Locoregional therapy of breast cancer: maximizing control, minimizing morbidity

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The goal of locoregional therapy in breast cancer has remain unchanged for a century: the eradication of all malignant cells from the breast and draining lymph nodes, hopefully prior to them having spread to distant organs. However, how we accomplish this goal has changed dramatically over this time period and our success in achieving this goal has been greatly enhanced by improvements in breast imaging and systemic therapies. The therapeutic importance of surgery and radiation has been underestimated in recent years and thought to have minimal impact on long-term outcome. More recent data have reputed this contention and the relationship between local control and survival in breast cancer is becoming increasingly apparent. This article will review the importance of attaining optimum local control with minimum morbidity and examine where the future of locoregional therapy of breast cancer may lie.

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For all the changes in breast cancer management, the paradigm of locoregional therapy for breast cancer is the same today as it was when Halsted described the radical mastectomy over 100 years ago [1]. Halsted's theory, although much maligned today, hinged upon the idea that there exists a population of breast cancer patients with disease in their breasts, which may have already spread to the lymph nodes, but has not yet metastasized elsewhere and for whom surgery will be curative. While Halsted was wrong in his assertion that the cancer progressed systematically from the breast to the nodes and then distally, what ultimately doomed his theory was his underestimation of the extent to which breast cancer had already metastasized and was beyond surgical cure at the time of diagnosis. Thus, the radical mastectomy, while dramatically affecting local recurrence rates, had no impact on overall survival [2].

When it was demonstrated that equivalent outcomes could be obtained with less drastic surgery, despite increased local recurrence rates [3], the paradigm changed. Breast cancer was thought of as a systemic disease from its inception, and the management of the disease in the breast and regional nodes would have minimal impact on the survival of the patient. While this helped usher in the increased use of systemic therapies and the dramatic impact they have had on breast cancer mortality, this paradigm was also slightly flawed. It failed to fully appreciate the temporal relationship between the primary cancer and the likelihood of distant disease, thereby diminishing the importance of screening, early detection and local therapy. It also downplayed the impact that local-regional control could have on overall survival. However, more recent evidence demonstrates how important local control is on long-term survival.

As surgeons, our goals today are essentially the same one that Halsted espoused; the eradication of all malignant cells from the breast and draining lymph nodes, hopefully at a time point prior to them having spread elsewhere. This possibility is more likely than during Halsted's era, given the smaller size at which breast cancers can be detected. In addition, there are effective systemic therapies to cure an additional subset of patients beyond the reach of surgery alone. However, the therapeutic importance of surgery and radiation should

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not be underestimated and, while the goal of therapy may be the same today as it was a century ago, the morbidity needed to achieve that goal has changed dramatically.

Local therapy of breast cancer: surgery

Breast conservation versus mastectomy

The evolution of breast cancer surgery through the radical, extended radical and modified radical mastectomies, has been well described, as have the randomized trials (now >20 years old) that established the equivalent survival of breast conservation therapy (BCT) [4–10]. In addition to the randomized data, a quarter century of experience has clearly demonstrated the appropriateness of lumpectomy and whole-breast irradiation. Today, the discussion must focus on the optimum use of BCT, as well as methods for improving both the applicability and cosmetic outcome of BCT, without compromising the results.

Despite the overwhelming evidence in favor of BCT for appropriate patients, there still exists wide variability in its application [11–17]. Some patients are not appropriate candidates for lumpectomy and some women, while technically candidates for BCT, will be better served by a mastectomy. Simply because a lumpectomy can be performed does not mean that the cosmetic result obtained will be satisfactory, or superior to that obtained with a mastectomy and reconstruction. This is particularly true with the advent of skin-sparing mastectomy and improvements in autologous flaps [18–21]. Nonetheless, many women for whom BCT would provide both excellent control and cosmetics are still undergoing mastectomies.

The reasons for this are multifactorial [22]. Part of this rests with physicians [23]. Many doctors recommend mastectomy if they estimate the 5–10-year risk of in-breast recurrence to be greater than 10–15%, thus women with higher risk lesions are more likely to undergo mastectomy. However, many physicians overestimate the risk of local recurrence based on these features and do not appreciate that the risk of local recurrence among these patients is elevated for both BCT and mastectomy.

Conversely, part of the underutilization of BCT is related to patient preference. In some cases, the physician may not clearly communicate to the patient the equivalence of the procedures or the differences between a local recurrence and a distant recurrence. However, armed with the appropriate information, it is not unreasonable for a patient to choose mastectomy. For any individual patient, the desire to avoid a second operation in the future or the time commitment and side effects of radiation therapy may outweigh their perceptions of the cosmetic or psychosocial implications of mastectomy.

Several studies have examined the intricacies involved in how patients choose between BCT and mastectomy, and much of this involves the perceived decision-making process between surgeon and patient [22,24–27]. It is therefore incumbent upon physicians to correctly exclude those patients for whom breast conservation is contraindicated, accurately communicate the relative advantages and disadvantages of the two approaches and then guide the patient through the decision-making process (including the involvement of plastic surgeons, radiation oncologists, social workers and/or therapists if necessary).

Contraindications to breast conservation

Not all patients are suitable candidates for breast conservation [28]. Before any patient is considered for breast conservation, they must satisfy three criteria. The first is the ability to achieve adequate negative margins around the cancer. The second is the ability to undergo breast irradiation; and the third is the likelihood of achieving a cosmetically acceptable result after surgery and radiation therapy. This third criterion is somewhat more subjective, as some patients with significant defects or volume loss may still find the end result more cosmetically appealing than a mastectomy with reconstruction.

Patients who have undergone prior chest wall irradiation should not undergo a second dose of radiation and, therefore should undergo mastectomy rather than lumpectomy. The most common example is the patient who was previously treated by breast conservation and now has a second primary tumor in the ipsilateral breast (or a local recurrence). Another example is the woman treated with irradiation for Hodgkin's disease. A second group of patients who can not undergo radiation therapy are patients with collagen-vascular disease, particularly scleroderma. These patients may experience excessive radiation toxicity and should avoid BCT [29–31]. Patients in their first or second trimester of pregnancy also cannot receive radiation, as there is no way to adequately protect the fetus. Women in their third trimester may undergo lumpectomy and defer the radiation until after delivery. In some cases, where adjuvant chemotherapy is indicated, patients in their second trimester may consider lumpectomy followed by adjuvant chemotherapy, with the radiation delivered after delivery.

If the surgeon is unable to obtain negative margins around the cancer, then mastectomy is indicated. How many attempts at re-excision is up to the surgeon and the patient, and depends upon her motivation for breast preservation, the likelihood of obtaining negative margins and how much volume loss the breast can accommodate. Multifocal disease is not a contraindication to breast conservation, assuming negative margins can be obtained. However, multicentric disease, defined as tumors in separate quadrants of the breast, is an indication for mastectomy. Even if two lumpectomies could be performed, there is likely microscopic disease elsewhere in the breast and recurrence rates are excessively high [32–34]. If multiple tumors are in close proximity and can be encompassed in one margin-negative lumpectomy specimen, this is also acceptable for BCT [35].

