, novel technology, and/or oncoplastic techniques, which remove segments of tissue often extending from the skin to the chest wall, to improve positive margin rates. In terms of lesion localization, Postma et al. found that radioactive occult lesion localization (ROLL) did not reduce positive margin rates despite more tissue being removed [10]. Others have found that intraoperative ultrasound [11, 12] and/or use of novel technology such as MarginProbe (Dune Medical) [13] may result in lower positive margin rates. More recently, there have been a number of randomized controlled trials evaluating the routine resection of cavity shave margins, all of which have found that this simple

Table 2.2 Trials to evaluate impact on margin status in patients undergoing breast-conserving surgery

	Intervention		Positive margin rate		Re-excision rate		Volume of tissue excised	
Study	Arm	*n*	%	*p*-value	%	*p*-value		*p*-value
Preoperative MRI								
COMICE	MRI	816	13%[a]	n/s	16%	0.77	n/s	n/s
	No MRI	807	15%[a]		19%		n/s	
MONET	MRI	74	n/s	n/s	45%[b]	0.069	69.1 cm^3	n/s
	No MRI	75	n/s		28%[b]		90.2 cm^3	
ROLL								
Postma et al.	ROLL	162	14%	0.644	12%	0.587	71 cm^3	0.017
	WGL	152	12%		10%		64 cm^3	
Intraoperative ultrasound								
Rahusen et al.	US	26	11%[c]	0.007	n/s	n/s	51 g	n/s
	WGL	23	45%[c]		n/s		53 g	
COBALT	US	65	3%	0.0093	2%	n/s	38 cm^3	0.002
	Palpation	69	17%		11%		57 cm^3	
MarginProbe								
Schnabel et al.	Device	298	30.9%	0.008	19.8%	0.097	87.5 mL	n/s
	SOC	298	41.6%		25.8%		71.7 mL	
Routine cavity shave margins								
Chagpar et al.	CSM	119	19%	0.01	10%	0.02	115.1 cm^3	< 0.001
	SOC	116	34%		21%		74.2 cm^3	
Jones et al.	CSM	45	15.6%	0.005	n/s	n/s	305.5 cm^3	0.193
	SOC	31	45.2%		n/s		243.2 cm^3	
SHAVE2	CSM	196	8.7%	<0.001	6.6%	<0.001	101.1 cm^3	<0.001
	SOC	200	32.5%		23.5%		73.4 cm^3	

n/s not specified, *ROLL* radio-occult lesion localization, *WGL* wire-guided localization, *US* ultrasound, *SOC* standard of care, *CSM* cavity shave margins

[a]Positive margins stated are for invasive disease only

[b]Re-excision rate stated are for re-excision (breast-conserving surgery) and conversion to mastectomy after initial surgery

[c]Positive margin defined as ≤1 mm

technique can reduce positive margins and re-excisions by at least 50% [14, 15].

2.2.5 Making Mastectomy more Cosmetically Acceptable

While the NSABP B-06 and Milan [3] trials had demonstrated that breast conservation and mastectomy were equivalent in terms of survival, some patients may not be eligible for or may choose to have mastectomy. Surgical techniques have evolved beyond the conventional mastectomy which leaves patients flat-chested to include techniques such as skin- and nipple-sparing mastectomy. While there have not been randomized controlled trials to assess these newer techniques, a number of large cohort studies and meta-analyses have demonstrated that skin-sparing mastectomies are oncologically equivalent to conventional mastectomies [16]. Other studies have also found that the ability to offer patients immediate reconstruction often results in improved body image and quality of life for breast cancer patients.

2.3 Transformation of Lymph Node Evaluation and Management

2.3.1 From Axillary Dissection to Sentinel Node Biopsy

It was clear from the NSABP B-04 [1] and Milan [3] trials that removing axillary nodes did not impart a survival benefit. The INT 09/98 trial [17]

randomized women aged 35–65 who had clinically T1N0 cancers to quadrantectomy with axillary node dissection vs. quadrantectomy alone. Similar to the earlier trials, they too found that axillary node dissection did not confer any survival advantage. However, knowledge of lymph node status did result in more patients being treated with chemotherapy (51.5% vs. 35.5%, $p < 0.001$); hence, the prognostic information was useful for clinicians.

