Optimal Surgical Treatment of Breast Cancer

Umberto Veronesi, Stefano Zurrida
European Institute of Oncology, Milan, Italy

Key Words. Breast cancer · Surgery · Conservation · Treatment

Abstract
Large-scale, controlled trials in the 1970s and 1980s demonstrated that wide resection (for example, quadrantectomy) was as effective as mastectomy for the treatment of breast cancer up to 3 cm in maximum diameter. Conservative treatment may also be extended to larger cancers following pre-operative chemotherapy to reduce tumor mass and leave sufficiently wide resection margins to ensure oncological radicality. Quadrantectomy is an operation of curative intent, distinct from "lumpectomy" or "tumorectomy," whose main aim is to debulk the tumor mass; nevertheless, wide resection should, in most cases, be flanked by radiotherapy to sterilize the tumor bed and by complete axillary dissection to remove any metastatic nodes and provide full prognostic information. This triple approach provides a high cure rate and low relapse rate for breast cancer, while providing an acceptable cosmetic outcome; we believe it is the optimal treatment for breast cancer at the present time. Modifications include simultaneous remodeling of the affected breast if, because of tumor position, the result of conservative surgery is less than satisfactory; and use of radioguided surgery to detect the sentinel node which, if not involved, may indicate that full axillary dissection is unnecessary. The Oncologist 1996;1:340-346

Introduction
Up to the end of the 19th century, breast cancer was considered invariably fatal. However, the American surgeon W.S. Halsted became convinced that breast cancer spread by direct extension into muscle and skin and through lymphatic ducts to regional lymph nodes, which held the cancer cells in check prior to widespread dissemination. If this were true, it meant that breast cancer was a mainly locoregional disease that could be cured definitively by timely and radical surgery.

In 1898, Halsted presented 76 mastectomized cases to the American Surgical Association [1] illustrating his thesis that breast cancer could be cured. Thereafter, radical mastectomy became the accepted treatment for breast cancer. In fact, in Western countries up to the 1970s, the Halsted mastectomy was the standard treatment even for small breast cancers. And although it undoubtedly saved the lives of millions of women, the treatment left an ugly scar, a depression beneath the clavicle, protruding ribs, and often required a skin graft.

Two currents of thought developed slowly from Halsted’s ideas. The first sought to convince ordinary people and physicians that if diagnosed early, breast cancer was curable; it implied the development of means to diagnose early disease, and also wide dissemination of the message that early diagnosis was vital.

The second current of thought has been concerned with reducing the extent of surgical and subsequent treatment, and has emerged as understanding of the natural history of breast cancer increased and the mode of initial presentation changed. At the beginning of the century, breast cancer was usually diagnosed when locally advanced: when the mass...
was large and the skin was involved and often ulcerated. Today, small, palpable lesions are the normal presentation or, with the aid of radiography, even preclinical nonpalpable lesions are identified.

As with many types of malignant tumors, surgeons became interested in the use of preserving surgery to treat small-size breast cancers in the 1970s. At that time, the disease came to be viewed as one generally involving only part of the breast, and not affecting the whole gland. The term quadrantectomy was coined in Milan at that time [2] to refer to a breast-conserving operation consisting of wide resection in surrounding healthy tissue; it took its rationale from the view that the probability of finding tumor cells around the primary tumor was inversely related to distance from the lesion, as confirmed by Holland [3] and that the intraductal spread of cancer cells occurred radially. Quadrantectomy aims to achieve effective local control and is therefore more extensive than lumpectomy or tumorectomy, whose principal objective is to debulk the tumor mass [4]. Other terms to define this type of operation are “sector resection,” “extensive breast resection,” “breast lobectomy,” etc.

**Quadrantectomy as Optimal Surgery**

A randomized trial began in Milan in 1973 to compare small-size breast cancer patients treated by Halsted mastectomy with those receiving quadrantectomy plus axillary dissection plus radiotherapy (QUART). The radiotherapy (50 Gy) was administered in two tangentially opposed fields using high-energy equipment, with a boost of 10 Gy to the scar given with orthovoltage equipment.

This trial concluded at the beginning of 1980 after 701 cases had been recruited; 349 underwent ablative surgery, and in 352 the breast was conserved. The preliminary results [2, 5] indicated similar survival in both groups. After 20 years, this trend was confirmed [6] and also indicated that local recurrences treated conservatively or by salvage mastectomy did not affect the prognosis. The survival curves showed that QUART gave identical results to the Halsted mastectomy; furthermore, subdivision of the patients by tumor size, site, and age still did not reveal any difference between the two treatments.