Not contraindications to breast-conserving therapy

Many physicians incorrectly include other factors that have been associated with a heightened anxiety about the risk of recurrence, but in fact are not contraindications to BCT. Several features of the primary tumor, such as multifocality, an extensive intraductal component (EIC) and histologies, such as lobular carcinoma, are associated with tumors that extend farther than

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anticipated on preoperative imaging studies and may require wider margins of excision to achieve negative margins. Often, a re-excision lumpectomy is necessary for a close or positive margin. In some cases, this will tilt things in favor of mastectomy if the resultant larger cavity would not be cosmetically acceptable. However, these features in themselves are not contraindications as long as negative margins are obtained.

A common misconception is that axillary nodal metastases, since they are associated with an increased risk of local recurrence, are an indication for mastectomy. This is not true, as the presence of nodal metastases also increases the risk of chest wall recurrence after mastectomy. In addition, the increased likelihood of distant metastases in node-positive women decreases the relative impact that local control will have on survival. Thus, there is very little reason why women with nodal involvement can not undergo breast conservation.

Older women more commonly undergo mastectomy, partially due to patient preference, but partially due to physician recommendations [22,36]. Age is not a contraindication to breast conservation. This is true for both older women, whose suitability for surgery or radiation should be based on their physiological age and comorbidities, and younger women. While increased rates of local recurrence have been described in younger women [37,38], the increased local recurrence rates are often secondary to surgeon reluctance to take appropriate margins for fear of disturbing the cosmetic result [39]. If negative margins can be obtained with an acceptable cosmetic result, young age itself should not prompt a recommendation of mastectomy.

Finally, there is the issue of a strong family history of breast cancer or a known *BRCA1* or *BRCA2* mutation. Women with a family history of breast or ovarian cancer should be informed of their risk of a second primary cancer and considered for genetic counseling and genetic testing, as this may ultimately help them decide whether bilateral mastectomy is warranted. However, if they opt not to proceed with bilateral mastectomy for treatment and prophylaxis, they do not require unilateral mastectomy instead of BCT to control their existing disease [40,41].

Increasing candidacy for BCT with neoadjuvant chemotherapy

One of the more common reasons a woman is not considered a candidate for BCT is the size of her tumor relative to the size of her breast. Breast conservation is hardly justified if the cosmetic result is undesirable owing to an unacceptably large defect or volume discrepancy. However, the size of the tumor is not an absolute contraindication to BCT. The delivery of systemic therapy prior to surgical intervention (neoadjvuant therapy) may decrease the size of the primary tumor. This allows for the potential resection of an inoperable cancer, or the use of BCT in a case where a mastectomy would have been indicated [42].

Using systemic therapy upfront is considered the standard treatment for patients who present with inoperable breast cancer. This includes patients with locally advanced tumors (T4 tumors), inflammatory breast cancer and patients with involvement of the supra or infraclavicular lymph nodes (N3). The success of primary systemic therapy in locally advanced breast cancer led to the suspicion that it may be preferable in operable breast cancer; that delivery of chemotherapy before surgery may increase survival by treating the occult micrometastases at an earlier time point. However, the large randomized trials of preoperative chemotherapy demonstrated equivalent disease-free and overall survival. The trials did demonstrate, however, that there was a higher rate of breast-conserving surgery in the patients who received neoadjuvant chemotherapy (TABLE 1).

Are local recurrence rates comparable after downstaging a tumor with chemotherapy? Of the major randomized studies of neoadjuvant chemotherapy, local recurrence rates have been either equivalent or higher in the preoperative chemotherapy arms, but within acceptable limits. Local recurrence rates varied between 3 and 27%, depending upon the duration of follow-up, type of surgery and margins obtained. The largest study, National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18, which involved over 1500 women with stages I through IIIA breast cancer, demonstrated a statistically significant increase in breast conservation (68 vs 60%), but with a median follow-up of 72 months, there was no statistically significant difference in local recurrence following BCT (7.9 vs 5.8%) [43]. However, this includes those patients who were candidates for lumpectomy before they received their chemotherapy. Looking at just those patients who would have required mastectomy, but were downstaged to become eligible for BCT, the rate of local recurrence was 16% compared with the 10% of patients who were considered candidates for BCT before chemotherapy. One must keep in mind, however, that most of these were T3 tumors and would have had an increased rate of chest wall recurrence had mastectomy been performed.

There are many additional advantages to neoadjuvant chemotherapy, such as the early initiation of systemic therapy, the evaluation of an individual's response to chemotherapy (possibly allowing for a change in therapy if the patient is not responding), and delaying surgery so that patients may deal

Table 1. Impact of neoadjuvant chemotherapy on breast conservation, data from selected randomized trials.

Study	N	Tumor size/stage	BCT rate		Ref.
			Neoadjuvant	Adjuvant	
Institute Bergonie	272	T > 3cm	63.1%	0%	[193,194]
Royal Mardsen	309	I–IIIB	89%	78%	[195]
Institute Curie	414	IIA–IIIA	82%	77%	[196]
EORTC	698	I–IIA	37%	21%	[197]
NSABP B-18	1523	I–IIIA	68%	60%	[43]

BCT: Breast conserving therapy; EORTC: European Organization for Research and Treatment of Cancer; N: Number of patients; NSABP: National Surgical Adjuvant Breast and Bowel Project.

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with issues related to the extent of surgery and reconstructive options. In addition, clinical trials in the neoadjuvant setting have facilitated the discovery of new chemotherapeutic agents. However, it should be remembered that for the patient with operable breast cancer, the primary indication for neoadjuvant chemotherapy is downstaging the primary tumor in patients who desire breast conservation. Delivering the chemotherapy preoperatively is an alternative to adjuvant chemotherapy. The determinant for the use of chemotherapy is the risk of distant recurrence, so neoadjuvant chemotherapy should only be offered to patients who, based on clinical staging (e.g., tumor size, grade, estrogen receptor [ER]/progesterone receptor [PR] status and palpable lymph nodes), would be candidates for chemotherapy.

The future: in situ *ablation*

While chemotherapy can expand the range of BCT to women with large primary tumors, that patient is becoming increasingly rare. Today, with increased screening and more sensitive imaging, a greater percentage of patients are being diagnosed with small tumors, often less than 1.0 cm [44]. As systemic therapies become more effective and their use in the neoadjuvant setting expands, another subset of women will have their primary tumors significantly downstaged. While a lumpectomy followed by radiation therapy is a significant esthetic improvement over a mastectomy, it is still an invasive procedure resulting in a scar and often a cosmetic defect in the breast.

