Surgical Considerations in the Management of Primary Invasive Breast Cancer

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14.1 Introduction

Surgical considerations and standards of care in the management of breast cancer have transformed since the early nineteenth century as advances in the knowledge and treatment of breast cancer have emerged. Although significant progress has been made in the modern treatment of primary breast cancer owing to the integration of breast-conserving surgery, radiation, and systemic treatments, surgery remains a principal cornerstone in overall breast cancer management. The primary aim of this chapter was to highlight the historical background, modern recommendations, and continuing developments in the surgical treatment of primary breast cancer.

14.2 Historical Background

In the nineteenth century, German pathologist Rudolf Virchow (Fig. 14.1) studied the morbid anatomy of breast cancer. He undertook a series of postmortem dissections and postulated that breast cancer spreads along fascial planes and lymphatic channels [1]. Little importance was given to the hematogenous spread of cancer. Virchow's hypothesis influenced the work of the American surgeon, William Halsted (Fig. 14.2). In the late nineteenth century, Halsted described radical mastectomy (MT), which is performed for the treatment of breast cancer [2]. This operation removed the breast, the underlying pectoralis muscles, and the ipsilateral axillary lymph nodes. Thus, in keeping with the postulates of Virchow' s hypothesis, the lymphatic channels connecting the breast and axillary lymph nodes were extirpated *en bloc*. Halsted argued that resection of a node-negative breast cancer was curative, believing that such tumors were extirpated before they spread through the lymphatics. Halsted also maintained that the extent of both the MT and axillary dissection were important determinants of outcome. Therefore, breast cancer recurrence and distant metastases were often attributed to inadequate surgery.

By the early twentieth century, the radical MT had become widely accepted as the standard treatment for breast cancer. The risk of local recurrence was far less with the radical MT than with other contemporary procedures. The radical MT was also credited with improving survival from breast cancer during the early years of the twentieth century [3]. This improvement in survival was probably largely attributable to the effect of lead time bias, rather than to any advancement in surgical technique. Indeed, by the turn of the century, patients were seeking medical attention sooner (with smaller tumors).

One important observation was inconsistent with the Halsted paradigm. About 30 % of node-negative breast cancer patients die of metastatic disease within 10 years after surgery [4]. This finding suggested that the lymphatics are not the only source for the distant spread of cancer. Yet, most surgeons in the early twentieth century were not willing to discard the Halstedian concept that the distant spread of breast cancer occurs solely through the lymphatics. Some proposed that metastatic spread through the internal mammary and supraclavicular lymph node chains might account for distant relapse in women whose axilla were free of nodal involvement [5, 6]. Extirpation of these additional nodal chains failed to improve outcome however, and these more extensive lymphadenectomies were soon abandoned [7, 8].

The radical MT remained the cornerstone for the treatment of breast cancer for about the first three quarters of the twentieth century. Thereafter, the operation lost favor. By the latter half of the twentieth century, many surgeons regarded the radical MT as too debilitating, and several centers reported good outcome with less extensive surgery

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Fig. 14.1 Dr. Rudolph Virchow (courtesy of the national library of medicine archives)

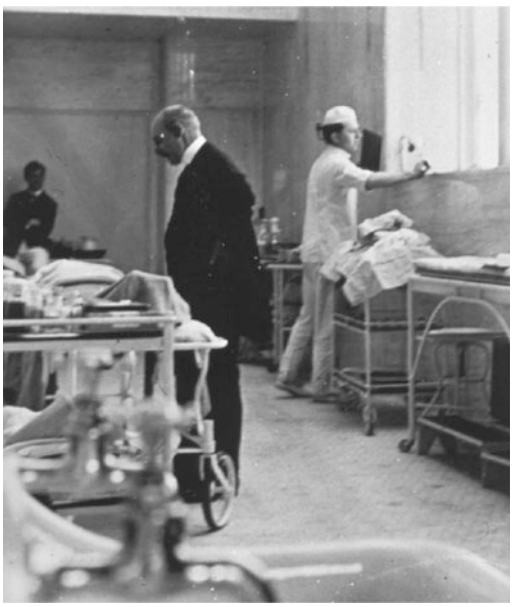

Fig. 14.2 Dr. William Halsted (courtesy of the national library of medicine archives)

[9, 10]. These lesser procedures included the modified radical MT (which spares the pectoralis muscles) and simple excision of the primary breast tumor. The trend toward less radical surgery was attributable to two important factors [11]. Firstly, surgeons during the latter half of the twentieth century were seeing patients with smaller tumors, and these were often amenable to local excision. Secondly, there were improvements in radiotherapy (RT) techniques, enabling tumoricidal doses to be delivered effectively without significant damage to surrounding tissues. Thus, many surgeons developed an interest in breast-conserving surgery (BCS), undertaken in conjunction with breast RT.

Skepticism concerning the merits of the Halsted radical MT surfaced in 1962, when Bloom et al. reported about the survival of 250 patients with primary breast cancer who received no treatment [12]. These patients were diagnosed clinically between the years 1805 and 1933 at the Middlesex Hospital in London, England, and the tissue diagnosis was established at autopsy. The survival rate of these untreated patients was almost identical to Halsted's patients who were treated with the radical MT. This seemed to suggest that surgery contributes little to reducing the risk of death from breast cancer but the impact of surgery 100 years ago might have been quite different from what it is today. Patients in the late nineteenth century generally presented with cancers at an advanced stage. In many instances, distant metastases were perhaps already present, and therefore, surgery might have had little impact on the natural history of the disease. In contrast, patients seen today generally present with early disease. Thus, in the absence of metastases, local therapy alone could cure some patients.

During the last 25 years, the tenets of the Halsted paradigm were put to test in several large, randomized prospective trials. These trials examined the effect of various surgical options in the treatment of breast cancer. None of these trials compared surgical treatment with any treatment, and so the true effect of surgery on breast cancer mortality was never established. The results of these trials suggested, however, that breast-conserving therapy (BCT) (partial removal of the breast in conjunction with RT) was a viable option for most women with breast cancer.

The National Surgical Adjuvant Breast Project-04 (NSABP-04) and King's/Cambridge trials randomized patients with clinically node-negative breast cancer to either early or delayed treatment of the axilla [13, 14]. In the NSABP-04 trial, 1665 clinically node-negative women received either no initial treatment to the axilla or initial treatment with either axillary lymph node dissection (ALND) or RT [13]. About 18 % of patients who received no initial axillary treatment developed axillary adenopathy and subsequently were treated with ALND. Yet, there was no significant difference in breast cancer mortality between patients in the three arms of the trial. In the King's/Cambridge trial, 2243 women with clinically node-negative breast cancer were randomly assigned to either total MT and immediate RT to the axilla or total MT and careful observation of the axilla [14]. In the group assigned to observation, RT was delayed until there was progression or recurrence of the disease in the axilla. No significant difference in breast cancer mortality was found between the two groups, however. The NSABP-04 and King's/Cambridge trials indicated that the

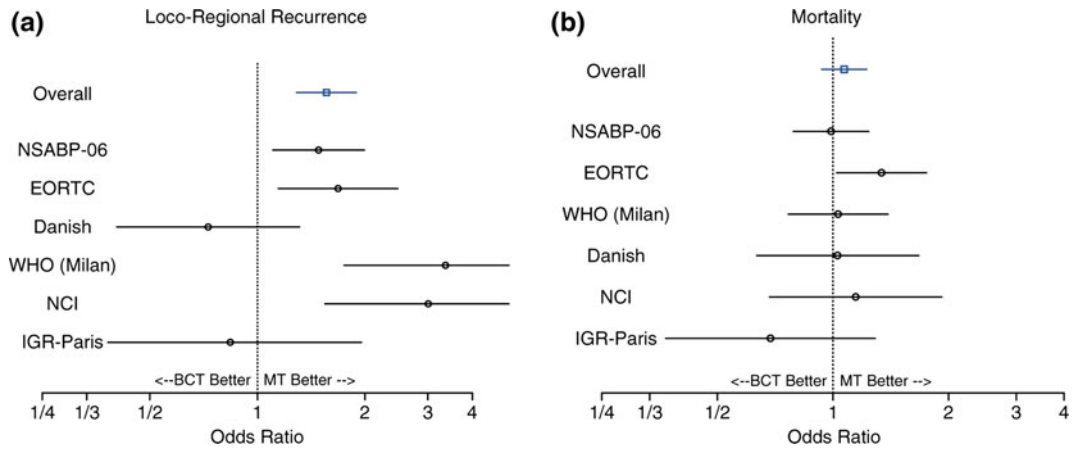

Fig. 14.3 Petograms showing locoregional recurrence (**a**) and mortality (**b**) results with odds ratios and confidence intervals for the six randomized trials comparing breast-conserving therapy (BCT) and mastectomy (MT) for early breast cancer. Reprinted with the permission from Jatoi and Proschan [28]

delayed treatment of the axilla does not adversely affect breast cancer mortality. This finding suggests that the axillary lymph nodes are not a nidus for the further spread of cancer, a finding that is inconsistent with the Halsted hypothesis.

