Advances in the surgical treatment of breast cancer

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Abstract: Breast cancer has become the top malignant neoplasm in Chinese women with an increasing risk of morbidity and mortality. As a crucial part of comprehensive treatment of breast cancer, breast surgical technique is ceaselessly ameliorating and enriching its features. With the purpose of achieving minimal surgical intervention and satisfactory cosmetic results, the trend of mammary surgery is focusing on minimally invasive treatment and aesthetics in the 21st century. This article gives an overview of the most representative surgical procedures, such as breast conservative surgery, sentinel lymph node dissection, oncoplastic technique and breast reconstructive surgery.

Keywords: Breast cancer; breast conservative surgery; sentinel lymph node dissection; oncoplastic technique; breast reconstructive surgery

Introduction

As one of the most frequent female malignant tumor, breast cancer has become the top malignant neoplasm in Chinese women with an increasing trend of morbidity and mortality since the 1990's. Benefiting from further understanding of basic research on biological behavior of breast cancer and numerous large-scale prospective clinical study, many progresses have been made on the quality of breast carcinoma treatment in the 21st century. Composing a crucial part of comprehensive treatment of breast cancer, local therapy, especially breast surgical technique, is ceaselessly ameliorating and enriching its features. With the purpose of achieving minimal surgical intervention and satisfactory cosmetic results, the development direction of mammary surgery is focusing on minimally invasive treatment and aesthetics in the 21st century. Thereinto, breast conservative surgery, sentinel lymph node dissection, oncoplastic technique and breast reconstructive surgery are the most representative surgical procedures.

Breast conserving surgery

Fisher reported 25-year findings of a randomized trial initiated in 1971 to determine whether less extensive surgery with or without radiation therapy was as effective as the Halsted radical mastectomy. A total of 1,079 women with clinically negative axillary nodes underwent radical mastectomy, total mastectomy without axillary dissection but with postoperative irradiation, or total mastectomy plus axillary dissection only if their nodes became positive. Data from the NSABP B-04 trail indicate that leaving positive nodes unremoved did not significantly increase the rate of distant-recurrence or breast-cancer-related mortality. This is an innovation that has radically transformed the surgical approach of Halsted's concept (1). Later, the NSABP B-06 trail, Milan I trail and EOTRC 10801 trail, with 20 years follow-up results provide strong evidence for the treatment of early breast cancer with breast conserving surgery (BCS) [quadrantectomy or lumpectomy combined with radiotherapy (RT)] (2-4).

Compared with radical mastectomy, BCS has less

postoperative complications and better cosmetic effect, and significantly improved the quality of life. Preoperative chemotherapy (neoadjuvant chemotherapy) allows downsizing of tumors, making previously ineligible patients eligible for breast conserving therapy (BCT). A number of studies have been confirmed that preoperative chemotherapy increased use of breast-conserving surgery (5-7).

Once there was still no universal agreement on what constitutes an adequate negative margin for patients being managed with the breast-conserving approach. Positive margins are associated with increased risk of local recurrence (LR) when compared with negative margins. The Society of Surgical Oncology indicated that tumor not touching ink was an adequate negative margin. The routine practice of obtaining wider negative margin widths than no ink on tumor does not appear to further reduce local recurrence rates (LRRs) (8). A meta-analysis of 33 studies showed that the overall median prevalence of LR in the analysis was only 5.3%, despite the fact that many of the included studies antedated the routine use of systemic therapy for small, node-negative breast cancer, and positive and close margins (combined) significantly increase the odds of LR (OR 1.96; P<0.001) relative to negative margins. But the odds of LR were not associated with margin distance [1 (referent) *vs.* 2 *vs.* 5 mm (P=0.90)], adjusting for study median follow-up time (9). A Danish study showed that the cumulative incidence of ipsilateral breast tumor recurrence (IBTR, defined as invasive recurrence) at 5 and 9 years was 2.4% and 5.9%, respectively. A final positive margin increased the risk of IBTR (HR 2.51; 95% CI: 1.02–6.23). No decrease in IBTR with a wider negative margin compared to a narrow but negative margin was observed in the adjusted analysis of margin width (10). A randomized, controlled trial showed that cavity shave margins (additional tissue circumferentially around the cavity left by partial mastectomy) may reduce the rates of positive margins (margins positive for tumor) and re-excision among patients undergoing partial mastectomy for breast cancer. In this trial, 235 patients with breast cancer of stage 0 to III who were undergoing partial mastectomy, with or without resection of selective margins, to have further cavity shave margins resected (shave group) or not to have further cavity shave margins resected (no-shave group). The rate of positive margins after partial mastectomy (before randomization) was similar in the shave group and the no-shave group (36% and 34%, respectively; P=0.69). After randomization, patients in the shave group had a significantly lower rate of positive margins than did those in the no-shave group (19% *vs.* 34%, P=0.01), as well