Following that and many subsequent trials, it is now generally accepted that a wide resection such as quadrantectomy represents the optimal surgical treatment for breast cancers up to 3 cm maximum diameter [7]. However, such treatment should generally be flanked by radiotherapy and axillary dissection to ensure the lowest possible relapse rate and highest cure rate. These aspects of the treatment are discussed more fully below, but we note here briefly that recent developments may eventually render one or both of these support therapies unnecessary. Another recent development is the extension of quadrantectomy to large tumors previously treated by chemotherapy to reduce the size of the mass and permit a safely conservative approach [8, 9]. We accept, nevertheless, that there are still infrequent situations in which mastectomy is preferable as part of a curative approach to breast cancer.

**Wide Resection Versus Lumpectomy**

The optimum indications for conservation versus mastectomy emerged as an area of uncertainty following the early breast conservation trials. These uncertainties provoked resistance to breast conservation among surgeons, many of whom still insist that mastectomy is preferable for all cases of breast carcinoma. However, the many clinical trials that followed the pioneering ones are now yielding results that are clarifying most of these uncertainties.

Following second-generation trials [10-13] which investigated different surgical approaches and types of radiotherapy, the randomized Milan II trial [14] was conducted from 1985 to 1987, recruiting 705 patients; 360 received QUART and 345 received TART — tumorectomy or lumpectomy (limited surgery whose purpose was exclusively reductive), plus axillary dissection, followed by external radiotherapy and a boost with 198Ir implant. Local relapses were few in the QUART group (5.3%) whereas 46 (13.3%) occurred in the TART group (Fig. 1). Other more recent findings also indicate that a wider margin of resection correlates with a lower rate of recurrence [15]. These studies clearly show that, even with subsequent radiotherapy to the breast, a wide excision like quadrantectomy carries a lower risk of local recurrence than lumpectomy. While there is considerable evidence that a local recurrence is not an instigator of new metastases (and does not seem to influence survival rate), such an event not only frustrates the objectives of breast conservation, because it often leads to mastectomy, but is highly stressing for the patient.

It has been claimed that careful assessment of resection margins may result in lower rates of recurrences in tumorectomy [16]. Our opinion, in fact, is that thorough pathological examination of the removed piece is important. The technique that has been generally adopted over the last ten years is to mark the margin surface of the specimen with India ink or tattoo dye that adheres to the tissue and is microscopically recognizable. The surgeon must also indicate the orientation of the specimen.

Although it is easy to recognize positive margins, it is difficult to identify borderline cases, and the tumor is sometimes vaguely indicated as being “close to the margins.” Nevertheless, even when margins are ascertained as negative, outcomes of limited surgery are disappointing. In the NSABP B06 trial [17], lumpectomies with negative margins had a local recurrence rate of more than 40%. Furthermore, efforts to find improved methods for
assessing margins, such as the use of monoclonal antibodies [18], have not improved the situation.

For all these reasons, the best policy would seem to be to maintain excision margins at a minimum of 2 cm, respecting the finding of Holland et al. [3] that the number of cancer foci at the periphery of the primary site decreases progressively with distance from tumor edge; they found cancer foci at 1 cm in 59% of cases, but in only 17% of cases (including in situ carcinomas) at 3 cm. We adhere to this view even though Schnitt [19] and we [14, and see below] have shown that postoperative radiotherapy can destroy a good portion of residual tumor.

When resection margins are positive, re-excision seems adequate treatment in most cases [20]; however, the presence of extensive intraductal component necessitates a very wide breast resection [3, 18, 19] (Fig. 2).

There is also the problem of how to treat local recurrences. In most cases, a carefully performed re-excision is sufficient. Whether or not systemic therapy should be initiated remains a matter for discussion. We tried to identify characteristics of local recurrence cases that indicated the need for additional treatment compared with recurrences which were simply the result of inadequate surgery [21]. We found that a recurrence less than two years after the original surgery, young age, and the presence of intravascular invasion were indicators of the need for additional treatment to forestall systemic disease.

EXPANDING THE INDICATION FOR CONSERVATION

The diameter of the tumor mass was long considered the most important prognostic factor in breast cancer, and breast conservation has generally been thought appropriate only for tumors up to 2-3 cm in maximum diameter (Fig. 3). However, new biological parameters allow us to determine the local aggressiveness of the cancer, rendering size less important. The results of an analysis using Cox’s multi-regression model on 2,233 patients receiving quadrantectomy plus axillary dissection and breast radiotherapy [21] showed that patients younger than 46 years at surgery had a much greater risk of local recurrence than those older than 65, thus indicating age as an important parameter for local aggressiveness. Furthermore, in the same series we found that risk of local recurrence was reduced in patients with metastatic axillary nodes compared with those without metastatic.
nodes. The analysis also showed that presence of extensive intraductal component and peritumoral lymphatic invasion were highly significant predictors of local recurrence.