Halsted also proposed that breast cancer is a locally progressive disease. He argued that metastases occurred by the contiguous and centrifugal spread of cancer from the primary tumor in the breast. If this were true, then the extent of the MT should influence survival. During the last 30 years, this hypothesis was tested in six large, randomized prospective trials. These were the Milan I, Institute of Gustave-Roussy (GR), NSABP-06, US National Cancer Institute, European Organization for the Research and Treatment of Cancer (EORTC), and Danish Group trials [15–20] (Fig. 14.3a, b). These trials compared either the radical MT or the modified radical MT with less extensive procedures (variously labeled as segmentectomy, lumpectomy, tylectomy, quadrantectomy, or wide local excision), undertaken in conjunction with an ALND. All these trials showed that the extent of the MT has no impact on breast cancer mortality.

The NSABP-06 was the largest of these six trials [17]. There were 1843 patients randomized to one of three groups: total MT and axillary dissection (modified radical MT), lumpectomy and axillary dissection, or lumpectomy and axillary dissection followed by breast RT. The NSABP-06 found no difference in survival between patients in the three arms of the study; however, the incidence of local breast tumor recurrence in the lumpectomy plus breast radiation group was significantly lower than in the lumpectomy group who received no radiation. Thus, RT is generally used today in conjunction with BCS in the treatment of primary breast cancer.

14.3 Local Recurrences

Local recurrences following total MT may occur on the chest wall; the skin overlying the chest wall; or the axillary, internal mammary, supraclavicular, and infraclavicular lymph nodes [21]. However, women treated with BCS are also at risk for recurrences in the ipsilateral breast [22]. Thus, breast cancer patients treated with BCS have, overall, a greater risk of local recurrence than those treated with total MT. For many years, Fisher argued that ipsilateral breast tumor recurrences following BCS are indicators of distant disease that is already present [23]. He argued that such recurrences were markers for poor prognosis but not the cause of the poor prognosis. Studies have shown that, following BCS, women who develop ipsilateral breast tumor recurrences have greater than a threefold increased risk of developing distant metastases when compared to those who do not develop such recurrences [24]. Also, patients who develop recurrences in the ipsilateral breast within 3–5 years following BCS seem to have a worse prognosis than those who develop such recurrences later [25].

Radiation therapy can reduce the risk of ipsilateral breast tumor recurrences. In the NSABP-06 study, the risk of ipsilateral breast tumor recurrences was about 40 % following lumpectomy and about 10 % following lumpectomy and RT [17]. For patients treated with total MT, the risk of ipsilateral breast tumor recurrences was essentially nil. Ipsilateral breast tumor recurrences are generally treated with salvage MT (total MT), and the 10-year actuarial survival for these patients is about 58 % [21]. In contrast, local recurrences in the chest wall, ipsilateral axilla, or supraclavicular and infraclavicular fossa carry a worse prognosis. More than 90 % of these patients will develop distant metastases, and

most will die of their disease within 10 years after recurrence [26].

What factors influence the risk of ipsilateral breast tumor recurrence following BCS? Several investigators have addressed this question. Borger et al. studied 1026 patients treated at the Netherlands Cancer Institute with BCS and RT [27]. Univariate analysis showed that seven factors were associated with an increased risk of ipsilateral breast tumor recurrence: age, residual tumor at re-excision, histologic tumor type, presence of any components of carcinoma in situ component, vascular invasion, microscopic margin involvement, and whole-breast radiation dose. Only two factors remained independently significant after proportional hazard regression analysis: age and the presence of vascular invasion. Thus, ipsilateral breast tumor recurrence rates were 6 % for patients less than 40 years of age and 8 % for patients with tumors showing vascular invasion at 5 years. In the absence of these factors, the risk of ipsilateral breast tumor recurrence after BCS was only about 1 % at 5 years.

An overview of the six major randomized trials comparing MT versus BCT (BCS + RT) confirmed that there was a substantial increase in the risk of locoregional recurrence associated with BCT, pooled odds ratio 1.561, 95 % CI, 1.289–1.890; $p < 0.001$ [28] (Fig. 14.3a). Yet, in this analysis, there was no significant difference in mortality between the two groups, odds ratio 1.070, 95 % CI, 0.935–1.224; $p > 0.33$ (Fig. 14.3b). However, this meta-analysis may have lacked the statistical power to discern a small but significant effect of local recurrence on breast cancer mortality. Alternatively, competing causes of mortality (heart disease, stroke, etc.) may have obscured a potentially small effect of local recurrence on mortality in this meta-analysis. It should be noted that, in these trials, women were followed closely, and those who developed ipsilateral breast tumor recurrences following BCT were immediately treated with MT (salvage MT).

In recent years, there has been mounting evidence to indicate that local recurrences are indeed associated with an increase in breast cancer mortality. A pooled analysis of 15 trials comparing RT versus no RT after BCS showed that the omission of RT was associated with a threefold increase in ipsilateral breast tumor recurrences and a small (8.6 %) but statistically significant increase in mortality [29]. Also, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported the results of a collaborative meta-analysis of randomized trials of RT and various types of surgery for early breast cancer [30]. Comparisons were made between RT versus no RT, more surgery versus less surgery (with or without RT), and more surgery without RT versus less surgery with RT, etc. These investigators found that the avoidance of local recurrence, either in the conserved breast or elsewhere (chest wall, regional lymph nodes, etc.), was important in reducing breast cancer mortality. Over a 15-year period, one breast cancer death could be prevented for every four local recurrences avoided.

Turner et al. reported that women who carry a *BRCA* mutation (*BRCA1* or *BRCA2*) are more likely to develop ipsilateral breast tumor recurrences following BCS and RT [31]. However, the median time to ipsilateral breast tumor recurrence was 7.8 years for patients with *BRCA1* or *BRCA2* mutations, compared with 4.7 years for patients without such mutations. The longer time to recurrence in the carriers of these mutations suggests that these were second de novo primary tumors. The *BRCA* genes play an important role in DNA repair, and some studies seem to suggest that persons who carry mutations in these genes are extremely sensitive to the effects of RT [32]. Thus, one might speculate that RT administered following BCS may play a role in the development of de novo ipsilateral breast cancers in the carriers of *BRCA* mutations. Pierce and colleagues followed 160 BRCA carriers and 445 matched controls who underwent BCS following a diagnosis of breast cancer. These authors reported that mutation carriers who had not undergone oophorectomy were at increased risk for ipsilateral breast tumor recurrences, while those who had undergone oophorectomy were not [33]. Yet, BRCA mutation carriers also face a high risk of developing breast cancer in the contralateral breast, and many are now opting for contralateral prophylactic MT at the time of initial breast cancer diagnosis. A recent study found that BRCA mutation carriers in North America were more willing to accept contralateral prophylactic mastectomy following a breast cancer diagnosis than were their counterparts in Europe [34]. Large variations in the acceptance of contralateral prophylactic MT were reported, ranging from 0 % in Norway to 49.3 % in the USA.

