

0959-8049(95)00461-0

Editorial

Lumpectomy Versus Quadrantectomy for Breast Conservation: a Critical Appraisal

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THE DETECTION of breast cancer is increasing, and it is estimated that, in the next decade, five million women worldwide could be affected by the disease. The report by the Milan group that appears in this issue (pp. 1574-1579) [1] and which updates previous findings by that group [2, 3], is, therefore, of particular significance. Since there is no sound scientific or clinical justification for using mastectomy for the management of a large number of such patients, the use of breast conserving operations will increase. Consequently, how best to accomplish breast conservation is an issue of fundamental importance. Whereas the Milan group is a proponent of quadrantectomy and breast irradiation (QU.A.R.T) to achieve breast conservation, the NSABP subscribe to the use of lumpectomy followed by breast irradiation to preserve the breast. This editorial will present a critical appraisal of the two widely diverse methods for achieving breast preservation.

The Halstedian paradigm, formulated at the end of the 19th century, governed surgical management of breast cancer for most of this century. The hypothesis that gave rise to that paradigm was formulated from the anatomical and mechanistic perception of tumour spread that was in keeping with the understanding of the biology of metastasis at that time. Consequently, the Halsted radical mastectomy, characterised by *en bloc* dissection, became the hallmark of the surgical approach. That operation was conceived and evolved as a result of the belief that greater curability could be achieved with more expansive, meticulously performed operative procedures. The use of radiation therapy after surgery was governed by the same principles. Three decades ago, after conducting a series of laboratory and clinical investigations to obtain a better understanding of the biology of metastasis, I proposed a second (alternative) hypothesis, which was biological, rather than anatomical and mechanistic, in concept [4]. Its components are completely antithetical to those of the Halstedian thesis. One of the tenets of the alternative hypothesis contends that "variations in the local regional therapy of breast cancer are unlikely to affect survival".

During the 1970s, the NSABP implemented two randomised clinical trials involving more than 3000 patients to test the alternative hypothesis by determining the outcome of patients

following the use of different regimens of surgical management. The first trial, NSABP B-04, was implemented in 1971. Patients with primary breast cancer and no clinical evidence of axillary node involvement were treated by Halstedian radical mastectomy, by total (simple) mastectomy with local-regional irradiation but no axillary dissection, or by total mastectomy without radiation, and removal of nodes only if they later became clinically involved. Patients with clinically positive axillary nodes were treated by either radical mastectomy or by total mastectomy and local-regional irradiation. After nearly 20 years of follow-up, despite the non-conformity of the treatment regimens, no significant difference in overall treatment failure, distant metastasis, or overall survival has been noted among the three node-negative treatment groups or between the two node-positive groups [5]. These findings support the concept of breast conserving surgery.

The second NSABP trial, B-06, which was originally planned in October 1973, was initiated in April 1976. Patients were assigned to one of three different treatment groups: total mastectomy, lumpectomy alone, or lumpectomy followed by breast irradiation. All patients had an axillary dissection, and those with positive nodes received chemotherapy. Results from that study, first reported in 1985 after 5 years of follow-up [6] and recently analysed after 12 years [7], have demonstrated no significant difference in either disease-free survival, distant disease-free survival, nor overall survival among the three groups. These findings provide further support for the hypothesis that variations in survival are unlikely to be affected by local-regional therapy, and have contributed greatly toward shifting the doctrine in breast cancer surgery from one that advocates mastectomy to one that has breast conservation as its hallmark.

The observations reported by the Milan group add further weight to this argument in that four different treatment regimens, i.e. Halstead mastectomy, QU.A.R.T, quadrantectomy without radiation therapy (QU.A.D), or lumpectomy followed by radiotherapy (tumorectomy, T.A.R.T), failed to result in a significant difference in survival of patients within the different treatment groups. For a physician to continue to select mastectomy instead of breast conservation because of bias, or fear that distant disease-free survival or survival will be poorer by not removing the breast has no justification, as indicated by the NSABP findings [5, 7], those by Baum and his colleagues from the British Cancer Research Campaign Study [8], and now those described by the Milan group [1].

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Received 9 Aug. 1995; accepted 10 Aug. 1995.

Although the findings on the similarities in distant disease and survival outcomes ensure the continuance of surgical management of breast cancer by breast conservation, there are several issues that remain unsettled. These issues do not challenge the verity of the new paradigm but are more concerned with its refinement. Such was the case during the mastectomy era, when the issues were unrelated to the propriety of the Halsted paradigm, but were concerned with resolution of disagreements relative to how thin skin flaps must be, how much skin should be removed, how extensive a lymph node dissection ought to be, and the qualitative and quantitative nature of radiation therapy to be administered postmastectomy. In the later years of the Halstedian era, issues regarding how a modified radical mastectomy or a simple total mastectomy should be performed were also debated extensively.

Currently, some of the most contentious issues regarding the use of breast conservation relate to the amount of normal breast tissue that should be removed and to whether there are predictors of the development of ipsilateral breast tumour recurrence (IBTR) that might be used for determining which patients are not good candidates for breast conservation. It is these and other issues on how best to employ breast conservation that have resulted in most disagreement.