As we expand our abilities in image-guided biopsies, a similar enthusiasm exists for image-guided treatment. There is intense interest in the possibility of ablating small cancers within the breast, without the need for surgery. In addition to greatly improving cosmetic outcomes, this could reduce the demands for operating-room time, decrease recovery time and complications, and lessen healthcare costs. Several methods of tissue ablation have been used for other cancers and are being investigated as a treatment for breast cancer.

Cryoablation, which destroys tumors by freezing tissue below -160°C, has attracted considerable attention. With ultrasound guidance, a cryoprobe can be inserted through a tiny incision in the breast and placed directly into the center of the tumor. Liquid nitrogen or argon gas flows through the cryoprobe, freezing the tip and generating an iceball around the tumor and surrounding tissue. This can be monitored with ultrasound to ensure the cancer is completely encompassed and prevent damage to the overlying skin. Cryoablation has been approved for the treatment of benign fibroadenomas [45] and cryo-assisted lumpectomy is being examined as a method of excising nonpalpable lesions [46]. Cryoablation alone may also someday replace lumpectomy for patients with small primary tumors. Along with preclinical studies, Staren and colleagues initially described a case of a patient with two foci of infiltrating lobular carcinoma (0.5 and 0.8 cm) who was successfully treated by cryoablation [47]. This led to several small trials of cryoablation followed by surgical excision, to better gauge the ability of cryoablation to completely destroy breast tumors [48–50]. While cryoablation was effective at ablating invasive ductal carcinomas of 1.5 cm or less, it was less effective when used to ablate larger tumors, lobular carcinomas or tumors with an extensive intraductal component. The latter two represent an inability of present imaging modalities (e.g., mammogram and ultrasound) to fully show the extent of the cancer, particularly the *in situ* component. With improved imaging, such as magnetic resonance imaging (MRI), patients may be better selected for cryoablation. Cryoablation is particularly attractive as a method for treating small breast cancers as it is easy to perform under ultrasound guidance, is associated with minimal to no discomfort, can be performed with local anesthesia only, has an excellent cosmetic result and may stimulate an anti-tumor immune response with implications beyond local control [48,51]. A Phase II trial of cryoablation is currently accruing patients.

In contrast to cryoablation, several modalities use high temperatures to destroy cancer. Radiofrequency ablation (RFA) uses high-frequency alternating current flows from the tips of an array of prongs that are deployed from the tip of a probe placed into the tumor. RFA leads to coagulative necrosis of the ablated tissue. RFA has typically been performed with sedation or general anesthesia. Several small series have examined the potential of RFA in breast cancer, starting with a pilot trial by Jeffrey and colleagues, who successfully treated four out of five women with large primary tumors (4–7 cm). Three larger series of RFA for smaller tumors showed high rates of complete tumor ablation, with minimal complications, although skin burns can occur and women with lesions too close to the skin are not optimal candidates [52–55]. MRI may be a valuable tool in selecting appropriate patients for RFA and monitoring the response to therapy [56]. Interstitial laser ablation (ILA) represents another hyperthermia-based ablative technology. This requires the insertion of a laser-emitting optic fiber into the center of a tumor to destroy the cancer. Using a field block, this has been successfully performed without intravenous sedation [57]. Placement of the fiber can be accomplished by either stereotactic or MRI guidance [57–61].

The above techniques are minimally invasive; they require a small incision in the skin followed by guidance of a probe or catheter to the center of the tumor. Other technologies are being developed that are truly noninvasive. Microwave ablation uses two microwave-phase array wave guide applicators to generate thermal energy [62]. This technology takes advantage of the fact that breast cancer cells have higher water content than normal breast cells, so they heat more rapidly during microwave ablation. Early trials have demonstrated the feasibility of this technique, but further refinements are necessary to improve the clinical applicability [63,64]. Focused ultrasound (FUS) ablation is another noninvasive technique that uses ultrasound beams to ablate a very well defined target in the breast. Since MRI yields such excellent anatomic resolution, it is ideal for guiding FUS. FUS has been performed without anesthesia or discomfort, although some minor skin burns have occurred. Again, early results are intriguing but further refinements of the technology are necessary [65,66].

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Table 2. Clinical studies of *in situ* ablation of breast cancer.

Technology	N	Tumor size	Results	Ref.
RFA	10	0.5–2.0 cm	No viable tumor cells on NADH-diaphorase staining in the RF-ablated region in all patients	[198]
RFA	5	4–7 cm	Complete ablation in 4/5 patients	[199]
RFA	26	T1-T2	Complete ablation in 25/26 patients. One skin burn	[53]
RFA	29	<2.0 cm	Complete ablation in 25/29 patients. One skin burn	[55]
RFA	10	T1	Complete ablation in 9/10 patients. No complications	[56]
RFA	22	<3.0 cm	Complete ablation in 19/22 No complications.	[200]
Cryosurgery	16	Average 21 mm	Complete ablation <16 mm, but not ≥23 mm. No complications	[49]
Cryosurgery	29	<2 cm	Complete ablation for invasive ductal, no EIC <1.5 cm. No complications	[48]
Cryosurgery	25	2.0–6.0 cm	Complete ablation in 13/25 patients MRI and scintimammography correlated with success of cryo	[50]
ILA	54	<23 mm	Residual disease in 16/54 patients Two minor skin burns	[58]
Microwave	10	1–8 cm	6/10 tumors shows some size reduction.	[63]
Microwave	25	Average 1.8 cm	100% tumor response with 49.7°C	[64]
Focused ultrasound	12	<3.5 cm	Two minor skin burns	[66]
Focused ultrasound	23	2.0–4.7 cm	No viable tumor cells on NADH-diaphorase staining in the RF-ablated region in all patients	[201]

EIC: Extensive intraductal component; ILA: Interstitial laser ablation; MRI: Magnetic resonance imaging; NADH: Nicotinamide adenine dinucleotide; RFA: Radiofrequency ablation

Although image-guided ablation of breast cancer would be a tremendous boon to women with small breast cancers, the technologies are still quite early in their development, with limited clinical experience (TABLE 2). Considerable research is still necessary to improve their capabilities and define their role. As imaging technologies improve, so will the ability of *in situ* ablation to more reliably destroy cancers, but this technology is still many years away from replacing lumpectomy.

Local therapy of breast cancer: radiation therapy

Several of the randomized trials that established the efficacy of breast conservation included arms where women underwent lumpectomy alone, without radiation. These studies demonstrated no significant survival difference between those two groups, despite a significant increase in local recurrence. This led to a shift in the way we think about breast cancer and, unfortunately, is often interpreted as 'local recurrence has no impact on survival'. For this reason, physicians are often willing to offer local therapies with an exceptionally high local recurrence rate under the impression that if patients do recur and undergo salvage mastectomy, this had no negative impact on their survival. While it has long been known that women who do recur have a higher incidence of developing distant disease, this has often been attributed to a more aggressive cancer being responsible for both local and distant recurrences. There was little evidence that preventing the local recurrence would have prevented the distant disease.