as a lower rate of second surgery for margin clearance (10% *vs.* 21%, P=0.02). There was no significant difference in complications between the two groups (11).

International guidelines suggest total mastectomy as treatment of choice for IBTR following lumpectomy and RT. Nevertheless, there is evidence that second BCS might be equally sufficient. No significant difference in local control, disease free survival (DFS), and overall survival (OS) was seen between IBTR patients treated either by secondary BCS or mastectomy (12).

A study from the Netherlands Cancer Registry showed that BCT (conserving surgery with radiation therapy, BCT) substantially improved OS compared to mastectomy without radiation therapy (MAST) in primary invasive T1–2N0–1M0 stage breast cancer. Regardless of tumor size (T1 and T2) and lymph node status (N0 and N1), the 10-year OS rate and DFS after BCS is better than mastectomy (76.8% *vs.* 59.7%), the 10-year DFS was comparable for both treatments (83.3% *vs.* 81.5%, respectively) (13).

In conclusion, we encourage consideration of BCT inappropriately selected patients in whom complete resection can be achieved with a negative margin (14).

Breast reconstruction

Although BCT remains the absolute gold standard for surgical breast cancer treatment, many women must or wish to undergo mastectomy. Consequently, reconstruction of the breast must be offered, particularly in young patients. Breast reconstruction depends primarily on the type of mastectomy and may be classified in various ways, such as reconstruction type and reconstruction time point. The latter includes delayed breast reconstruction (DBR; secondary breast reconstruction) and immediate breast reconstruction during the same surgery (IBR; primary breast reconstruction). IBR has the advantage of reducing the total number of surgical procedures.

IBR is advantageously associated with a reduced recovery time, a better esthetic outcome, an improved quality of life, and, finally, lower surgery and recovery-related costs. Patients who underwent IBR showed no increased risk of overall recurrence of breast cancer, had similar DFS (P=0.10) and OS (P=0.24) as those of mastectomy only patients (15). Despite very effective diagnostic work-up of breast cancer and highly standardized neo- and adjuvant treatment regimes, IBR bears the risk that unforeseen adjuvant radiotherapy may compromise the final result of the reconstructed breast, such as capsular contracture in

implant-based reconstructions, respectively flap shrinkage in autologous reconstructions. Therefore, many surgeons may tend to a DBR when using free flaps in cases of an invasive tumor requiring adjuvant radiotherapy. Nowadays, the seek for bilateral prophylactic mastectomy in women with a genetic predisposition for breast cancer (e.g., BRCA-1, BRCA-2, p53) increases and accordingly represents an ideal indication for IBR of any type (16).

There are three different approaches of breast reconstruction: (I) breast reconstruction using implants and skin expanders; (II) breast reconstruction using flaps (vascularized autologous tissue), a combination of both (flap and implant); (III) breast reconstruction using non-vascularized lipoaspirate autologous fat.

The use of implants and skin expanders is not only the oldest way to reconstruct a breast but also the quickest and presumably easiest method of breast reconstruction. Accordingly, implant-based breast reconstruction is by far the most often used technique worldwide (17). The prerequisite for implant-based breast reconstruction (IBBR) is an adequate skin envelope that allows covering the implant that is usually introduced in a submuscular plane detaching the medial insertions of the pectoralis major muscle from the ribs. IBBC may yield very nice long-term results that suffice many patients. However, IBBC prone to develop implant-related local complications, such as severe capsular contracture (24.6%) and implant rupture (35.4%) (18), and will not allow recreating a naturally shaped ptotic breast in most patients, and therefore often requires adaptive surgery of the contralateral breast to achieve symmetry.