The difference between lumpectomy used by the NSABP and quadrantectomy by the Milan group is neither semantic nor trivial, and the two procedures differ in more than just how much "normal" breast tissue is removed. Not only are the surgical procedures of considerably different magnitude, but they also seem to be conceptually unrelated. Lumpectomy was designed to remove, through a limited curvilinear incision, the tumour, together with enough "normal" tissue to ensure that the margins of the resected specimen are tumour-free. The reason for insisting that specimen margins be tumour-free is to provide greater certainty that no gross tumour at the operative site remains. Inked specimen margins were recommended to aid pathologists in determining that the tumour is not transected and that the margins are free of tumour, because it is recognised that radiation therapy is most effective in eliminating a minimal tumour burden. When a lumpectomy is performed, *en bloc* dissections are not carried out, not even for upper-outer quadrant lesions. Nodal dissections are limited to the lower two levels of the axilla. No skin, fascia or muscle is removed. While lumpectomy was initially performed in patients with tumours of 4 cm or less, the criterion for tumour size was subsequently expanded to include patients with tumours of 5 cm. The procedure is used to treat patients of any age or axillary nodal status (positive or negative), regardless of the site of the tumour in the breast and regardless of any particular tumour characteristic.

In sharp contrast, a quadrantectomy, as described by the Milan group, uses a long radial incision through which tumours ≤ 2 cm and, more recently, ≤ 2.5 cm in size are removed with a 2–3 cm cuff of normal tissue circumscribing the tumour. Skin, pectoral fascia, and the pectoralis minor muscle are also removed. Moreover, an *en bloc* dissection is employed for removal of at least 50% of lesions, i.e. those in the upper-outer quadrant, in conjunction with a total axillary nodal dissection. Those requirements limit the feasibility of attaining a satisfactory cosmetic result and of removing even "small" tumours in women with "small" breasts. For example, in a woman who has a tumour of 2 cm, the diameter of the resected specimen would be 6–8 cm. In a large proportion of women, the anatomical location

of the tumour may obviously preclude removal of that amount of breast tissue in all directions.

Conceptually, quadrantectomy can be viewed as a "next step" in redefining the Halstedian paradigm, a step beyond the Patey operation (modified radical mastectomy) and simple mastectomy, all of which maintain attachments to the Halstedian paradigm. Lumpectomy, in contrast, has abandoned every vestige of Halstedian surgery and, in that regard, is conceptually and technically different from quadrantectomy.

The NSABP findings differ from those of the Milan group, which indicate a considerable difference in local failure between age groups and that in "limited surgical resection and radiotherapy (T.A.R.T.), the local recurrence rate varied markedly with EIC (extensive intraductal component) positivity". In an effort to identify patients in the NSABP B-06 study who were either more or less likely to develop an IBTR following lumpectomy, 32 pathological features were examined, including EIC and age [9]. None of the features were found to be related to IBTR following lumpectomy and irradiation. Age was unrelated to IBTR, except in women younger than 35 years, where breast recurrence was more frequent. Because our studies demonstrated that EIC had no influence on the incidence of IBTR, in contrast with those from Milan, we do not exclude the use of lumpectomy and irradiation when the pathological condition is encountered. (To my knowledge, those investigators who originally proposed that EIC was a contraindication for the use of lumpectomy have retracted that conclusion. [Refs]) The presence of EIC is meaningful only when specimen margins are involved.

The Milan II study indicates that QU.A.R.T. resulted in significantly fewer local recurrences than did T.A.R.T. When taken at face value, these findings suggest to the surgeon who is treating patients with breast cancer that, since QU.A.R.T. is more efficacious than T.A.R.T. in the treatment of small (≤ 2.5 cm) tumours, the procedure might be even more appropriate than T.A.R.T. for managing larger tumours and, consequently, should be used for all patients. However, there are two main problems with this argument which prevents me from subscribing to their conclusions.

It should be noted that in the Milan II study, a substantial number of local recurrences present in T.A.R.T. patients had resected specimens with tumour-involved margins. Contrary to NSABP policy, patients with tumour-positive margins, or those whose margins were not examined, were not subjected to re-resection in an effort to obtain tumour-free margins. They were evaluated with those who had tumour-free margins. In those whose margin status was determined, a local recurrence was observed in 8.6% of Milan patients with negative margins, an incidence similar to that observed in NSABP B-06 lumpectomy-treated patients, all of whom had tumour-free margins. In contrast, 17.4% of the Milan T.A.R.T. patients with positive margins had recurrent tumours. Since 34% of the total number of recurrences in the Milan study were observed in patients in whom specimen margins were not examined, it is possible that many had tumour-involved margins. This emphasises the importance of tumour-free specimen margins when carrying out breast conserving surgery.