14.4 Surgical Options

Today, a patient with primary breast cancer might consider three surgical options: modified radical MT, modified radical MT with contralateral prophylactic MT or BCS (Table 14.1). A modified radical MT refers to the removal of the breast and the ipsilateral lymph nodes (the sentinel lymph node is first removed, and if metastatic cancer is evident, then the patient generally undergoes an ALND). If the patient chooses this option, she can often avoid RT (although post-mastectomy RT is recommended for patients with large tumors (>5 cm) and/or extensive lymph node involvement [35]). Patients treated with the modified radical MT should generally be offered breast reconstructive surgery, which is discussed later. Also, some women with unilateral breast cancer might opt for a modified radical MT and a contralateral prophylactic MT (i.e., bilateral MT), particularly if they carry the BRCA 1 or BRCA 2 gene mutations or have anxiety over the possibility of developing a new cancer in the opposite breast.

Table 14.1 Surgical options for primary invasive breast cancer

Modified radical MT	Resection of entire breast
	Sentinel lymph node biopsy (SLNB)/axillary dissection
	Breast reconstruction
	Radiotherapy (RT) sometimes required
Modified radical MT and contralateral prophylactic MT	Resection of both breasts
	SLNB/axillary dissection on side containing the cancer
	Bilateral breast reconstruction
	RT sometimes required
Breast-conserving surgery	Resection of tumor and margin of normal tissue
	SLNB/axillary dissection
	RT generally required

Finally, a patient with unilateral breast cancer may choose to undergo a breast-conserving procedure along with removal of axillary lymph nodes. This is often the preferred option because it results in the best cosmetic and tactile outcome. If a patient elects this option, she will generally require RT to reduce the risk of ipsilateral breast tumor recurrence. However, lumpectomy plus adjuvant endocrine therapy alone (without RT) might be a suitable option for women 70 years of age or older with early estrogen-receptor-positive breast cancer [36].

Various terms are used to describe breast-conserving procedures, including segmental MT, lumpectomy, tylectomy, wide local excision, and quadrantectomy. Essentially, these terms refer to the extirpation of the breast tumor with various margins of normal breast tissue. The terms *segmental MT* and *lumpectomy are* used interchangeably. These terms refer to the resection of the breast tumor with enough surrounding normal tissue to result in microscopically tumor-free surgical margins. By definition, tumor cells may approach to within one cell's breadth of the surgical margin. The term *extended tylectomy* was used at the Guy's Hospital in London to describe resection of the breast tumor plus surrounding breast tissue within 3 cm of the tumor mass [37]. The microscopic status of the surgical margins was not defined. In the *quadrantectomy,* described by Veronesi et al. at the Tumor Institute of Milan, Italy, the entire quadrant of the breast containing the tumor is removed [15]. In the six randomized trials comparing BCT and MT, there was considerable heterogeneity with respect to the risk of ipsilateral breast tumor recurrence, and this was most likely attributable to variations in surgical procedures [28]. For example, in the Milan trial, patients treated with BCT underwent quadrantectomy (excision of the tumor with 2–3-cm margin of normal tissue around it), whereas in the Danish and US National Cancer Institute trials, a simple excision of the tumor (with no gross involvement of the margins) was performed.

After any breast-conserving procedure, RT is generally administered to eliminate occult tumor foci remaining in the ipsilateral breast. RT to the breast can be initiated 10–14 days after surgery. If chemotherapy is also planned, RT is postponed until one or more doses of chemotherapy are administered. RT is discussed in a separate chapter in this book.

Most patients with primary breast cancer are suitable candidates for BCS, but there are a few contraindications [31] (Table 14.2). These are only relative contraindications however, and each patient's circumstances should be examined closely [38]. For example, pregnant patients are generally advised not to undergo BCS because RT carries substantial risk to the fetus. Yet, it is important to remember that several months of chemotherapy are generally given before RT. Thus, if RT is to be administered after delivery, BCS is an acceptable option. Patients who have had previous RT to the breasts are also often advised not to undergo BCS. However, radiation oncologists may wish to consider the previous dose of radiation administered, and some of these patients might be successfully treated with BCS and RT. Additionally, certain coexisting medical problems, such as collagen vascular diseases, may adversely affect the cosmetic results after RT and thereby increase the risk of complications. Collagen vascular disease is an issue only when there is active disease.

Patients with large tumors often are advised to undergo a modified radical MT rather than a breast-conserving procedure [39]. The appropriate tumor size for BCS is poorly defined, however. The various clinical trials used different criteria to recruit patients for BCS. In the Milan trial, BCS was an option only for patients with tumors smaller than 2.5 cm, and those patients underwent excision of the entire quadrant of the breast (quadrantectomy) containing the tumor [15]. In the NSABP-06 trial, patients with tumors smaller than 4 cm were eligible for BCS (lumpectomy), whereas the subsequent NSABP trials accepted patients with

Table 14.2 Factors that may influence surgical option for primary breast cancer (breast-conserving surgery (BCS) vs. MT)

Patient preference	Multi-centricity
Pregnancy	Mutation carriers
Previous RT	
Active collagen vascular disease	
Tumor size in relation to breast size	
Multicentric disease	

tumors as large as 5 cm [17]. An important consideration is the size of the tumor in relation to the size of the breast. Today, in some centers, preoperative chemotherapy is used to decrease the size of large tumors, making BCS feasible for more women [40]. Thus, a patient with a large tumor and a small breast might be a suitable candidate for BCS if she is prepared to receive preoperative chemotherapy.

Some surgeons argue that BCS should be contraindicated if the tumor is close to or involves the nipple–areola complex. Yet, the nipple–areola complex can be easily excised along with the tumor. Although sacrifice of the nipple–areola complex may result in a cosmetic deformity, many women prefer this to losing the entire breast. Thus, the patient's wishes should be considered.

A patient with multicentric cancer (involving more than one quadrant of the breast) is generally not a suitable candidate for BCS. Careful physical examination of the breasts and a preoperative mammogram are helpful in determining the presence of multicentric disease. A patient with a suspicious breast mass should have a mammogram prior to any diagnostic biopsy. Mammograms obtained immediately after a breast biopsy are often difficult to interpret due to post-biopsy changes. Thus, if cancer is confirmed with a biopsy, a post-biopsy mammogram might make it difficult to determine whether a patient is a suitable candidate for a breast-conserving operation.

In recent years, breast magnetic resonance imaging (MRI) has been widely utilized in women with newly diagnosed breast cancers to help determine eligibility for BCT. MRI will occasionally identify additional cancer foci in either the ipsilateral or contralateral breast that are not evident on either clinical examination or mammography [41]. On the basis of MRI findings, MT (and even bilateral MT) might be recommended for patients who otherwise might have been considered suitable candidates for BCT. The use of breast MRI in the initial evaluation of women with primary breast cancer has therefore generated considerable controversy. Many investigators argue that the additional cancer foci detected on MRI might be adequately treated with RT and systemic therapy, and that the use of breast MRI needlessly increases MT rates. A retrospective study from the University of Pennsylvania compared women with early-stage breast cancer who underwent preoperative evaluation with or without breast MRI [42]. In this study, all women underwent BCT, but in some cases the eligibility for BCT was determined by MRI and conventional mammography, while in others it was determined by conventional mammography alone. The authors found that breast MRI at the time of initial diagnosis was not associated with improvements in outcome.

BCS is a more complex treatment than the modified radical MT. The procedure generally requires two separate incisions, one to remove the primary breast tumor and the other to remove the axillary lymph nodes. In addition, patients treated with BCS require postoperative RT. Nattinger et al. analyzed the US National Surveillance, Epidemiology, and End-Results Tumor Registry and found that, with the increased use of BCS, a greater number of patients were receiving inappropriate surgical treatment for primary breast cancer [43]. *Appropriate* surgical therapy was defined as either total MT with ALND (modified radical MT) or BCS with ALND and RT. During the period from 1983 through 1995, the proportion of women undergoing an inappropriate form of modified radical MT remained stable at 2.7 %. During this period, however, the proportion receiving an inappropriate form of BCS (omission of RT or ALND or both) increased from 10 % in 1989 to 19 % at the end of 1995.