The technique of skin expansion has been used in order to recreate the amount of lost skin after mastectomy through stepwise expansion of the remaining chest skin (19), preparing for subsequent breast reconstruction (expander removal for permanent implant or flap). This approach is particularly helpful in patients who are sure to get adjuvant radiotherapy of the thoracic wall.

The myocutaneous flaps that are being used for breast reconstruction have a long history. The initial attempts were still not able to really reconstruct the breast and therefore primarily aimed at resurfacing the thoracic wall's defects after radical mastectomy.

Finally, it was the introduction of the myocutaneous latissimus dorsi flap with its overlying skin island, which allowed to reconstruct the breast (20). In 1980, Bostwick described the combined use of the myocutaneous latissimus dorsi flap and a silicone implant to reconstruct the breast (21). The advantage of the latissimus dorsi flap is its rather consistent anatomy and therefore easy flap harvest. However, flap transfer from the back can be associated with highly visible scars, contour deformity of the thorax ventrally and the back dorsally. Otherwise, the muscle undergoes atrophy of 50–75% of its volume unconditionally, almost always requiring an implant to restore volume, unless the patient is rather thin. In 1987, Hokin and Silfverskiold described the use of an extended latissimus dorsi flap which the flap's volume was significantly increased by dissecting the subcutaneous fat surrounding the skin island, to avoid the use of an implant (22). In most patients, the extended latissimus dorsi flap alone, without an implant, can provide good to excellent autologous a reconstruction of small to medium sized breasts. In selected patients, larger breasts may be reconstructed with the extended latissimus dorsi flap alone. This flap's main disadvantage is donor-site morbidity with prolonged drainage and risk of seroma (23).

In 1982, Hartrampf and colleagues used the cranially pedicled rectus abdominis muscle flap with a horizontally oriented adipo-cutaneous skin island (transverse rectus abdominis myocutaneous, TRAM flap) to anatomically reconstruct volume and shape of the breast in one single stage without using implants (24). Although this procedure was able to restore the ablated breast and improve abdominal contour, following significant disadvantages have to be taken into consideration: protracted recovery of the patient and abdominal wall weakness, including bulging and herniation due to sacrifice of the rectus abdominis muscle and large part of its anterior fascia. Further refinement of the surgical technique over time aimed at decreasing as much as possible the weakening of the abdominal wall, including muscle sparing free TRAM flap (25), fascia sparing free TRAM flap (26), to finally achieve complete muscle preservation [deep inferior epigastric perforator (DIEP) flap] (27).

However, not every woman is suitable for breast reconstruction using abdominal skin and fat, many more donor sites were described in the following years, aiming at harvesting the most suitable micro-vascular flap to best personalize breast reconstruction. Such as the superior gluteal artery perforator (sGAP) flap (28), the inferior gluteal artery perforator (iGAP) flap (29) from the gluteal region, and the transverse myocutaneous gracilis (TMG) flap from the inner thigh region (30).

Autologous fat grafting (lipofilling) describes the harvesting of the patient's fat using liposuction followed by its reinjection into the tissue to be corrected or augmented. However, fat grafting is predominantly used to refine post-

reconstructive asymmetries. To date, some experimental studies including animal trails raise the question of the safety for patients undergoing a lipofilling. They shows that adipose tissue, specially progenitors and mature adipocytes are able to secrete adipokines (leptin, L1 *et al.*), which can promote breast cancer cells growth and metastasis (31). However, there is lack of translational research that proves this concern in clinical aspect. A paper survey about the safety of fat grafting in breast reconstruction published in 2012. This survey includes 60 papers and 4,600 patients. Most studies published in the literature focus on technique complications, only three studies which used Coleman technique focus on cancer recurrences after lipofilling (616 patients, average follow up 45.2 months). The results showed that there is no evidence indicated the lipofilling would increase the risk LR of breast cancer patient (32-34). Our cooperative group: oncology institute of Milan processing a retrospective matched cohort study, with median follow up of 56 months from primary surgery and 26 months from the lipofilling, showed that lipofilling will not increase the LR in invasive breast cancer (34). However, higher risk of local event (LE) was observed in intraepithelial neoplasia patients following lipofilling. And a subgroup analysis showed that lipofilling increased the risk of LE in women <50 years, with high grade neoplasia, ki-67 ≥14 or who had undergone quadrantectomy (35). A prospective clinical registry including high-volume multicenter data with a long follow-up is warranted to demonstrate the oncologic safety.