The issue arises of the extent of residual tumour remaining in the breasts of T.A.R.T. patients with tumour-positive margins, which is particularly important when considering radiation therapy for those patients. It seems that more aggressive radiation therapy was administered to the QU.A.R.T. than to the T.A.R.T.-treated patients in the Milan study. Not only was the

total dose to the whole breast 10% higher in the former than in the latter (50 Gy versus 45 Gy), but there was also a difference in the boost used. Whereas the QU.A.R.T group received external beam irradiation, interstitial implants were placed in the tumour bed of the T.A.R.T patients. Thus, the volume of breast tissue treated by the boost in the QU.A.R.T group was likely to have been greater than in those treated by T.A.R.T, where the irradiation was confined to a smaller area of the breast. Thus, it can be speculated that, in a substantial number of patients, incomplete tumour excision and less aggressive irradiation may account for at least some of the difference in the incidence of local recurrence between the two treatment groups, and for the higher incidence of IBTR following T.A.R.T than has been noted in NSABP lumpectomy-treated patients, where the total dose of radiation to the whole breast was 50 Gy.

The incidence of IBTR in the NSABP B-06 trial should be viewed as "historical", when many American surgeons learnt how to perform a lumpectomy and numerous radiation oncologists learnt the technique for breast irradiation. Moreover, in the B-06 study, only node-positive patients received systemic therapy, whereas, in more recent trials, node-negative as well as node-positive patients have received chemotherapy and/or tamoxifen therapy. Nonetheless, a recent update of the B-06 study demonstrates that, in all patients receiving lumpectomy and breast irradiation, there was a 10% cumulative incidence of IBTR after 12 years of follow-up; 12% for node-negative patients and 5% for node-positive patients, values considerably lower than those observed at 8 years following T.A.R.T.

Results from three recent NSABP studies in which node-negative patients received systemic therapy following lumpectomy and irradiation indicate that the incidence of IBTR was similar to that noted following QU.A.R.T and much less than following T.A.R.T. In one trial (B-13), node-negative, ER-negative patients received methotrexate followed by 5-fluorouracil (M→F). After 8 years of follow-up, the incidence of IBTR was 2.6% and the annual rate of local recurrence was 0.38. In another study (B-19), patients similar to those in B-13 received CMF (cyclophosphamide, methotrexate, 5-fluorouracil). The incidence of IBTR after 5 years was 1.5% and the rate was 0.37. When tamoxifen was administered to node-negative, ER-positive patients (B-14), after 5 years of follow-up, only 2.1% demonstrated an IBTR.

Since therapy administered to decrease the probability of distant metastases effectively reduces the incidence of IBTR, it is no longer appropriate to evaluate the influence of local-regional

treatments, i.e., surgery and radiation, on the occurrence of IBTR independent of the effect of systemic therapy. Moreover, it must be strongly emphasised that, despite the comparisons made here between the Milan and NSABP data, decisions by physicians on the choice of a breast conservation operation should not be made on the strength of such comparisons. They are meaningless if for no other reason than that the patient populations are so different. For example, in the Milan II trial, 89% of women had tumours ≤ 2 cm and 71% were node-negative. In contrast, 45% of NSABP patients had tumours > 2 cm and nearly 40% were node-positive.

In conclusion, I continue to believe that lumpectomy with tumour-free specimen margins, followed by breast irradiation and systemic adjuvant therapy, when indicated, is the appropriate therapy for most patients with stage I and II breast cancer. Since survival and IBTR rates are similar in NSABP lumpectomy-treated patients to those in QU.A.R.T-treated patients, and the cosmetic results following lumpectomy are superior, the use of lumpectomy is preferable.

1. Veronesi U, Salvadori B, Luini A, *et al.* Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomised trials on 1973 patients. *Eur J Cancer* 1995, **31A**, 1574-1579.
2. Veronesi U, Saccozzi R, Del Vecchio M, *et al.* Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med* 1981, **305**, 6-11.
3. Veronesi U, Volterran F, Luini A. Quadrantectomy versus lumpectomy for small size breast cancer. *Eur J Cancer* 1990, **26**, 671-673.
4. Fisher B. Laboratory and clinical research in breast cancer—a personal adventure. The David A. Karnofsky memorial lecture. *Cancer Res* 1980, **40**, 3863-3874.
5. NSABP Progress Report, August 1995, 135-142.
6. Fisher B, Bauer M, Margolese R, *et al.* Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985, **312**, 665-673.
7. Fisher B, Anderson S, Redmond C, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and twelve-year results of a randomised clinical trial comparing total mastectomy to lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med*, submitted.
8. Cancer Research Campaign Working Party (Baum M, Haybittle JL, Berstock DA, *et al.*). Cancer Research Campaign (King's/ Cambridge) trial for early breast cancer. *Lancet* 1980, **ii**, 55-60.
9. Fisher ER, Anderson S, Redmond C, Fisher B, and NSABP Collaborating Investigators. Pathologic findings from the National Surgical Adjuvant Breast Project protocol B-06: ten year pathologic and clinical prognostic discriminants. *Cancer* 1993, **71**, 2507-2514.