The purpose of lymph node evaluation was twofold: for staging and for local control. The popularization of sentinel node biopsy in melanoma [18] laid the path for the technique to be tried in breast cancer, and early work by Giuliano [19], Krag [20], and others confirmed the fact that this procedure was feasible in breast cancer. Large cohort studies, like the Louisville Breast Sentinel Node Study [21], which asked surgeons to perform a sentinel node biopsy followed by a routine axillary dissection, provided a plethora of data regarding the technique. In particular, they were able to show that surgeons were able to not only identify the sentinel node but that the false negative rate was fairly low. The NSABP B-32 [22] was a randomized controlled trial that confirmed these findings. Randomizing patients between routine axillary dissection and axillary dissection only if the sentinel node was positive, this study found no difference in survival nor in locoregional recurrence. Hence, sentinel node biopsy became standard of care.

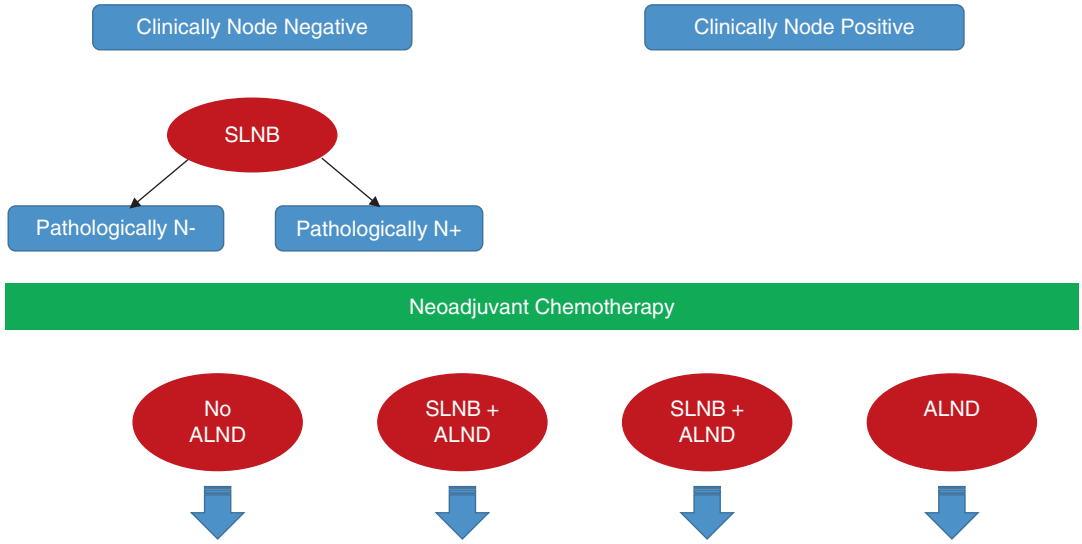
2.3.2 Sentinel Node Biopsy in the Setting of Neoadjuvant Therapy

With the increasing use of neoadjuvant chemotherapy, the question of timing of sentinel node biopsy came into question. A number of studies had indicated that the false-negative rate of this technique was higher if done after neoadjuvant chemotherapy [23], prompting some surgeons to opt to do the sentinel node biopsy prior to the initiation of neoadjuvant chemotherapy. Other studies, however, felt that sentinel node biopsy was feasible and accurate after neoadjuvant chemotherapy [24]. They argued that doing so obviated the need for two surgical procedures and could spare some patients an unnecessary axillary dissection. The ACOSOG 1071 [25] and SENTINA [26] trials (Fig. 2.2), each using a slightly different schema, were designed to settle this debate. The identification rates were acceptable in both studies (92.7% and 80.8% for the ACOSOG 1071 and SENTINA trials, respectively). False-negative rates after neoadjuvant chemotherapy were also thought to be acceptable, especially if two or more sentinel nodes were removed.