Despite this complex decision-making including many aspects, the overall number of breast reconstruction has lately considerably increased. Breast reconstruction should be personalized at its best, first of all taking into consideration not only the oncological aspects of the tumor, neo-/adjuvant treatment and genetic predisposition, but also its timing (IBR *vs.* DBR), as well as the patient's condition and wish.

Oncoplastic surgery

Oncoplastic surgery (OPS) is a sort of cosmetic surgery in the setting of breast-conserving treatment for breast cancer, which combines the technique of oncological surgery and plastic surgery to reshape breast after tumor resection. This technique is principally based on breast volume displacement by taking advantage of the adjacent breast tissue or extra mammary autologous tissue to decrease the risk of local cosmetic defect. Consequently, it broadens the indication of breast conservative surgery and decreases the rate of positive margin and re-excision. Meanwhile, patient satisfaction is improved (36). Commonly used techniques are volume displacement mammoplasty techniques and volume replacement techniques, such as peri-areolar technique, superior pedicle technique, inverted-T mammoplasty and so on (37).

Instead of being a simple plastic surgery, more importantly, OPS plays an important role in treating breast carcinoma. As a result, its oncological outcomes should be followed closely. Although the concrete value of negative margin or close margin varies in different medical teams, a consensus that patients with negative margin had lower LRR than those with positive margin has been reached (38). According to current clinical research, OPS permits larger mass resection and greater pathological negative margin distance (40 mm for some patients) compared with traditional breast-conserving surgery (TBCS). The rate of positive margin is in the range of 6–22% for OPS, which is lower than the 10–40% in traditional breast conserving group (39-48). Therefore, since greater excision and lower positive margin rate can be achieved, the tumor resection effect of OPS is satisfactory.

Present research shows that the LRR of OPS is between 0–3%, which has no significant statistical difference with the 2–5% of TBCS (37-46). With analyzing the subtype of cancer, the triple negative breast cancer, HER2-positive non luminal subtype and ductal carcinoma *in situ* account for the majority among the patients with relapse. Whereas the lobular carcinoma, which is considered as a subtype of breast cancer with more diffusing lesions, was not associated with a higher rate of positive margin, LRR and mortality. In addition, patients aged <40 years had two times higher LRR compared with patients aged >40 years in the group of OPS (49). Speaking on postoperative OS, the 5-year survival rate of OPS patients ranges from 93–96%, which is comparable with that of TBCS (36,41,50). Surgery is only one of the many factors that affect the LRR and survival rate. Apart from that, postoperative recurrence risk factors (age, tumor size, lymph node involvement or the state of hormone receptors) and quality of adjuvant therapy (chemotherapy, radiotherapy or endocrine therapy) also have a great impact on LR and OS. Consequently, operation method cannot serve as the only variable affecting the prognosis of breast cancer, more clinical comparative trials with enough follow-up time and sufficient number of patient are necessary.

By contrast, OPS can obtain better mammary contour

than TBCS. Generally speaking, the percentage of OPS patients who were satisfied with the aesthetic effect is 84–89%, which is higher than the 60–80% of TBCS (44,51,52). Nevertheless, due to lack of a unified evaluation criteria of breast appearance, the majority of current researches solely based on questionnaire survey, that is patient self-evaluation, to draw the conclusion. While the relatively objective method of panel evaluation and breast retraction assessment (BRA) were barely applied (53). What's more, an unanimous evaluation timing has not yet been agreed by different medical team. Since radiotherapy or secondary operation, such as secondary contralateral breast symmetrisation may cause breast shape change then misguide the judgement of evaluator, their disturbance should be excluded while assessing aesthetic result. A recommended timing for evaluation is 2–3 years after operation when breast form has stabilized (54). OPS helps breast cancer patients who originally had an indication of mastectomy to successfully conserve their breasts with satisfaction. With the guarantee of sound aesthetic effect, adequate resection, negative margin and lower re-excision rate can be achieved. In a word, OPS has become a third option except for TBCS and mastectomy.