Since publication of the results of the NSABP-06 trial, there has been a gradual increase in the use of BCS in the USA. There has also been considerable geographic variation in the acceptance of this procedure, however. Several years ago, Nattinger et al. reported that the frequency of BCS in the various states ranged from 3.5 to 21.2 % [44]. The highest frequency was reported in the mid-Atlantic (20 %) and New England states (17 %), and the lowest in the eastern (5.9 %) and western South-Central states (73 %). A similar geographic variation in the use of BCS was reported in an analysis of patients treated within the US Department of Defense (DoD) Healthcare System [45]. In the DoD system, physicians rotate through various hospitals in the USA and abroad. Yet, geographic variation in the use of BCS persists. Thus, patient preferences in various parts of the USA might differ, resulting in variation in the acceptance of one procedure over another.

In the USA, the use of unilateral MT for women with primary breast cancer declined from about 76.5 % in 1988 to 38 % in 2004, while use of BCS dramatically increased

during this same period [46]. But this study also found that radiation is frequently omitted after BCS, particularly among racial/ethnic minorities and younger and older women. Paradoxically, in the USA, the use of bilateral mastectomies for early-stage unilateral breast cancer has more than doubled between the years 1998 and 2004 [47].

By 1990, 18 states had passed legislation requiring physicians to disclose options for the treatment of breast cancer. Nattinger et al. studied the effect of this legislation on the use of BCS [48]. They found that such legislation has only a small, transient effect on the rate of use of BCS. Dolan et al. reported that medically indigent women treated in public hospitals are less likely to receive BCS when compared with more affluent patients treated in private hospitals [49]. A recent study suggests that when fully informed of the two available options for the treatment of primary breast cancer (BCS or MT), many women will choose MT [50]. Women may choose MT for peace of mind or to avoid RT. Thus, several complex factors, and not insurance coverage alone, appear to be influencing trends in the surgical treatment of primary breast cancer.

14.4.1 Contralateral Prophylactic Mastectomy

Contralateral prophylactic mastectomy (CPM) refers to the surgical removal of the opposite, uninvolved breast in women diagnosed with unilateral breast cancer. A surprising trend toward the increased utilization of CPM began in the USA in the late 1990s (first reported in 2007) and is dramatically increasing worldwide. This trend is paradoxical as it exists in spite of an overall decrease in the risk of contralateral breast cancer development, which can be attributed to the widespread use of adjuvant systemic therapy for early-stage breast cancer. Thus, in recent years, the surgical treatment of breast cancer in the USA seems to be polarizing, with more and more women opting for either BCS or more aggressive surgery (bilateral MT), while use of unilateral MT diminishes.

There are several factors that may be attributed to the increased utilization of CPM. Firstly, there has been wider use of genetic testing for mutations such as BRCA1/BRCA2 that greatly increases the risk for contralateral breast cancer [51]. CPM is often recommended for women who harbor these mutations given the three- to fourfold increased risk for contralateral breast cancer development compared to the average risk patient. Secondly, wider use of preoperative breast MRI has improved the sensitivity of detection of potentially suspicious lesions in the contralateral breast and may thus prompt the decision toward CPM [52]. Recent evidence has supported that women who obtain a preoperative breast MRI are twice as likely to opt for CPM [53]. Additionally, increased use of CPM may be partially attributable to improvements in breast reconstruction techniques with some women opting for bilateral mastectomy with reconstruction over unilateral mastectomy with reconstruction on the premise of achieving better cosmetic symmetry [54]. Lastly, overestimation of the risk of development of contralateral breast cancer by patients themselves may potentially contribute to the recent trend toward CPM, despite the overall decreased rate of contralateral breast cancer development since the implementation of adjuvant systemic therapy (annual risk 0.1 % per year).

The impact of CPM on breast cancer mortality has never been studied in a randomized prospective trial. However, a large number of observational studies have suggested that CPM is associated with reductions in breast cancer specific and all-cause mortality (e.g., death from any cause) in women who are at an increased risk for developing contralateral breast cancer (BRCA1/BRCA2 mutation carriers as well as ER-negative tumors) as well as those with an average risk for the development of contralateral breast cancer (annual risk 0.1 % per year). It is important to note that datasets which form the basis for observational studies often omit important covariates, such as overall health and socioeconomic status/backgrounds, and these studies can therefore produce biased estimates of treatment effects. Close examination of the association between CPM and noncancer mortality, utilizing the 1998-2010 Surveillance, Epidemiology, and End-Results (SEER) dataset [55], confirmed that an association between CPM and reductions in breast cancer specific and all-cause mortality exists but, more importantly, demonstrated an even-stronger association between CPM and reduced noncancer mortality (e.g., death from a cause other than cancer) [56]. The overall stronger association between CPM and noncancer mortality is suggestive of the presence of selection bias in that unmeasured confounders may have contributed to the previously identified associations between CPM and lower breast cancer specific as well as all-cause mortality. Potential confounders that may influence preferential selection for CPM include generally healthier women (better able to tolerate a longer surgical procedure) or women from higher socioeconomic backgrounds.

Thus, the increased utilization of CPM (bilateral mastectomy for the treatment of unilateral breast cancer) is difficult to justify in most cases. CPM might be justifiable in women who harbor mutations (such as the BRCA 1 or BRCA 2) or in women who have previously received mantle radiation, where risk of developing contralateral breast cancer is high, but otherwise CPM should generally be discouraged.

14.4.2 Breast Reconstructive Surgery

For some patients with primary breast cancer, BCS is not a suitable option. As mentioned previously, for some pregnant

patients, those with large or multicentric cancers, patients who have been previously treated with RT to the breast, and those with active collagen vascular disease, BCS might not be suitable. These patients are often advised to undergo modified radical MT (total breast removal and ALND). Most of these patients are good candidates for breast reconstructive surgery, which may be performed either at the time of surgery for primary breast cancer (immediate reconstruction) or later (delayed reconstruction). For several years, there were concerns that immediate reconstructive surgery might mask locoregional recurrences and thereby contribute to a worse outcome [57]. Thus, many investigators recommended delayed reconstruction; however, studies suggest that immediate reconstruction does not adversely affect outcome [58, 59]. Furthermore, immediate reconstruction allows two procedures (the cancer operation and reconstruction) to be performed with the use of one anesthetic and might even be associated with less psychosocial morbidity [60].

Several options are available for breast reconstruction, including the placement of implants or the creation of latissimus dorsi myocutaneous, transverse rectus abdominis myocutaneous (TRAM) and free flaps. Additionally, the deep inferior epigastric artery perforator (DIEP) flap has been gaining popularity in recent years [61]. A detailed review of breast reconstruction is found in a separate chapter in this text and in surgical atlases [62].

Reconstruction with breast implants is used widely [63]. Several methods are now available, including permanent implants, permanent expandable implants, and serial expansion of tissue with an expandable implant followed by implant exchange. Tissue expanders are placed beneath the pectoral muscles and then gradually inflated over several weeks by injecting saline through a subcutaneous port. Once a skin mound is produced that is slightly larger than required, a permanent implant is inserted. Tissue expanders are feasible only for women with small- or medium-sized breasts who have not had prior skin radiation. Both silicone gel and saline implants have been used. There have been concerns that silicone gel implants may result in an increased risk of connective tissue disorders. Indeed, this concern has resulted in considerable litigation and debate [64]. Several studies, however, failed to demonstrate any association between silicone implants and connective tissue disorders [65, 66].