On the other hand, the ratio between tumor size and quantity of surrounding breast tissue is important. In a voluminous breast, conservation is possible even if the tumor is large. Furthermore, as noted previously, conserving treatment is feasible in large-size breast cancer after several cycles of preoperative chemotherapy, or chemo- plus radiotherapy. In our experience on 226 patients [9], preoperative chemotherapy permitted conservative surgery in 90% of cases, and did not depend on the chemotherapy regimen adopted. Nevertheless, this approach requires careful attention to several details, including the extent of tumor regression in the area of breast involved, which must be carefully evaluated by the pathologist, as well as the presence of microcalcifications, which must be identified prior to surgery and all removed during surgery. Particular care must be taken with the esthetic outcome—which is, after all, the reason the patient underwent the ordeal of chemotherapy. Finally, in rare cases, the tumor does not regress with chemotherapy. These cases must be identified quickly so that mastectomy can be performed.

The results of our more recent pilot study employing preoperative radiotherapy in association with chemotherapy showed that the approach can be useful in small-size breast cancer, not only to permit more limited surgery but to increase the efficacy of the chemotherapy. The approach seems promising enough to merit further study, but cannot be recommended as routine treatment [22].

**IMPROVING THE AESTHETIC OUTCOME**

Tumors localized in quadrants other than the upper-outer may present technical problems for the surgeon when balancing the need for oncological radicality with the need of a good aesthetic outcome. Thus, if margins of at least 2 cm are accepted as necessary, the usual radial incision makes it difficult to obtain good cosmesis in these quadrants. For the case of a tumor in the central quadrant, a skin-gland flap can be defined within a lower quadrant adjacent to the central quadrant and moved up to fill the void. This technique provides excellent objective results as well as patient satisfaction [23].

The general solution we propose, in fact, is to extend the interdisciplinary collaboration that is already necessary for optimal breast cancer treatment and include a plastic surgeon...
in the senology team so that the affected breast can be remodeled immediately. Often, the patient is not so worried about the disease itself, which she understands is curable, but is concerned about the integrity of her body, and may even request immediate remodeling of the contralateral breast as well as the affected one. We sometimes propose bilateral surgery which, in addition to facilitating a good aesthetic result, also provides information on the biological state of the other breast.

**Axillary Lymph Node Dissection: Can It Be Avoided?**

The recognized surgical adjunct to the conservative approach is axillary lymph node dissection. This is performed in continuity with the breast incision when the tumor is in the upper-outer quadrant of the gland, while a separate incision is normal when the tumor is located elsewhere. In the latter case, the best incision is one which crosses the axillary skin along fold lines. The indications for, and techniques of, axillary clearance are still a matter of intense controversy. Some surgeons believe that upper-arm lymphedema is such a severe complication of complete dissection that it is preferable to remove the first level only or to perform a random sampling [24, 25].

We believe that if axillary dissection is indicated, it should be complete [26], i.e., it must include the three levels defined by Berg [27]: A) all lymph nodes lateral to the lateral margin of the pectoralis minor muscle; B) the nodes behind the pectoralis minor muscle, and C) the nodes medial to the medial margin of the muscle, in the space known as the apex of the axilla. The adipose tissue situated between both muscles, which includes the Rotter lymph nodes, must also be carefully explored. If nodes are palpable, they must be removed, sparing always the thoracic acromial peduncle and the interpectoral vessels [28].

It is our conviction that failure to remove all three node levels risks understaging the case, not only because there may be skip metastases (Table 1), but also because, as demonstrated in a preliminary study on 777 cases [26], involvement by level is important prognostic information additional to that provided by the number of nodes involved.

Furthermore, the idea that arm edema is due to extension of the dissection to the axilla and to radiotherapy to residual breast parenchyma is not borne out by experience. Arm edema was frequent following the classic Patey mastectomy in which only the first two levels were removed; whereas our experience is that edema occurs in 5%-6% of cases treated by surgery involving complete axillary dissection but which spares the two pectoral muscles and all vessels between.

However, with improved detection measures, we now treat greater numbers of patients with small tumors, often less than 1 cm in maximum diameter, in whom the chances of finding histologically positive nodes in a clinically clear axilla are very low (of the order of 6%) [30]. This implies that in more than 90% of such patients, healthy lymphatic tissue (i.e., precious, immunocompetent tissue) is being removed mainly to provide prognostic information that can now be obtained from biological and biomolecular analysis of the primary carcinoma.

In view of this we do not now, as a rule, perform the dissection in T1a breast cancer in women over 45 years of age. Furthermore, we are conducting a trial at the European Institute of Oncology designed to address this problem in breast cancers of less than 1 cm. The aim is to determine the incidence of axillary metastases in untreated clinically negative axilla and assess the protection afforded by prophylactic axillary irradiation, adjunt treatments being decided on the basis of prognostic factors (grading, proliferative rate, estrogen receptors) derived from the primary tumor.