Although better treatment effects can be achieved by OPS, adjuvant therapy and follow-up may be negatively affected due to the structural rearrangement. The classic radiotherapy after BCS is whole breast radiation therapy (WBRT) combining with tumor bed boost irradiation, which means the irradiation of remaining ipsilateral breast with additional local radiation at tumor bed and a precise localization of tumor bed is the premise of its efficiency. However, the rearrangement of breast parenchyma caused by oncoplastic techniques relocates the tumor cavity wall to other quadrant of breast, which may lead to wrong tumor bed localization, so as to inaccurate local boost (55). Therefore, future studies should build up more scientific protocol of tumor bed localization and radiation method to prove the credibility of OPBS.

The rate of secondary mastectomy for patients with positive margin is significantly higher than that of BCS. A possible explanation is that the rearrangement of breast tissue made by the previous OPS makes the localization of original tumor bed more difficult and then mastectomy is chosen instead of re-excision to ensure a complete secondary removal of residual carcinoma tissue (49). Differently, without tumor bed displacement, traditional BCS can easily perform local re-excision.

Moreover, postoperative follow-up could be influenced by OPS. Compared with traditional BCS, patients who underwent OPS were observed a higher abnormal image rate which eventually turned out to be the particular changes after surgery (56).

Hence, radiologist should be more and more habitual with these specific mammographic findings to ameliorate diagnostic specificity.

Axillary management in primary breast cancer

Sentinel lymph-node biopsy (SLNB)

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial randomized 1,159 clinically node negative patients to radical mastectomy versus total mastectomy with postoperative axillary radiation versus total mastectomy followed by axillary dissection for those patients who subsequently developed clinically positive nodes. There was no difference in survival between the three treatment arms. And it was noted that approximately 40% of the patients who underwent axillary lymph node dissections (ALND) had lymph nodes harboring metastases (1). The morbidities associated with ALND include lymphedema, sensory disturbances, limited arm mobility. If node-negative patients could be identified appropriately, then the morbidity associated with ALND could be spared. Many subsequent studies indicated that SLNB is a reliable axillary staging technique, although a limited number of false negative results have been a feature of all the reports published to date (57-59). The NSABP B-32 trial randomized 5,611 women with clinically node-negative breast cancer either to SLNB plus ALND or to SNLB alone, with ALND performed only if there was evidence of metastasis to the sentinel nodes. With a median time of follow-up of 95.6 months, the OS, DFS, and regional control were equivalent between the two groups (60). Thus, the use of SLNB in the management of patients with primary breast cancer has been widely implemented into routine clinical practice.

In 2002, the American Joint Committee on Cancer (AJCC) has incorporated the size of regional lymph node metastases into its pathological staging system. The AJCC refers to foci of disease ≤0.2 mm as isolated tumor cells [pN0 (i+)], >0.2–2.0 mm as micro-metastases (pN1mi), and >2.0 mm as macro-metastases (61). Weaver *et al.* reported outcome data for patients with occult metastases of node-negative breast cancer within the NSABP B-32 trial. Using both hematoxylin and eosin and immunohistochemical

staining for cytokeratin, occult metastases were detected in 15.9% of the 3,887 patients (300 patients in the SNB alone group and 316 in the ALND group): 11.1% with isolated tumor-cell clusters, 4.4% with micro-metastases, and 0.4% with macro-metastases. The 5-year Kaplan-Meier survival estimates for patients in whom occult metastases were detected were 94.6% for OS, 86.4% for disease-free survival, and 89.7% for distant-disease free interval; the survival estimates for patients in whom occult metastases were not detected were 95.8%, 89.2%, and 92.5%, respectively (P<0.05) (62). At ten years, no statistical differences were found between the occult groups with and without axillary dissection for OS (HR: 0.98, P=0.91) or DFS (HR: 0.82, P=0.2) (63).