A breast mound can be refashioned using a myocutaneous flap, where skin and muscle from one anatomic region are transferred to the chest wall, with the vascular pedicle remaining attached. The latissimus dorsi myocutaneous flap is quite popular and is suitable for patients with large breasts or who have been previously treated with RT [67]. Thus, it is often used in women who have had RT as part of BCS and who subsequently develop a recurrence requiring salvage MT. Unfortunately, it does not contain sufficient tissue bulk, and so an implant is generally required beneath the flap.

The TRAM has a greater risk of potential complications than does the latissimus dorsi flap [62]. It has several advantages as well however, and is now the most commonly used flap in the USA. The TRAM flap provides sufficient bulk of tissue so that an implant beneath the flap is not necessary. The TRAM flap is useful for patients with a moderate or excessive amount of lower abdominal fat who require additional soft tissue on the chest wall. Thus, it not only provides sufficient tissue for breast reconstruction, but also results in an abdominoplasty.

Finally, a breast mound can be refashioned using free flaps; the free TRAM flap is the most popular [68]. In a free flap, the skin and underlying muscle are detached from their vascular pedicle, and microvascular techniques are used to reestablish the blood supply once the flap is placed on the chest wall. The free TRAM flap has several advantages over the standard TRAM flap. Less rectus abdominis muscle is required, and the medial contour of the breast generally looks better because a tunnel for the vascular pedicle is not required. Surgeons must have special expertise in performing microvascular procedures.

Among women treated with MT, less than 20 % will undergo breast reconstruction [69]. In 1999, the Women's Health and Cancer Rights Act (WHCRA) was implemented, mandating insurance coverage for breast reconstruction after MT, and additional legislation was passed in 2001, imposing penalties on noncompliant insurers [70]. However, this legislation has not significantly increased the overall use of breast reconstruction in the USA or reduced variations across geographic regions and patient subgroups.

14.5 Management of the Axilla

Since the late nineteenth century, breast cancer surgery has been closely linked to surgery of the axilla. Today, axillary surgery remains an integral part of BCS and the modified radical MT. Nonetheless, surgical management of the axilla is a topic of intense controversy. Axillary lymph node metastases are no longer considered a prerequisite for distant metastases. Thus, the impact of axillary surgery on survival, local control, and staging is frequently debated.

ALND refers to the extirpation of lymph nodes in the axilla. The lymph nodes in the axilla are divided into three compartments based on their anatomic relationship to the pectoralis minor muscle [71]. Lymph nodes lateral to the pectoralis minor muscle are classified as level I nodes, those posterior to its lateral and medial borders are classified as level II nodes, and those medial to the muscle are classified as level III nodes. A *complete* ALND refers to the

extirpation of lymph nodes from all three compartments. In contrast, a *partial* ALND refers to the extirpation of lymph nodes only from levels I and II, and axillary sampling indicates only resection of the level I nodes.

Metastases to the axillary lymph nodes generally occur in an orderly fashion. Thus, lymph nodes in level I are generally involved first, followed by involvement of nodes in level II and then level III. *Skip metastases* indicate the involvement of lymph nodes at level II or level III but not level I; these occur rarely. Veronesi et al. studied the distribution of nodal metastases in 539 patients who underwent complete ALND [72]. Level I nodes were involved in 58 % of patients, levels I and II in 22 %, and all three levels in 16 %. In their series, skip metastases were present in only 4 % of cases. Today, most authorities recommend extirpation of lymph nodes from levels I and II (a partial ALND); ten or more nodes are usually removed [73]. A partial ALND correctly stages 96 % of patients with primary breast cancer as either node-positive or node-negative and rarely gives rise to significant lymphedema of the upper extremity. The 4 % false-negative rate associated with a partial ALND is attributable to skip metastases. This false-negative rate can be further reduced with resection of nodes from levels I–III (complete ALND), but this may increase the risk of upper-extremity lymphedema.

The technique of partial ALND is discussed in surgical atlases [62]. Essentially, the procedure involves resection of lymph nodes superiorly to the level of the axillary vein, laterally to the latissimus dorsi muscle and medially to the medial border of the pectoralis minor muscle. Particular attention should be paid to identifying the long thoracic and thoracodorsal nerves. The long thoracic nerve (nerve of Bell) runs along the lateral aspect of the chest wall and supplies the serratus anterior muscle. Injury to this nerve results in a *winged scapula.* The thoracodorsal nerve accompanies the subscapular artery along the posterior aspect of the axilla and supplies the latissimus dorsi muscle.

What impact does ALND have on survival, local control, and staging in patients with primary breast cancer? In recent years, several clinical trials have shed some light on this question. The impact of ALND on the management of patients with primary breast cancer remains a contentious issue.

14.5.1 Survival

For many years, the ALND was considered an important determinant of survival for patients with primary breast cancer. Halsted and his disciples fostered this notion more than 100 years ago, arguing that breast cancer spreads first to the regional lymph nodes and then to distant sites. Subsequently, some investigators provided retrospective data suggesting that the extent of the ALND does influence survival for patients with primary breast cancer. Such data are misleading, because there is no accounting for a *stage migration effect.* Consider, as an example, a patient with a 1.5-cm tumor and one metastatic lymph node to the axilla. Surgeon A may perform an extensive lymph node dissection and remove that node. On the other hand, surgeon B may perform a less extensive lymph node dissection and fail to uncover the metastatic node. Thus, if treated by surgeon A, this patient would be diagnosed as having stage II breast cancer. If treated by surgeon B, the same patient would be diagnosed as having stage I disease. When survival rates are compared for any given stage, it may seem that patients treated by surgeon A do better, but this may be attributable to the stage migration effect rather than any therapeutic benefit of the more extensive lymph node dissection.

The best way to determine whether the ALND has any effect on mortality is to compare treatment with ALND and without ALND in a randomized prospective trial. Such a study has never been conducted, although the results of the NSABP-04 and the King's/Cambridge trials, discussed already, indicate that the delayed treatment of the axilla has no effect on breast cancer mortality [13, 14]. The results of these trials might be interpreted to mean that the axillary lymph nodes are not a nidus for the further spread of cancer. Nonetheless, some investigators argue that the NSABP04 and King's/Cambridge trials did not include sufficient numbers of patients to detect small differences in survival between those randomized to either early or delayed treatment of the axilla [74]. Additionally, meta-analyses of randomized trials seem to suggest that there is a survival benefit associated with ALND, but this benefit might diminish in women who receive adjuvant systemic therapy [30, 75].

14.5.2 Axillary Relapse

Axillary lymph node metastasis is found in 35–40 % of patients with palpable breast cancers [76]. In many instances, nodal involvement is not clinically evident when the patient first presents with primary breast cancer. Indeed, up to 30 % of clinically node-negative patients are shown to have nodal involvement following ALND [77]. In the absence of ALND, many of these patients eventually would develop clinical evidence of nodal involvement. The NSABP-04 and King's/Cambridge trials provide important information on the effect of axillary treatment in clinically node-negative patients. These trials indicate that RT and ALND are equally effective in achieving local control of the axilla. In the NSABP-04 trial, clinically node-negative patients with primary breast cancer received either no treatment to the axilla or treatment with ALND or RT [13]. About 18 % of the patients who received no initial axillary

treatment went on to develop axillary adenopathy within 5 years. In contrast, axillary adenopathy developed in only 2 % of patients whose axilla had been treated. Similar results were reported in the King's/Cambridge trial, where clinically node-negative patients were randomized to receive total MT, and RT to the axilla or total MT and observation of the axilla [14]. Taken together, these studies suggest that treatment of the axilla (with either ALND or RT) will reduce the 5-year risk of axillary relapse by about 90 %.

The importance of axillary treatment on local control is also reported in retrospective studies. Baxter et al. reviewed the records of 112 breast cancer patients who underwent lumpectomy without ALND [78]. When these patients first presented with breast cancer, they had no evidence of axillary lymph node involvement on clinical examination. During the subsequent 10-year period, about 28 % of these patients developed axillary adenopathy. Axillary adenopathy developed in 10 % of patients who presented with tumors 1 cm or less in diameter, in 26 % of those who presented with tumors 1.1–2.0 cm, and in 33 % of those with primary tumors greater than 2.1 cm in diameter.