2.3.3 Avoiding Axillary Dissection in Node-Positive Patients

Often, the sentinel nodes are the only ones harboring cancer, and a number of studies had found the chances of non-sentinel node metastases are approximately 20–40%. There would be little benefit to performing an axillary dissection in these cases; despite a number of nomograms and clinical prediction rules that have been formulated to predict non-sentinel node metastases, none of these is perfect. In the current era where the majority of cancers are found early and where there is nearly ubiquitous use of systemic therapy, some wondered if completion axillary node dissection was truly necessary. Given that radiation therapy had been shown to improve local recurrence in the breast for patients undergoing breast conservation, some considered whether axillary radiotherapy may provide adequate local control in sentinel node-positive patients. Indeed, the tangent fields used in whole breast radiation therapy in patients undergoing breast-conserving therapy tend to cover the lower two thirds of the axilla. Hence, investigators began to ask whether axillary dissection was always mandatory in sentinel node-positive patients.

A number of clinical trials, including the ASCOSOG Z-0011 [27, 28], IBCSG 23-01 [29], and AMAROS [30] studies, sought to answer this question. Each of these had different inclusion and exclusion criteria and randomization arms, yet the results were remarkably similar (Table 2.3). Confirming the results of the NSABP



	Arm A	Arm B	Arm C	Arm D
N	662	360	592	123
ID rate	98.8%	60.8%	80.1%	n/a
FN rate	n/a	51.6%	14.2%	n/a

Fig. 2.2 Schema of SENTINA trial

B-04, none found a difference in survival; more importantly, the axillary recurrence rates in all arms of all trials were remarkably low. Of note, the AMAROS trial also found the rate of lymphedema was less after axillary radiation than after axillary dissection (5% vs. 13% based on >10% increase in arm circumference at 5 years, $p = 0.0009$). Hence, many surgeons have changed their practice and no longer routinely perform axillary dissections in all sentinel node-positive patients.

2.4 Future Directions

As the genomic revolution continues, and we move toward more personalized therapies, it is undoubtable that surgery will move in this direction as well. Already, there are studies ongoing that ask the question whether all breast cancer patients require surgery, thus furthering the movement from radical surgery to more minimalist approaches. The ongoing COMET trial seeks to understand whether patients with small low-to-intermediate-grade DCIS lesions can be treated with endocrine therapy alone, and the Exceptional Responder trial is evaluating whether patients with her-2-neu-positive and triple-negative breast cancer who have an imaging-guided biopsy complete response after neoadjuvant therapy can be observed without surgery. On the other hand, some trials are evaluating the role for breast cancer surgery in the setting of metastatic disease. As large paradigm-shifting studies are done, there will be a metamorphosis in the surgical management of breast cancer that will rival the significant progress that has occurred over the last several decades.

Table 2.3 Comparison of ACOSOG Z-0011, IBCSG 23-01, and AMAROS trials

	ACOSOG Z-0011	IBCSG 23-01	AMAROS
Inclusion criteria			
Tumor size	≤5 cm	≤5 cm	≤5 cm
Number of SLN+	<3	Any	Any
Size of SLN metastasis	Any	≤2 mm	Any
Exclusion criteria			
Mastectomy	X		
Neoadjuvant therapy	X	X	X
Patient characteristics			
Median patient age	55	54	55 years
Median tumor size	1.6 cm	n/s (69% < 2 cm)	1.8 cm
% grade 3	28.3%	28.4%	27.5%
% adjuvant systemic tx	97%	96%	90%
% mastectomy	n/a	9%	17%
Results[a]			
Axillary recurrence rate in patients with ALND	0.5%	0.2%	0.43%
Axillary recurrence rate without ALND	0.9%	0.9%	1.19%

[a]Axillary recurrence rate is at median of 6.3 years for ACOSOG Z-0011 trial and 5-year axillary recurrence rate for IBCSG 23-01 and AMAROS trials

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