The American College of Surgeons Oncology Group (ACOSOG) undertook a prospective study (Z0010) to evaluate the incidence and impact of sentinel node and bone marrow micro-metastases on outcome in patients with early-stage breast cancer treated with BCS and radiation therapy. Of 3,326 H&E-negative sentinel node specimens that were examined by immunohistochemistry, 349 (10.5%) were positive for tumor. Although bone marrow micro-metastases were associated with a significantly worse OS, sentinel lymph node micro-metastases were not (64). Similar results were obtained from IBCSG23-01 trail (65).

Whether ALND should remain standard practice in the patients with sentinel lymph node macro-metastases remains controversial. In the ACOSOG Z0011 trial, patients with clinical T1–T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section were randomized to undergo either an ALND or no further treatment. Patients in this trial were treated with lumpectomy, adjuvant systemic therapy, and tangential field WBRT. At a median follow-up of 6.3 years (last follow-up, March 4, 2010), 5-year OS was 91.8% with ALND and 92.5% with SLND alone; 5-year disease-free survival was 82.2% with ALND and 83.9% with SLND alone. The 5-year rates of LR were 3.1% in the ALND group and 1.6% in the SLND-alone group (P=0.11) (66).The EORTC 10981-22023 AMAROS trial aimed to assess whether axillary radiotherapy provides comparable regional control with fewer side-effects. A total of 4,806 patients with T1–T2 primary breast cancer and no palpable lymph adenopathy were eligible for randomisation. Patients were randomly assigned (1:1) by a computer-generated allocation schedule to receive either axillary lymph node dissection

or axillary radiotherapy in case of a positive sentinel node, stratified by institution. Of the 1,425 patients with a positive sentinel node, 744 had been randomly assigned to axillary lymph node dissection and 681 to axillary radiotherapy. Local treatment of the breast consisted of breast-conserving treatment including whole-breast radiotherapy or mastectomy (17–18%) with irradiation of the chest wall at least four positive nodes were found. Axillary radiotherapy included the contents of all three levels of the axilla and the medial part of the supraclavicular fossa. The use of adjuvant systemic treatment was applied at the discretion of the treating multidisciplinary team. At a median follow-up of 6.1 years, 5-year axillary recurrence was 0.43% after axillary lymph node dissection versus 1.19% after axillary radiotherapy. Five-year DFS was 86.9% in the axillary lymph node dissection group and 82.7% in the axillary radiotherapy group (P=0.18). Five-year OS was 93.3% in the axillary lymph node dissection group and 92.5% in the axillary radiotherapy group (P=0.34). Lymphoedema in the ipsilateral arm was noted significantly more often after axillary lymph node dissection than after axillary radiotherapy at 1 year, 3, and 5 years (67).

Thus, for patients who meet the criteria for inclusion in the ACOSOG Z0011 and the IBCSG 23-01 trials, SLNB alone without completion ALND is adequate for staging the axilla. For patients who meet the criteria for inclusion in the AMAROS trial, axillary radiotherapy appears to represent a better option than completion ALND.

In patients with large primary tumors or involved lymph nodes, neoadjuvant chemotherapy is often delivered preoperatively in order to assess response to chemotherapy and to increase the likelihood of BCS. Accurate determination of axillary involvement after chemotherapy is important; however removing all axillary nodes to assess for residual nodal disease subjects many patients to the morbidity of surgery while potentially only a subset will benefit. In the clinically negative axilla, some advocate a sentinel node biopsy before initiation of neoadjuvant chemotherapy. Proponents of this approach believe that this would allow for more accurate staging, avoiding the chemotherapy effects that may cause a high false-negative rate (68). A total of 3,746 patients with clinically node negative T1–T3 breast cancer underwent SLN surgery in M.D Anderson Cancer Center from 1994 to 2007. Of the patients, 575 (15.3%) underwent SLN surgery after chemotherapy and 3,171 (84.7%) underwent surgery first. The false-negative rates were similar between groups (5.9% in neoadjuvant vs. 4.1% in the surgery first group, P=0.39).