The extent of the ALND seems to influence the risk of axillary relapse. Graverson et al. reviewed the records of 3128 patients with primary breast cancer who were clinically node-negative at initial presentation [79]. The 5-year risk of axillary relapse ranged from 19 % when no nodes were removed to 3 % when more than five nodes were removed. In the NSABP-04 study, no patient who had more than six nodes removed developed a relapse in the axilla. Thus, an adequate ALND is essential in reducing the risk of relapse in the axilla.

Axillary relapse is generally considered a marker of tumor biology, indicating an increased risk of distant metastasis and death. These relapses are not considered the cause of poor prognosis. Yet, many women are emotionally devastated following axillary relapse. Additionally, axillary relapses can cause significant morbidity. Major vessels and nerves of the axilla sometimes are invaded by the tumor, causing lymphedema or pain. In such instances, the axilla is difficult to manage. Surgical clearance of such axilla often is associated with increased morbidity. Thus, adequate treatment of the axilla at the time of initial diagnosis of primary breast cancer is important.

14.5.3 Staging

For patients with primary breast cancer, clinical assessment of the axilla is notoriously inaccurate. About 30 % of patients with palpable axillary nodes prove to be node-negative following ALND, and about 30 % of clinically node-negative patients prove to have nodal involvement [77]. Thus, the ALND traditionally played a vital role in staging patients with primary breast cancer (as either node-negative or node-positive).

The prognostic significance of nodal metastasis is poorly understood. For many years, physicians assumed that nodal status was simply a chronological variable. Thus, it was argued that node-positive patients fare worse than node-negative patients because their cancers are discovered later in their natural history. However, a study using the San Antonio Tumor registry seemed to suggest that nodal status is also a marker of tumor biology, because nodal status at initial diagnosis was found to also predict outcome after relapse [80]. In that study, patients with four or more involved nodes at initial diagnosis were found to have a significantly worse outcome after relapse compared with node-negative cases. Additionally, node-positive, high-risk tumors (>2 cm, ER-negative, high grade, and node-positive) are more common in younger patients (with a peak age of onset at 50 years), while node-negative, low-risk tumors (<2 cm, ER-positive, low grade, and node-negative) tend to occur later in life (with a peak age of onset at 70 years) [81]. This observation is also consistent with the notion that nodal status is a predictor of tumor biology and not simply tumor chronology.

The importance of ALND as a staging procedure was underscored in a study from the Institute Curie in Paris, France [82]. In that study, 658 breast cancer patients treated with lumpectomy and breast RT were randomly assigned to either ALND or axillary RT. Adjuvant chemotherapy was administered to a few of these patients, and the decision to administer adjuvant therapy was based on nodal status. However, nodal status was not assessed in patients whose axillae were treated with RT, and so none of those patients received adjuvant chemotherapy. There was a small but significantly greater overall 5-year survival rate ($p > 0.014$) in the group treated with ALND (96.6 %) compared with the group treated with axillary RT (92.6 %). Many investigators attribute this small benefit to adjuvant chemotherapy. Therefore, if nodal status will influence the decision to administer adjuvant systemic therapy, the axilla should be managed with ALND and not with RT.

Node-positive patients have a worse prognosis than node-negative patients. Nodal status, however, does not predict response to therapy. Indeed, for both node-negative and node-positive patients, adjuvant systemic therapy reduces the annual odds of relapse and death by approximately 30 and 25 %, respectively [83], although the absolute benefit of adjuvant systemic therapy is greater in node-positive patients because their risk of relapse and death is greater. As an example, consider two groups of breast cancer patients: a node-positive group with a 60 % risk of death from breast cancer over the next 10 years and a node-negative group with a 20 % risk of death. For both groups, the appropriate systemic therapy would reduce the risk of death from breast

cancer by about 25 %. For this node-positive group, however, the absolute benefit would be 15 % (25 % of 60 % is 15 %), whereas for this node-negative group, the absolute benefit would be only 5 % (25 % of 20 % is 5 %). Thus, nodal status provides important information not only about prognosis, but also about the impact of adjuvant systemic therapy. An older woman with a good prognosis, node-negative tumor might be less willing to accept the toxicity of systemic therapy compared with a younger woman with a poor prognosis, node-positive tumor. However, in more recent years, the adjuvant treatment of breast cancer has been increasingly based on tumor predictive factors (ER status and HER2 status), which determine the responsiveness of a particular tumor to a specific treatment [84]. Thus, endocrine therapy (either tamoxifen or aromatase inhibitors) is administered to patients with ER-positive tumors, and Herceptin is administered to patients with HER2-positive tumors.

14.6 Sentinel Lymph Node Biopsy

The ALND is not without risks. The procedure is associated with wound infections and morbidity of the upper extremity. Wound infection rates between 8 and 19 % have been reported, but the reasons for this are poorly understood [85–87]. Some investigators speculate that the high rate of axillary wound infection might be due to the dead space beneath devascularized skin flaps or to an altered local immune response from disruption of local lymphatics. The ALND is also associated with significant morbidity of the upper extremity. In one series, the following upper-extremity complications were reported: paresthesia in 70 % of patients, pain in 33 %, weakness in 25 %, arm lymphedema in 10 %, and stiffness in 10 % [88]. Today, more than half of the patients with primary breast cancer are node-negative. If identified appropriately, these patients could be spared the potential morbidity associated with ALND. In recent years, attention has turned to sentinel lymph node biopsy (SLNB) as a means of achieving this goal.

The sentinel lymph node is the first node to receive lymphatic drainage from a tumor. For any nodal basin, one might assume that if the sentinel lymph node is free of metastatic tumor, then all other nodes in the basin should be free of tumor as well. Alternatively, involvement of the sentinel lymph node may mean that other nodes in the basin are involved. Thus, the SLNB is a diagnostic test that is useful in determining the status of the regional lymph nodes. This technique allows the surgeon to determine the status of the regional lymph nodes and avoid the morbidity associated with a more extensive lymph node dissection. For patients with primary breast cancer, the contraindications to SLNB include the presence of palpable axillary lymph node metastasis and prior breast or axillary surgery that might interfere with lymphatic drainage [89].

The SLNB technique was first described by Cabanas in 1977 as a means of assessing patients with penile carcinoma who might benefit from inguinofemoroiliac dissection [90]. Subsequently, Morton et al. demonstrated the feasibility and accuracy of SLNB for nodal staging in melanoma. [91]. More recently, SLNB has been widely used to stage patients with primary breast cancer, with the goal of reducing the morbidity of ALND [92]. Once identified, the sentinel node is excised and sent for histopathologic evaluation. Several studies have shown that the SLNB is quite accurate in predicting the status of the axillary lymph nodes [93, 94]. Surgeons can identify the first draining (sentinel) lymph node by injecting blue dye or radioactive colloid intradermally around the primary tumor. Subareolar injection appears to be as accurate as peri-tumoral injection [95]. In fact, for nonpalpable, mammographically detected cancers, subareolar injection might be preferable. There has also been debate as to whether injection with radioactive colloid and blue dye is more accurate than injection with blue dye alone as a means of identifying the sentinel node. Morrow et al. compared the two methods in a randomized trial and found that they were equally effective [96]. Thus, the preferences of the surgeon determine which method is used.

Giuliano et al. compared 134 patients with primary breast cancer who received standard ALND with 164 patients who underwent SLNB followed by completion ALND [97]. The reported incidences of nodal metastasis were 29 and 42 %. Thus, the reported incidence of node-positive cases is greater with SLNB than with standard ALND. Following ALND, one or two sections of each nonsentinel lymph node are generally examined with routine hematoxylin and eosin (H and E) staining; however, pathologists pay more attention to the sentinel lymph node. These nodes often are evaluated with multiple sectioning, H and E staining and immunohistochemical staining for cytokeratin. Thus, the SLNB results in a focused histopathologic evaluation of a single lymph node, and the probability of identifying micrometastases is thereby increased.