The original randomized trials that demonstrated no difference in survival between lumpectomy alone and lumpectomy with radiation did not have the power to detect a small survival advantage from the addition of RT. In addition, the morbidity and mortality associated with RT negated some survival advantage, particularly with older methods for delivering radiation. More recent data have refuted the notion that local control has no impact on overall survival. The most recent update of the Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis demonstrates that the 15-year breast cancer mortality risks were significantly lower in the patients who received RT (30.5 vs 35.9; p = 0.002) [67]. A pooled analysis of mortality data from 13 randomized trials also showed a worse survival in women who did not receive RT, with an 8.6% excess mortality [68]. These data clearly demonstrates that improved local control does impact survival, and women with an exceedingly high risk of in-breast recurrence with BCT compared with mastectomy may be better served by the latter. It also establishes that radiation is a critical component of BCT.

Radiation as a component of breast conservation

The improved local control rate achieved with RT is impressive. The EBCTCG meta-analysis demonstrated a 5-year local recurrence rate of 7% for breast conservation with RT and 26% when RT was excluded [67]. While these data clearly cement the routine addition of radiation to lumpectomy for optimal local

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control, the question remains as to whether or not there exist subsets of patients for whom the in-breast recurrence risk is low enough that RT may be excessive. Attempts to identify such a subset of patients, who have a low enough risk of local recurrence to justify surgery alone, have not been successful. In a prospective trial of women with the most favorable features (tumor size ≤ 2 cm, histologically negative axillary nodes, absence of angiolymphatic invasion or EIC and margins >1 cm) who underwent surgery alone, the trial had to be stopped early owing to the high local recurrence rate (20%) [69]. NSABP B-21 included 1009 women undergoing lumpectomy for invasive breast cancer less than or equal to 1 cm in size and found that women treated by lumpectomy with tamoxifen had a 16.5% local recurrence rate compared with 2.8% for lumpectomy, radiation and tamoxifen (and 9.3% for lumpectomy and RT without tamoxifen) [70]. This demonstrates that even with the use of systemic therapy, RT significantly decreases local recurrence in patients with small tumors.

One subset of patients for whom the avoidance of radiation seems possible is older women with hormone receptor-positive tumors. Several retrospective series of conservative surgery alone in older women have shown varying rates of local recurrence, but similar distant recurrence and survival rates [71–73]. Two randomized trials have shown comparable results. In a Canadian trial randomizing women over the age of 50 years undergoing lumpectomy with adjuvant tamoxifen to radiation or none, RT significantly decreased the risk of local recurrence (17.6 vs 3.5% at 8 years), but did not appear to impact rates of distant metastases, overall survival and the number of deaths due to breast cancer [74]. However, given what we now appreciate regarding local control and overall survival, this local recurrence rate seems uncomfortably high. A Cancer and Leukemia Group B (CALGB) trial of women over the age of 70 years also showed a difference in the risk of local recurrence in women treated with tamoxifen with or without RT (4 versus 1%), but no impact on overall survival (86 vs 87% at 5 years) [75]. Rates of mastectomy for local failure were also similar. While the Canadian trial included tumors up to 5 cm, the CALGB trial was limited to tumors less than 2 cm. Thus, in selected women over the age of 70 with small ER-positive breast cancer, treatment with tamoxifen alone may be a reasonable option.

Postmastectomy radiation

It is often presented to patients that one of the advantages of mastectomy over breast conservation is that RT will not be necessary. However, chest wall recurrence after mastectomy alone is not an infrequent event. The risk of locoregional failure after mastectomy increases with increasing tumor size [76,77], as well as increasing numbers of involved axillary nodes [76–79]. Early trials of postmastectomy radiation, accruing patients in the 1960s and 1970s, demonstrated that while radiation decreased chest wall recurrences, there was no significant increase in overall survival compared with control patients, and possibly a decreased survival [80]. However, meta-analysis of these trials, with long-term follow-up and cause-specific mortality recorded, suggested that mortality from late cardiac effects were responsible for canceling out any survival advantage to RT, something not present to the same degree today using modern RT techniques. The most recent meta-analysis by the Early Breast Cancer Trialists' Collaborative, including 46 randomized trials involving over 23,000 patients, found that postmastectomy RT was associated with a significant reduction in both local recurrence (5.8 vs 22.8% at 5 years) and in breast cancer mortality for node-positive women (54.7 vs 60%; p = 0.0002) [67].

Several trials using more modern radiotherapy and adjuvant systemic therapy have further demonstrated the impact of postmastectomy radiation. The first Danish Breast Cancer Cooperative Group trial included 1708 premenopausal women with either positive nodes or T3 or T4 tumors to undergo A Cancer and Leukemia Group B (CALGB) and then be randomized to receive chest wall and regional nodal irradiation or not [81]. With a median follow-up of approximately 10 years, postmastectomy radiotherapy was associated with a significant improvement in locoregional failure (32 vs 9%), disease-free survival (48 vs 34%) and overall survival (54 vs 45%). However, this trial required only axillary sampling, not a complete dissection and most recurrences were in the axilla, a relatively rare occurrence in patients who had a level I and II dissection [82]. It is unclear what the results of this trial would have been had the patients had a complete Axillary lymph node dissection (ALND), as is performed routinely in the USA.

In the British Columbia trial, 318 premenopausal women with node-positive breast cancer undergoing modified radical mastectomy were randomly assigned to cyclophosphamide, methotrexate and fluorouracil (CMF) plus chest wall radiotherapy versus CMF alone [83]. Improvements in local-regional recurrence and DFS were again seen, with a trend towards improved survival. With 20-year follow-up, the overall survival benefit was statistically significant (overall survival: 47 vs 37%; hazard ration [HR]: 0.73 95%; confidence interval [CI] 0.55–0.98) [84]. A third trial, also from the Danish Breast Cancer Cooperative Group, randomized 1375 postmenopausal women with stage II or III breast cancer to adjuvant tamoxifen (30 mg/day for 1 year) alone or with postoperative chest wall irradiation [85]. Once again, significant improvements were seen with postmastectomy RT with regards to local-regional recurrence (8 vs 35 %), 10-year DFS (36 vs 24%) and overall survival (45 vs 36%; p = 0.03).

Based on these studies, postmastectomy radiation is recommended for several subsets of patients [86]. Patients with four or more positive lymph nodes clearly benefit from postmastectomy RT. The data are less clear for patients with one to three positive nodes. While the impact of treatment on survival might be similar, the risk of recurrence and death is less, and given the questions regarding the surgery used in the Danish trials, it is difficult to translate these findings to the American practice of axillary clearance. For now, there is insufficient evidence to recommend routine chest wall RT for women with one to three axillary nodes, but these women should have the relative pros and cons of postmastectomy radiation presented to

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them. Other patients who should undergo postmastectomy RT include women with T3 and T4 tumors, those with positive margins after mastectomy, patients with advanced nodal disease (N2 or N3) or with gross extranodal extension.