The identification of sentinel nodes is under investigation for assessing locoregional spread in breast cancer [31]. We also are engaged in a study on sentinel nodes. Its objectives are to identify the first node that receives lymph from the tumor area by radioguided probe following injection of 99mTc-labeled human colloid albumin into the skin overlying the tumor, followed by lymphoscintigraphy to determine the feasibility of isolating this node surgically with the aid of a radioguided probe. If a clear sentinel node correlates with the lack of involvement of all the other nodes, then a negative sentinel node can be used as an indicator that further axillary dissection is not necessary. Other centers are using methylene blue dye and its uptake by the sentinel node instead of 99mTc-labeled human albumin.

**Multicentricity**

While the two major histotypes, ductal and lobular carcinoma, do not seem to differ much in determining either treatment or disease prognosis, this is not the case for multicentric

<table>
<thead>
<tr>
<th>Levels involved</th>
<th>Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>455 (54.2)</td>
</tr>
<tr>
<td>I + II</td>
<td>187 (22.3)</td>
</tr>
<tr>
<td>I + II + III and I + III</td>
<td>186 (22.2)</td>
</tr>
<tr>
<td>Total number of cases with regular distribution</td>
<td>828 (98.7)</td>
</tr>
<tr>
<td>II</td>
<td>10 (1.2)</td>
</tr>
<tr>
<td>III</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Total number of cases with “skip” distribution</td>
<td>11 (1.3)</td>
</tr>
<tr>
<td>Total</td>
<td>839 (100.0)</td>
</tr>
</tbody>
</table>

Adapted from Veronesi et al. [29].
lesions. When disease is present at multiple sites in different quadrants, irrespective of size, more extensive surgery is mandatory, from subcutaneous mastectomy for non-infiltrating lesions to total mastectomy for multiple infiltrating lesions associated with other non-infiltrating localizations.

THE IMPORTANCE OF RADIOTherapy
In the Milan II trial [14], only 8 of 46 patients with positive local margins experienced recurrences, implying that radiotherapy destroyed malignant tissue in the other 38 cases, and leading us to conclude that more than 80% of breast cancers are radiosensitive. The subsequent large-scale Milan III trial [32] compared quadrantectomy with and without radiation to the breast and showed significantly lower rates of local recurrence in the irradiated group (Fig. 1). Based on these findings, we regard radiotherapy as an essential component of breast conservation, although further research is required to establish whether it may be safely avoided in postmenopausal women [31] as we suggested in the conclusion of the Milan III trial.

It is likely that a subset of postmenopausal patients with small, well-differentiated tumors of low proliferative rate may be treated by conservative surgery without adjuvant radiotherapy.

Conclusions
We believe that the triple approach of wide conservative surgery, flanked in most cases by complete axillary dissection and radiotherapy, represents the optimal approach to breast cancer at the present time. Wide local resection plus aggressive radiotherapy are necessary to keep the risk of local recurrence as low as possible. This is important because, as noted above, recurrence is traumatic for the patient and also because, as Lippman has pointed out [33], it is difficult to exclude that a local recurrence carries increased risk of dissemination and mortality. Most randomized trials do not show any correlation between local recurrence rates and mortality, but they do not have the power to detect a modest increase in mortality as a result of inadequate local treatment. Perhaps a meta-analysis might detect such an effect. We are in the process of changing our philosophy that axillary dissection should be performed in all cases; however, until the alternatives have been demonstrated equally effective, we would continue to recommend it.

It is gratifying that mortality from breast cancer is now showing a decline in the USA and many European countries, even though the incidence continues to rise [34]. Clearly, information programs and screening should continue to ensure that the disease is diagnosed as early as possible; furthermore, it is important that the optimal treatment protocols now identified be adopted by all oncologists. The challenge facing surgeons in the future is that of tailoring the treatment ever more precisely to the local and general aggressiveness of the disease. Advances on this front will depend on continuing large-scale multicentric trials that evaluate the influence of more subtle markers of the biological behavior of breast cancer.

Acknowledgments
We thank D. C. Ward for help with the English.

References
3 Holland R, Connolly JL, Gelman R et al. The presence of an extensive intraductal component following a limited excision correlates with prominent residual disease in the remainder of the breast. J Clin Oncol 1990;8:113-118.
33 Lippman ME. How should we manage breast cancer in the breast, or buddy, can you paradigm? J Natl Cancer Inst 1995;87:3-4.

---

Meet The Professor

A FORUM FOR DIALOGUE…

The editors of The Oncologist encourage you to participate in this interactive section of the Journal. Please send your questions and comments to:

**MEET THE PROFESSOR—DR. VERONESI**

*The Oncologist*

AlphaMed Press

One Prestige Place

Suite 290

Miamisburg, Ohio 45342-3758, USA

Fax: +937-291-4229

e-mail: alphamed@dialup.oar.net