The false-negative rate of SLNB might be as high as 10 %, compared with 4 % following a level I and II ALND [98]. The false-negative rate refers to the percentage of patients with nodal metastases who are incorrectly designated as node-negative. False-negatives may lead to incorrect decisions concerning adjuvant therapy, thereby affecting outcome. These and other concerns about SLNB will be addressed in ongoing trials comparing long-term outcome following SLNB or ALND. However, randomized trials have now shown that SLNB can significantly reduce the morbidity associated with ALND [99–101]. SLNB has therefore been widely accepted now in the management of early breast cancer.

14.6.1 Sentinel Lymph Node Biopsy Versus Axillary Lymph Node Dissection

SLNB has now become an integral part of the conservative treatment of early breast cancer. Multiple published single institutional, multi-institutional, and prospective randomized controlled studies have exhibited the safety of omitting ALND in women who are identified to have a negative SLNB (free of metastatic disease). The gold standard for achievement of locoregional control in those patients who are identified to have metastatic disease on SLNB has, until recently, been completion ALND. However, in approximately 40–60 % of patients with clinically node-negative disease, the sentinel node is identified as the only involved node [102]. Consequently, ALND may be viewed as overtreatment in a large majority of clinically node-negative patients, particularly when taking into account potential long-term complications of lymphedema, pain, and reduced upper-extremity mobility.

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial examined the effect on local–regional control in patients with early-stage breast cancer and positive SLNB who received completion ALND versus no further axillary treatment [103]. In the study, 856 patients with T1 or T2 N0 M0 disease treated with SLNB and lumpectomy were randomized to undergo completion ALND or no further axillary surgery after identification of sentinel node-positive metastatic disease. Women with clinically positive nodal disease (palpable lymphadenopathy), matted notes, or gross extranodal disease were excluded from the study as were patients identified to have a high tumor burden (3 or more positive sentinel nodes) on SLNB. Only 1.8 % of the patients who received SLNB alone (no further axillary surgery) were identified to have local recurrence at a medial follow-up of 6.3 years, compared with 3.6 % on the group that received standard completion ALND ($P = 0.11$). Regional recurrences were further noted to be similar between the two groups with 0.9 % in the group that underwent SLNB with no further axillary surgery and 0.5 % in the ALND group ($P = 0.45$). No significant difference in the locoregional recurrence free survival rate was noted between the two groups. The ACOSOG Z0011 study thus showed that SLNB without completion ALND in patients with early-stage breast cancer treated with breast-conserving therapy, whole-breast irradiation, as well as adjuvant systemic therapy can offer excellent locoregional control.

With the development of sentinel lymph node biopsy came more comprehensive methods of evaluating the sentinel lymph node for disease. Tumor-involved sentinel nodes can now be further classified into those with macrometastasis (>2 mm in diameter), micrometastasis (≥0.2–2 mm in diameter), and isolated tumor cells (ITCs) (<0.2 mm in diameter) [104]. Although the overall prognostic/clinical significance of micrometastasis and ITCs remains uncertain, completion ALND for patients with such low sentinel node tumor burdens is a controversial topic. Wherein the ACOSOG Z0011 trial evaluated SLNB in patients with macrometastasis, the International Breast Cancer Study Group (IBCSG) Trial 23-01 sought to compare outcomes in randomized patients with sentinel node micrometastasis and ITCs who received standard completion ALND versus no further treatment [105]. The study evaluated 931 clinically node-negative women with a primary breast tumor of <5 cm in maximum diameter who were found to have one or more micrometastatic (≥0.2–2 mm) foci in the sentinel node, without macrometastatic disease. The 5-year disease-free survival rate was noted to be 84.4 % (95 % CI, 80.7–88.1 %) for those patients who underwent ALND and 87.8 % (95 % CI, 84.4–91.2 %) for those who had no further axillary treatment. Additionally, the reported 5-year overall survival rate was 97.6 % (95 % CI, 96.0–99.2 %) for the ALND group and 97.5 % (95 % CI, 95.8–99.1 %) for the SLNB only (no further axillary treatment) group. No significant difference in either disease-free survival or overall survival was noted between the two groups. The study further demonstrated a low <1 % rate of regional recurrence in the group randomized to receive no further axillary treatment.

The AATRM trial additionally evaluated the notion that SLNB and close clinical follow-up alone can be safely utilized in women with early-stage breast cancer identified to have sentinel micrometastasis, specifically [106]. The prospective clinical trial randomized 233 women with newly diagnosed early-stage breast cancer (primary tumor <3.5 cm, N0, M0) who were identified to have micrometastic foci on SLNB to receive standard completion ALND versus clinical follow-up (no further axillary treatment). A total of four patients were identified to have disease recurrence over a 5-year period: 1 of 108 (1 %) women randomized to the ALND group and 3 of 119 women in the group that received SLNB and no further axillary treatment. In accordance with the results of the IBCSG 23-01 trial, no significant difference in disease-free survival was identified between the two groups ($P = 0.325$).

Conclusively, the IBCSG 23-01 and AATRM trials provided further evidence to support the recent ACOGSOG Z0011 findings that SLNB alone is safe in clinically node-negative patients with early-stage breast cancer and a low burden of positive sentinel node metastasis, provided they receive traditional whole-breast irradiation and systemic adjuvant treatment. Collectively, the ACOSOG Z0011, IBCSG 23-01, AATRM, and AMAROS (discussed below) trials have lead to a change in the clinical management of early-stage breast cancer patients with positive SNLB.

While the American Society of Clinical Oncology has recommended that ALND can be safely avoided in patients with 1–2 sentinel node macrometastases provided they undergo conventional whole-breast irradiation following breast-conserving surgery, based on the results of the Z0011 trial, other professional societies have criticized the study secondary to its lack of generalizability and lack of radiation therapy quality assurance. Specifically, the results of the Z0011 study are not applicable to mastectomy patients. An ongoing randomized, multi-center, noninferiority trial known as the UK–Austria New Zealand (UK-ANZ) "POsitive Sentinel NOde: Adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy" trial (POSNOC) seeks to specifically address the limitations of the Z0011 study by evaluating patients undergoing both breast-conserving surgery and mastectomy [107]. One thousand nine hundred participants with uni-focal or multi-focal invasive breast cancer (primary lesion ≤5 cm) identified to have 1–2 positive sentinel nodes with macrometastases will be randomized to receive either adjuvant systemic therapy alone (chemotherapy and/or endocrine therapy; no further axillary specific treatment) versus adjuvant therapy plus ALND or axillary radiotherapy. The POSNOC trial will additionally include a radiotherapy quality assurance program. The primary designated end-point of the study is axillary recurrence at 5 years with secondary end-points including arm morbidity, quality of life, locoregional recurrence, and survival/economic evaluation. The results of the study will hopefully provide further evidence to clarify the safety and generalizability of the Z0011 study results.

14.6.2 Radiotherapy of the Axilla

Evidence from the NSABP-04 trial revealed that radiotherapy of the axilla has an equivalent rate (4 %) of axillary recurrence in comparison with ALND; however, this primary aim of this study, as previously discussed, was to evaluate early versus delayed treatment of the axilla. The multicenter, phase 3 noninferiority EORTC 10981-22023 AMAROS (After Mapping of the Axilla Radiotherapy or Surgery) trial sought to further evaluate the efficacy of axillary radiotherapy in comparison with ALND in achieving regional control by randomizing clinically node-negative patients with T1-2 breast cancer and a positive SNLB to either axillary lymph node dissection or axillary radiotherapy [108]. The results of study revealed a noninferior five-year axillary recurrence rate in the axillary RT group (1.19 %; 95 % CI, 0.31–2.08 %) in comparison with that in the ALND group (0.43 %; 95 % CI, 0.00–0.92 %). No significant difference in disease-free survival and overall survival between the two treatment groups was noted. The study thus demonstrated that for women with early-stage breast cancer and a clinically node-negative axilla who are recommended to undergo further axillary treatment (based on tumor size, grade, vascular invasion, and/or extra-capsular extension of tumor cells), axillary RT can be offered over ALND as it provides comparable regional control with considerably less morbidity secondary to development of lymphedema (Table 14.3).