It is important to keep in mind that if postmastectomy radiation is to be utilized, this may impact the timing and method of reconstruction. The cosmetic outcome of immediate breast reconstruction will be affected by radiation. This is particularly true if tissue expanders and implants are used, but radiation can also negatively affect autologous reconstructions. Another less-recognized problem is that the reconstruction can negatively impact the delivery of radiation [87]. One option is to simply delay reconstruction until all treatment is completed. However, if immediate reconstruction is desired, there are options. If the nodal status is the question, one option is to perform the SLN biopsy as a separate procedure prior to mastectomy. This can be combined with ligation of the inferior epigastric vessels when indicated for reconstruction purposes. If the SLN is negative, the next step is mastectomy and reconstruction. If the patient is node positive, reconstruction can be delayed, especially if tissue expanders were planned. An alternate approach used at the MD Anderson Cancer Center is to conduct a delayed-immediate reconstruction [88]. The first stage consists of a skin-sparing mastectomy followed by a tissue expander. Once the pathology is reviewed, if patients will not require radiation, they return to the operating room for immediate reconstruction. If radiation is to be used, the tissue expander is fully deflated and then reinflated after radiation, followed by delayed breast reconstruction.

The future: partial breast irradiation

Standard radiation therapy after breast conservation uses a total dose of 45–50 Gy in single fractions of 1.8–2.0 Gy each, delivered to the entire breast. Because most local recurrences occur close to site of the lumpectomy, a boost of 12–20 Gy to the tumor bed is often recommended, extending the time necessary for treatment. The argument for treating the entire breast is based on pathological studies of mastectomy specimens. In the classic study by Holland and colleagues, 27% of patients had tumor cells outside of a 2 cm margin of the primary tumor [89]. However, standard whole-breast irradiation can often add additional inconvenience and cost to both the patient and the healthcare system [90]. The time and travel involved are often a burden on women, so many women who are candidates for BCT may still choose mastectomy to avoid the inconvenience and toxicity of whole-breast irradiation.

Methods to decrease the time needed for whole-breast irradiation have been examined. One such approach is the use of more rapid fractionation schedules. As opposed to the standard 45–50 Gy over 35 days, shorter schedules may be used, such as 42.5 Gy over 22 days, as was found to be equivalent in a randomized trial from Canada [91]. However, the radiation component of breast conservation may change even more dramatically over the next few years. Recent observations that the overwhelming majority of local recurrences occur in close proximity to the tumor bed [92–97], has raised the question of whether or not whole-breast irradiation is truly necessary. Patients may receive the same benefit from irradiating only the tumor bed, sparing the remainder of the breast. This may not only improve the cosmetic outcome, but would shorten the costs associated with treatment and the time necessary to complete therapy. Several techniques for delivering partial-breast irradiation (PBI) have been evaluated [98].

Of all the techniques, multicatheter, interstitial brachytherapy has been in use the longest. Multiple hollow catheters are placed in the breast tissue around the lumpectomy cavity, depending on its size and shape. The radioactive source is then placed within the catheters. Either a continuous low dose rate (LDR) is delivered by leaving the radioactive sources in for 96 h (which requires admission to designated hospital rooms with radiation shielding), or a high dose rate (HDR) is used, typically twice daily for 30 min, on an outpatient basis. Although catheter placement and dosimetry planning is complex, the procedure is surprisingly well tolerated by patients and can be used in a variety of situations, regardless of the size, shape or location of the lumpectomy cavity.

The MammoSite RTS is a balloon catheter device that greatly simplifies brachytherapy. A catheter sits centrally in a distally located balloon, resembling a Foley catheter. This is placed in the lumpectomy cavity, either at the time of surgery or as a second procedure, and inflated. Treatment is then delivered with a single, centralized HDR source. While much simpler than multicatheter brachytherapy, its use is limited to patients with adequate distance between the cavity and the skin, and a lumpectomy cavity that conforms well to the balloon surface. Use of MammoSite appears to be extremely safe and well tolerated [99], and early results seem promising [100].

As opposed to brachytherapy, external beam radiation can be used to deliver PBI. Recent technological advances in CT-based planning have allowed the introduction of 3D conformal external beam APBI. This allows for improved dose homogeneity within the target volume and does not require additional technology beyond what most radiation facilities already have. One disadvantage is that a larger area of normal breast tissue may need to be irradiated than with other PBI techniques, as the breast is a moving target. One way to improve upon this is the use of intensity-modulated radiation therapy (IMRT), which delivers radiation using a variable-intensity pattern that is determined with the aid of a computerized optimization algorithm [101–103]. While more costly and labor intensive than 3D conformal APBI, IMRT delivers a more uniform and standardized radiation dose without excessive treatment of the surrounding tissue. Finally, the need for post-operative radiation therapy can be avoided all together by the use of intraoperative radiation. Following lumpectomy, all of the adjuvant radiation is delivered in the operating room, using either low-energy x-rays delivered by a portable, spherical device [104,105], or by electrons generated by a mobile linear accelerator [106].

All of these technologies seem promising, but clinical experience is limited and long-term follow-up is not available for the newer approaches (TABLE 3). In addition, these trials are highly selective and, for the most part, from single institutions. Partic-

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Table 3. Selected studies of PBI in breast cancer.

Method of PBI	N	Median F/U (months)	LRR (%)	Ref.
Multicatheter interstitial brachytherapy	90	27	4.4	[202]
Multicatheter interstitial brachytherapy	50	60	18	[203]
Multicatheter interstitial brachytherapy	51	75	2	[204]
Multicatheter interstitial brachytherapy	119	30	2.5	[205]
MammoSite	43	29	0	[99]
External beam	31	10	0	[206]
Intraoperative irradiation	590	20	0.5	[207]
Multicatheter interstitial brachytherapy	199	65	1.2	[208]
Multicatheter interstitial brachytherapy	39	60	16.2	[209]
Multicatheter interstitial brachytherapy	44	42	0	[210]
MammoSite	28	19	0	[211]
MammoSite	32	11	0	[212]
External beam	47	18	0	[213]
Multicatheter interstitial brachytherapy	99	44	3	[214]
Multicatheter interstitial brachytherapy	99	38	2	[215]

F/U: Follow-up; LRR: Locoregional recurrence; PBI: Partial breast irradiation

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ipation is limited to a patient population with an expected excellent cosmetic outcome and low risk of recurrence with whole-breast irradiation (older patients, node negative, smaller tumors). PBI is presently being directly compared with whole-breast irradiation in a randomized trial, which will hopefully secure the role of PBI in BCT.