After adjusting for clinical stage, there were no differences in local-regional recurrences, disease-free or overall survival between the two groups (69). However, the utility of SLN surgery following neoadjuvant chemotherapy for cN1 patients has been questioned. Anthracyclines and taxane-based chemotherapy regimens have been shown to eradicate nodal disease in approximately 29% of patients (70). Sentinel lymph node biopsy may be an alternative in these patients. The ACOSOG Z1071 trial enrolled women with clinical T0–4 N1–2, M0 breast cancer who received neoadjuvant chemotherapy. Of 663 evaluable patients with cN1 disease, 649 underwent chemotherapy followed by both SLN surgery and ALND. A SLN could not be identified in 46 patients (7.1%). Only one SLN was excised in 78 patients (12.0%). Of the remaining 525 patients with 2 or more SLNs removed. In 39 patients, cancer was not identified in the SLNs but was found in lymph nodes obtained with ALND resulting in a FNR of 12.6%. Bivariable analyses found that the likelihood of a false-negative SLN finding was significantly decreased when the mapping was performed with the combination of blue dye and radiolabeled colloid (P=0.052; FNR: 10.8% *vs.* 20.3%) and by examination of at least 3 SLNs (P=0.007: 9.1% *vs.* 21.1%) (71). Similar results were obtained from SENTINA trail, with FNR of 8.6% (the combination of blue dye and radiolabeled colloid) and less than 10% (three or more sentinel lymph nodes removed) (72). Adoption of this approach has the potential to further decrease the use of ALND in patients who present with documented axillary lymph node involvement.

Regional nodal irradiation

In the ACOSOG Z0011 and the IBCSG 23-01 trials, patients with SLNs micro-metastases or 1 to 2 SLNs containing metastases, completion ALND could be avoided by breast-conserving surgery including radiotherapy. However, this requires sophisticated understanding of the characteristics of patients who enrolled on these trials, including their risk factors and systemic management, as well as the radiation fields actually treated. Results from AMAROS trial shows that axillary lymph node dissection and axillary radiotherapy after a positive sentinel node provide excellent and comparable axillary control for patients with T1–2 primary breast cancer.

The NCIC Clinical Trials Group MA.20 trial compared whole-breast irradiation plus regional nodal irradiation (including internal mammary, supraclavicular, and axillary lymph nodes) with whole-breast irradiation alone in women with node-positive or high-risk node-negative breast cancer who were treated with BCS and adjuvant systemic therapy. A level I or II axillary dissection was required for patients with positive results on sentinel-node biopsy.

The median follow-up was 9.5 years. At the 10-year follow-up, there was no significant between-group difference in survival, with a rate of 82.8% in the nodal-irradiation group and 81.8% in the control group (P=0.38). The rates of disease-free survival were 82.0% in the nodal-irradiation group and 77.0% in the control group (P=0.01). Patients in the nodal-irradiation group had higher rates of grade 2 or greater acute pneumonitis (1.2% *vs.* 0.2%, P=0.01) and lymphedema (8.4% *vs.* 4.5%, P=0.001) (73). EORTC 22922/10925 trail randomly assigned women who had a centrally or medially located primary tumor, irrespective of axillary involvement, or an externally located tumor with axillary involvement to undergo either whole-breast or thoracic-wall irradiation in addition to regional nodal irradiation (nodal-irradiation group) or whole-breast or thoracic-wall irradiation alone (control group). Eligible patients had undergone mastectomy or breast-conserving surgery and axillary dissection. During the last years of the trial, patients were eligible if they had undergone a sentinel-node biopsy followed by an axillary dissection in the case of a positive node. At ten years, OS was 82.3% in the nodal-irradiation group and 80.7% in the control group (P=0.06). The rate of disease-free survival was 72.1% in the nodal-irradiation group and 69.1% in the control group (P=0.04), the rate of distant disease-free survival was 78.0% versus 75.0% (P=0.02), and breast-cancer mortality was 12.5% versus 14.4% (P=0.02). Acute side effects of regional nodal irradiation were modest (74).

Recognizing how the patient populations treated on the NCIC MA20 and EORTC 22922 trials may have differed from those on ACOSOG Z0011 and IBSCG 23-01 is necessary to help reconcile the findings of these studies and guide us in optimizing our patients' radiotherapeutic management decisions.

Footnote

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