14.6.3 Axillary Surgery in the Neo-Adjuvant Chemotherapy Setting

Neo-adjuvant chemotherapy is increasingly utilized for the treatment of early-stage breast cancer as it often allows for downstaging of the primary tumor and thus increases the likelihood of breast-conserving surgery. Among patients who present with clinical node-positive disease and receive neo-adjuvant chemotherapy, only 50–60 % are found to have residual axillary nodal disease. While sentinel lymph node biopsy has been established as a reliable means for staging the axilla while offering considerably less morbidity than axillary lymph node dissection, ideal timing for performance of SLNB for patients treated with neo-adjuvant chemotherapy is controversial. The prospective, multicenter cohort

Table 14.3 Studies evaluating sentinel lymph node biopsy

Trial	Number of patients	Design	Sentinel node metastases evaluated
ACOSOG Z0011	856	Sentinel node-positive: randomized to ALND versus not	Micrometastasis, macrometastasis
AMAROS	1425	Sentinel node-positive: randomized to ALND versus axillary radiotherapy	Micrometastasis, macrometastasis
AATRM	233	Sentinel node-positive: randomized to ALND versus not	Micrometastasis
IBCSG 23-01	931	Sentinel node-positive: randomized to ALND versus not	Micrometastasis, ITCs
POSNOC	1900 planned	Sentinel node-positive: randomized to adjuvant systemic therapy alone versus adjuvant systemic therapy + axillary treatment (either ALND or radiotherapy)	Macrometastasis

"SENTinel Neo-Adjuvant" (SENTINA) study sought to evaluate the false-negative rate of SLNB after administration of neo-adjuvant chemotherapy in clinically node-positive women as well as clinically node-negative women with positive sentinel nodes [109]. The study allocated patients into four treatment arms: Arm A consisted of patients with clinically node-negative disease who were found to have a negative SLNB prior to neo-adjuvant chemotherapy and received no further axillary treatment; arm B consisted of clinically node-negative patients identified to have a positive sentinel node before administration of neo-adjuvant chemotherapy who subsequently underwent a second SLNB after completing neo-adjuvant chemotherapy; arm C consisted of clinically node-positive (N1 or N2) patients who converted to a clinically negative axilla after neo-adjuvant chemotherapy and underwent both a SLNB and an ALND; and arm D consisted of node-positive patients who remained node-positive after neo-adjuvant chemotherapy and thus underwent gold-standard completion ALND. The sentinel lymph node detection rate was noted to be 99.1 % (95 % CI, 98.3–99.6 %) in clinically node-negative women who underwent SLNB before neo-adjuvant chemotherapy (arms A and B), whereas the detection rate was significantly lower at 80.1 % (95 % CI, 76.6–83.2 %) in patients who underwent SLNB after neo-adjuvant chemotherapy. Additionally, no more than two-thirds of sentinel nodes [detection rate 60.8 % (95 % CI, 55.6–65.9 %; 219 of 360)] were successfully detected in patients who underwent a second SLNB after neo-adjuvant chemotherapy (arm B). The false-negative rate was noted to be 14.2 % (95 % CI, 9.9–19.4 %) for patients who converted from a clinically node-positive to a clinically node-negative axilla after neo-adjuvant chemotherapy (arm C).

The ACOSOG Z1071 (Alliance) trial further sought to evaluate whether SLNB could be utilized for axillary staging following neo-adjuvant chemotherapy in women with initial node-positive cancer by determining its false-negative rate (FNR) [110]. The acceptable FNR has consistently been accepted as ≤10 %, based on the established rate for women with clinically node-negative disease undergoing SLNB. Seven hundred and one women with N1 or N2 disease were enrolled in the study and underwent both SLNB and ALND after completion of neo-adjuvant chemotherapy. A complete nodal pathologic complete response (pCR) rate of 41 % (95 % CI, 36.7–45.3 %) was identified. In concordance with findings from the SENTINA trial, the phase two clinical study demonstrated a FNR of 12.6 % (90 % Bayesian credible interval, 9.85–16.05 %) in women with cN1 disease who had at least 2 or more sentinel nodes examined, suggesting that SLNB cannot reliably detect the presence of all axillary lymph node metastasis following chemotherapy administration. One might speculate that the decreased accuracy of SLNB after chemotherapy may be attributed to increased fibrosis, which in turn disrupts lymphatic drainage and makes radiotracer update/surgical dissection more difficult. Alternatively, one might speculate that tumor cells in the sentinel nodes are preferentially ablated following neo-adjuvant chemotherapy, leaving disease in other nodes intact. Notably, the ACOSOG study additionally identified that the FNR was significantly lower when three or more sentinel nodes were evaluated (FNR 9.1 % (95 % CI, 5.6–13.7 %) for ≥3 SLNs versus 21.1 % (95 %, 13.2–31.0 %) for 2 SNLs) and when a combination of blue dye and radiolabeled colloid was utilized (FNR 10.8 %; 95 % CI, 7.2–15.3 %) with combination agents versus 20.3 % (95 % CI, 11.0–32.8 %; $P = 0.05$) with a single agent).

The prospective, multi-centric "Sentinel Node Biopsy Following Neo-adjuvant Chemotherapy" (SN FNAC) study also evaluated the accuracy of SLNB after chemotherapy in patients who presented with biopsy-proven node-positive breast cancer [111]. In this particular study, sentinel nodes were evaluated with standard hematoxylin and eosin staining, and if determined to be negative, further evaluation using immunohistochemistry was mandatory. In comparison with the ACOSOG Z1071 study wherein only sentinel nodes with metastasis >0.2 mm were considered positive, sentinel node metastases of any size were considered positive in the SN FNAC study. By mandating more sensitive pathologic analysis via immunohistochemistry and by including metastases of any size, the study reported an acceptable FNR of 8.4 % (95 % CI, 2.4–14.4 %) for SNLB after neo-adjuvant chemotherapy. A notable limitation of the study, however, is the relatively small sample size (153 patients).

The SENTINA, ACOSOG Z1071, and SN FNAC studies collectively suggest that for clinically node-positive patients undergoing neo-adjuvant chemotherapy greater sensitivity in patient selection and sentinel node evaluation may lower the FNR. An acceptable FNR ≤ 10 % would ultimately be necessary to support use of SLNB as an alternative to ALND in patients with early stage, clinically node-positive breast cancer who receive neo-adjuvant chemotherapy.

14.7 Conclusion

The modern surgical treatment of primary breast cancer dates back to the late nineteenth century, with Halsted's description of the radical MT. However, the radical MT is now rarely utilized in breast cancer management. Today, BCS with RT is the preferred option for most women with primary breast cancer. For those who are not suitable candidates for BCS, the modified radical MT is an acceptable alternative, and in recent years, greater numbers of women have been opting for modified radical MT and a contralateral prophylactic MT (i.e., bilateral MT). However, there is very

little justification for use of bilateral mastectomy for the treatment of unilateral breast cancer, unless the patient is a mutation carrier or has a history of mantle irradiation, and in both these situations, the risk of contralateral breast cancer is dramatically increased. Patients treated with the modified radical MT or bilateral MT will generally seek breast reconstructive surgery. It should also be noted that it now appears that local recurrences may increase the risk of death from breast cancer, with four local recurrences resulting in one additional breast cancer death over a 15-year period. Thus, RT should be considered for most women who opt for BCS. Over the years, the management of the axilla has been a topic of considerable interest. Today, SLNB is considered the preferred alternative to the standard ALND. Several recently published randomized studies have provided additional evidence that SLNB alone is a safe alternative to completion ALND in women with early-stage breast cancer who have a low burden of axillary disease, particularly if these patients will be receiving adjuvant radiotherapy and adjuvant systemic therapy.

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