Regional therapy of breast cancer

The advent of SLN biopsy as a method for staging the axilla has dramatically changed the surgical staging of breast cancer. For all intents and purposes, ALND in clinically node-negative patients is no longer necessary unless the SLN biopsy is unsuccessful. The theory behind the SLN hypothesis is that tumor cells metastasize to the regional lymph nodes in a predictable and orderly fashion, so that the use of tracers injected in the breast and allowed to migrate to the regional nodes should accurately identify the node(s) most likely to harbor disease [107,108]. If, after serial sectioning, the SLN is negative, the likelihood of disease being present in other nodes should be very low, precluding the need for a more morbid ALND. Several studies have confirmed the accuracy of the procedure, including four systematic reviews [107,109–118]. The largest of these systematic reviews, performed by the ASCO expert guidelines panel, included 69 eligible trials of SLNB in early stage breast cancer, representing 8059 patients [118]. Overall, 95% had a SLN successfully identified, with a false-negative rate of 8.4%.

Many surgeons rapidly adopted sentinel node biopsy as the standard of care in breast cancer prior to any randomized controlled trial data. Several large nonrandomized series with reasonable follow-up, and one randomized trial, have demonstrated an extremely low regional recurrence rate among patients with a negative SLN and no completion ALND, suggesting that a negative impact on survival is highly unlikely [113–115]. However, it is worth mentioning that the patients included in these series were of surgeons with considerable experience with SLN biopsy and after an appropriate learning curve where the SLN biopsy was followed by an immediate ALND to accurately determine the false-negative rate. It is recommended that no surgeon begin performing SLN biopsy without completion ALND unless they have documented an adequate number of cases (20–30) where a suitably low false-negative rate is verified on completion ALND [119–122]. However, many surgeons have adopted this technique without documenting an adequate learning curve, which may adversely affect the false-negative rate as SLN biopsy becomes universal.

The only randomized trial published to date is a small study from Italy that randomized 516 patients to SLN biopsy plus ALND or SLN biopsy followed by ALND only if the SLN was positive [123]. There were no axillary recurrences in the group who did not proceed to have an ALND and short-term survival was the same for both groups. Several prospective, randomized trials are ongoing to address the impact of SLN biopsy on recurrence and survival (TABLE 4). The NSABP-B32, the ALMANAC and the SNAC trial have similar designs to the Italian trial, but are much larger, with the power to detect a small survival difference. Preliminary data show results similar to the systematic

Table 4. Randomized studies of sentinel node biopsy in breast cancer.

Study	Arms	Eligibility	Patients	Dates	Ref.
Studies comparing ALND with SLN biopsy in clinically node-negative patients					
NSABP-32	ALND vs SLNB with ALND for SLN^+	Clinically node negative	5612	Activated March, 1999 Closed February, 2004	[216]
Trial 185	ALND vs SLNB with ALND for SLN^+	Clinically node negative, T <2cm	516	Activated March, 1998 Closed December, 1999	[123]
ALMANAC	ALND vs SLNB with RT or ALND for SLN^+	Clinically node negative, T1 – T3	1031	Activated November, 1999 Closed October, 2003	[217]
RACS SNAC	ALND vs SLNB with ALND for SLN^+	Clinically node negative, T1 – T3	789 as of 11/03	Activated May, 2001	[218]
Studies evaluating treatment for sentinel node-positive patients					
ACOSOG Z0011	ALND vs observation for SLN^+ patients	T1 or T2, SLN positive		Activated November, 2002 Closed owing to poor accrual	[217]
AMAROS-EORTC	ALND vs RT for SLN^+ patients	T < 3 cm, SLN positive		Activated February, 2001 Open to accrual	[217]

ACOSOG: ?; ALND: Axillary lymph node dissection; ALMANAC: ?; AMAROD–EORTC: ?; NSABP: National Surgical Adjuvant Breast and Bowel Project; RACS: ?; RT: Radiation therapy; SLN: Sentinel lymph node; SNAC: ?.

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reviews; with a high success rate (97 to 98%), a false-negative rate of 9.7% in the NSABP trial, and a significant decrease in morbidity with SLN biopsy compared with ALND [124,125].

Although SLN biopsy has become an acceptable, if not the standard, choice for determining the nodal status of clinically node-negative patients, there are still questions surrounding its use. By allowing the pathologist to thin section only one or two lymph nodes, as opposed to simply bivalving the 10–20 lymph nodes in an ALND specimen, SLN biopsy is a more accurate diagnostic test. However, this more rigorous analysis identifies patients with micrometastatic disease, particularly if immunohistochemical (IHC) staining for cytokeratin is used. This raises the predicament of whether these micrometastases are clinically relevant? With the increased use of neoadjuvant chemotherapy, the optimum timing of SLN biopsy remains in question. Finally, although ALND has in effect been replaced as a staging procedure, it is still the standard of care to complete the node dissection if the SLN is positive. Whether or not this truly impacts survival, however, remains one of the most important questions in breast cancer surgery.

Micrometastases in the sentinel lymph node

With increased scrutiny of the SLN, smaller and smaller metastases can be identified. It would seem reasonable that the discovery of any disease in the lymph node would portend a worse prognosis. However, this is not necessarily the case. Several retrospective studies have involved re-examining the lymph nodes by serial sectioning and IHC among patients who underwent negative ALND, and the outcomes of patients with occult metastases compared with those without. While some studies found a worse outcome associated with these micrometastases [126–129], most found no negative impact on prognosis [130–137]. The clinical significance of IHC-detected micrometastases is also called into question when one considers the high incidence of finding disease in patients with ductal carcinoma *in situ* (DCIS), which has a nearly 99% survival and for which axillary recurrences are extremely rare [138,139]. Three studies have demonstrated that IHC-detected micrometastases correlate more with the method of biopsy than with the biology of the cancer, suggesting they may be an artifact rather than a biological phenomenon [140–142]. Thus, the available evidence does not support the routine use of IHC in the evaluation of the SLN [143]. Patients with micrometastases less than 0.2 mm are considered node negative (current AJCC staging stages these patients as N0mic) and should not be considered for completion dissection or adjuvant chemotherapy based on their nodal status. Patients with metastases more than 0.2 mm should continue to be treated as node positive. Pending data from recent prospective trials will hopefully help clarify these issues.

Sentinel lymph node biopsy & neoadjuvant chemotherapy

Prior to the introduction of sentinel lymph node biopsy as a method of staging the axilla, there was little consequence surgically on whether patients received neoadjuvant chemotherapy or not, since either way they would be receiving an axillary lymph node dissection. The most significant impact of preoperative therapy was that there were some patients who may have been node positive initially but were node negative after chemotherapy and thus their true nodal status remained unknown. This did not alter their surgery, and at the time there was less use of nodal status in guiding RT.

This changed dramatically as lymphatic mapping and Sentinel Lymph Node Biopsy (SLN) biopsy became standard in the surgical therapy of breast cancer. Now patients who opted for

neoadjuvant chemotherapy to shrink their primary tumor were obligated to undergo ALND as part of their surgery, whereas if they had surgery first, they could opt for a sentinel node biopsy and avoid ALND if they were node negative. In addition, the nodal status plays a larger role in therapy decisions. Some medical oncologists would reserve the use of taxanes or dose-dense regimens for patients they know to be node positive. Also, the use of postmastectomy radiation for node-positive patients has become more prevalent. These practices made it more important to know prior to therapy whether the patient was node positive. Thus the question arose of how to best integrate SLN biopsy with neoadjuvant chemotherapy for clinically node-negative breast cancer.

Sentinel node biopsy is only necessary in clinically node-negative patients. Patients with palpable disease in the lymph nodes can have this confirmed by FNA and proceed with neoadjuvant chemotherapy, with a planned ALND at the completion of systemic therapy. Clinically node-negative candidates for neoadjuvant chemotherapy should have an ultrasound of the axilla looking for abnormal lymph nodes. Ultrasound-guided FNA can then document these patients to be node positive prior to neoadjuvant chemotherapy [144,145]. For patients who are clinically and ultrasonographically node negative, there are two options for the use of SLN biopsy if they are candidates for neoadjuvant chemotherapy.

The first option is to perform the SLN biopsy prior to beginning chemotherapy [146–148]. There are several advantages to this approach. The first is that the true nodal status is known before initiating chemotherapy, which may be important if this will help decide what regimen and schedule to use. Likewise, this will help the radiation oncologist decide whether they would recommend postmastectomy radiation should the patient not become a candidate for breast conservation. For many physicians, there is increased confidence in the feasibility and accuracy of the procedure, as there has been some concern that the chemotherapy may affect the lymphatic drainage and make identification of the SLN more difficult. In addition, performing SLN biopsy after chemotherapy supposes that if there was disease in the lymph nodes, it will either completely disappear from all the nodes, or if not, it will remain in the sentinel node. However, if it is eradicated from the sentinel node but not the nonsentinel nodes, this will lead to a false negative finding. Unfortunately, performing SLN biopsy prior to the onset of chemotherapy means an extra procedure and a delay in the initiation of therapy.

The second option is to perform the SLN biopsy after completing chemotherapy [149–152]. Several studies of SLN biopsy after neoadjuvant chemotherapy have been performed and although some have suggested an unacceptably high false-negative rate, overall this seems to be reasonable [153]. While a clear disadvantage of this approach is not knowing the true pretreatment nodal status, if this would not impact the chemotherapy decisions, this is less of a factor. With regards to postmastectomy radiation, some might argue that the nodal status after chemotherapy might serve as a better indicator of whether to offer radiation to the chest wall. Delaying the SLN biopsy to after chemotherapy also allows the chemotherapy to start immediately and may preclude the need for an additional surgery. The most important advantage to SLN biopsy after chemotherapy is that patients who may have been node positive prior to chemotherapy, but are now node negative, will be spared from ALND. Approximately 20% of patients may be converted from node positive to node negative [154,155] and use of SLN biopsy prior to chemotherapy would obligate those patients to undergo ALND.

The future: the end of axillary surgery in breast cancer

What does the future hold for the regional management of breast cancer? As the strongest impetus for axillary surgery is for staging purposes, improvements in the resolution of imaging modalities may identify the presence of nodal disease without surgery. More likely, advancements in staging cancers through gene expression may preclude the need to know the regional status altogether.

The need for ALND for a positive sentinel node

Just as lumpectomy greatly minimized the morbidity of breast surgery compared with mastectomy, SLN biopsy has done the same for axillary surgery compared with ALND. As described previously, ALND may be safely avoided in the 80% of women with negative sentinel nodes. This begs the question, however, of how much benefit is added by the ALND if the SLN is positive?

Today, the standard of care in breast cancer is to perform a level I and II lymph node dissection in patients with evidence of metastatic disease in the sentinel node. Nearly half of patients with a positive SLN will have additional disease in the nonsentinel lymph nodes (NSLN) [107,156–158]. Documenting the number of involved nodes provides further staging information, which may impact adjuvant therapy decisions, as multiple involved lymph nodes is associated with increased recurrence rates and decreased survival. In many patients, however, simply knowing the patient is node positive or node negative may be enough information to determine the remainder of their therapy. In these patients, is there a therapeutic benefit to gaining regional control, or can these patients be observed, with ALND performed only if they recur?

If one could accurately predict which patients are so unlikely to harbor additional disease in the NSLN, a selective approach to completion ALND could be applied. While some clinicopathological features, such as the size and grade of the primary tumor, the size of the lymph node metastases or the ratio of positive SLN to the number of SLN removed, may help stratify risk, no factor appears sufficient to select patients who may avoid dissection [159]. Even the lowest risk groups have a 10–20% chance of harboring additional disease. While the use of statistical models or nomograms may better select patients with a low likelihood of harboring disease in the NSLN [160,161], it must be cautioned that these studies underestimate the risk of additional disease, as the NSLN are not subjected to the serial sectioning that is performed with SLN biopsy.

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Nevertheless, even if microscopic disease is left behind, this may not impact survival. As almost all patients with node positive disease will receive adjuvant systemic therapy, regional recurrence in this situation may be extremely low. But if recurrence does occur and the patient undergoes a delayed ALND, does this impact their survival? This is unknown, but as discussed, there is an increasing body of evidence that improving local control may improve survival, suggesting that failure to control regional disease may be detrimental.

The NSABP B-04 trial specifically addressed this issue, randomizing clinically node-negative patients to simple mastectomy, modified radical mastectomy or simple mastectomy with axillary radiation. After a 25-year follow-up, there was no difference in overall survival between the three groups [162]. This is the strongest evidence against the need for ALND. However, this study had two significant flaws. First, the study was not large enough to detect a small but meaningful difference in survival. Second, many surgeons, in the habit of routinely performing modified radical mastectomies, still removed a substantial number of axillary lymph nodes when performing a simple mastectomy, clouding the results.

Other studies do suggest a benefit to regional control. A randomized trial of lumpectomy versus lumpectomy and ALND demonstrated a significantly better 5-year survival with ALND (97 vs 93%) and a decreased incidence of distant metastases 163]. However, some of this may have been secondary to an increased use of chemotherapy based on the improved staging in the ALND arm. Two large, population-based, retrospective studies suggested a survival advantage associated with ALND compared with observation only [164,165]. While all retrospective data may be biased by patient selection, these findings were significant on multivariate analysis. A meta-analysis of over 3000 women involved in 6 trials randomizing patients to ALND or no ALND showed a 5% improvement in 10-year overall survival with ALND [166]. However, much of these data are from several decades ago, and it is unclear whether the same results would be seen today given the widespread use of adjuvant systemic therapy.

While these data suggests a benefit to controling regional disease, one cannot assume that the results obtained with the omission of ALND among clinically node-negative patients from years ago would be the same as among SLN-positive patients today. Neither the risk of distant disease, nor the amount of residual disease in the axillary nodes, is directly comparable. The only way to determine whether ALND may be safely omitted for patients with a positive SLN would be a randomized trial, which was initiated by the American College of Surgeons Oncology Group (ACoSOG), but closed prematurely owing to poor accrual. Thus, the question remains unanswered, and based on our best available evidence, ALND remains the standard of care. Hopefully, future trials will provide a more definitive answer to this important oncological question.

Completion ALND is not the only option available to patients with a positive SLN. Axillary radiation may be a reasonable alternative, as evidenced by data from before the emergence of SLN biopsy. In a series of 418 women treated with axillary RT after either no or limited ALND, only 1.4% developed a regional failure after 8 years of follow-up [167]. Of the subset of patients who had a limited ALND with positive nodes, the regional failure rate was 7% (3 of 42 cases). A randomized trial in Italy of ALND versus axillary RT accrued 435 patients and, after a mean follow-up of 66 months, recorded only one axillary recurrence in the radiation arm and two in the surgery arm [168]. While these data suggest that axillary radiation may be effective in obtaining regional control, it is difficult to transpose these numbers to the SLN-positive population. A randomized trial of axillary radiation versus ALND for SLN-positive patients is presently accruing patients and will not only answer these questions, but also help determine whether axillary radiation truly decreases the morbidity of treatment compared with surgery.

The need for axillary staging at all

Although the therapeutic benefits of axillary clearance are debatable, the role of axillary staging for prognostic purposes is not, and still plays a crucial role in the management of breast cancer. However, based on the present prognostic factors (nodal status, tumor size and tumor grade), predictive factors (hormone receptors, Her2/*neu*) and the current recommendations for adjuvant therapy, only 10% of patients who are exposed to chemotherapy derive a benefit [169,170]. This is unfortunately due to the inadequacy of present markers to select out those patients who will be cured by local and regional control alone. While metastases to the lymph nodes is the most significant prognostic sign, 30% of node-negative patients will still relapse, while up to 40% of node-positive patients will be alive at 10 years [171–173]. It is clear that superior methods of predicting outcomes in breast cancer are needed.

Many additional factors have been identified as correlating with poor outcome, including angiolymphatic invasion within the primary tumor, tumor cells within the bone marrow and multiple tumor and serum markers, such as the epidermal growth factor receptor, p53, E-cadherin, Ki-67, bcl-2, cathespin D, enhancer of zeste homolog (EZH2), cyclins and cyclin-dependent kinase inhibitors, and more [174–184]. While expression of these markers may correlate with outcome, their ability to further stratify patient's risk beyond size and nodal status and to reliably identify patients who may safely avoid chemotherapy, has been limited.

A more promising method of staging breast cancer patients than looking at single tumor markers is to look at the tumor genome. DNA microarray analysis uses mRNA from fresh frozen tissue to create double-stranded DNA. Using reverse transcription, amplified cRNA is labeled with fluorescent dye and hybridized to a panel of tens of thousands of genes on a chip. Computer-aided programs can then discern whether the gene is up- or down-regulated within the cancer cells. This is an extremely powerful tool that may revolutionize the management of cancer, especially breast cancer. Van't Veer and colleagues established a 70-gene profile that could reliably predict

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outcome among node-negative breast cancer patients [185,186]. While these were retrospective data, they demonstrated the potential for gene microarray analysis to accurately identify patients with different risks of recurrence despite otherwise similar appearing tumors. Other groups have pursued alternate clusters of genes to stratify risk [187–189].

One drawback to microarray analysis is the need for high-quality RNA derived from fresh frozen tissue. A new technique uses reverse transcriptase polymerase chain reaction to obtain gene expression data from paraffin-embedded tissue [190]. This not only increases the clinical utility of gene expression, it allows for the testing of archived tumor samples, allowing the predictive ability of the genes to be validated. Using stored tumor samples from the NSABP B-14 trial, Paik and colleaguesl developed and validated a 21-gene assay that could predict the likelihood of distant recurrence among ER-positive, node-negative breast cancer patients [191] and, subsequently, the benefit of adjuvant tamoxifen and chemotherapy [192]. This gene assay, known as Oncotype DX® is now available as a commercial test to help ER-positive, node negative women decide whether adjuvant chemotherapy is appropriate for them.

This represents the first step in moving from staging patients based on histopathological features to staging patients based on genomic features. Since the 21-gene assay was developed and validated on trials limited to ER-positive, node-negative women, this is the population for whom it may be utilized. It is conceivable, however, that in the not too distant future, gene assays will be developed that can predict nodal involvement or response to therapy, regardless of tumor size or nodal status. When that time arrives, the need for SLN biopsy for staging purposes may disappear, and ALND could become an obscure operation reserved for the unusual isolated axillary recurrence.

Expert commentary

With clear evidence that local control does impact long-term survival, the focus of breast cancer treatment should not be on how much locoregional recurrence is acceptable, but rather how we can achieve optimum control while minimizing morbidity. Today, this is achieved through the appropriate use of BCT and increasing candidacy for lumpectomy through the use of neoadjuvant chemotherapy. If mastectomy is necessary, postmastectomy radiation should be used when indicated and skin-sparing mastectomies with immediate reconstruction performed when possible. The appropriate use and timing of SLN biopsy will help not only achieve regional control, but also assist in determining the most appropriate therapy for an individual patient. Navigating patients through this myriad of complex choices is the challenge for today's breast cancer specialist and highlights the benefit of, if not the need for, a multidisciplinary approach.

As new approaches and technologies become available, we must not be too hasty in adopting them based on patient preference or personal belief, but rather subject them to rigorous scientific evaluation and base our decisions on the best available clinical evidence. Letting one's mind wander, however, it is possible to envision a not too distant future where the typical breast cancer patient undergoes a core needle biopsy to provide all the necessary information on which to base treatment. Surgery is unnecessary; the tumor is ablated, possibly followed by partial breast irradiation. Targeted systemic therapy, with minimal toxicity, is then initiated only in that small percentage of patients deemed likely to benefit, based on gene expression analysis. With a continued dedication to both bench research and clinical trial design and participation, this vision may not be as far in the future as we may think.

Key issues

- After the randomized trials demonstrated no survival difference between lumpectomy alone and lumpectomy with radiation, despite a significant increase in local recurrence, many incorrectly interpreted this as 'local recurrence has no impact on survival.'
- Recent meta-analyses and randomized trials have demonstrated that improved locoregional control does indeed impact long-term survival.
- Despite the overwhelming evidence in favor of breast conservation therapy (BCT) for appropriate patients, there still exists wide variability in its application. Many patients are incorrectly thought to be poor candidates for BCT.
- Conversely, BCT is often offered to poor candidates, leading to increased local recurrence rates and possibly decreased survival.
- The use of neoadjuvant chemotherapy can increase the likelihood of breast conservation among patients who may otherwise require mastectomy.
- Postmastectomy radiation not only decreases chest wall recurrence, but may also improve survival among high-risk patients.
- Sentinel lymph node biopsy has dramatically altered the surgical staging of breast cancer, but many questions still remain regarding its most appropriate use and the role of axillary lymph node dissection for node-positive patients.
- Promising developments in both *in situ* ablation and partial breast irradiation may further decrease the morbidity of treatment for women with breast cancer.

Author Proof

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