

## Conservative treatment evolution in breast cancer

Umberto Veronesi

*European Institute of Oncology, Milan, Italy*

In the late 1960s, we became interested in the possibility of preserving the breast in patients with small breast carcinomas for a number of reasons: new information on the natural course of this disease, tendency that smaller tumors are being detected on diagnosis, and the fact that aggressive local-regional treatments have failed to improve prognosis. For example, at the end of the 1960s an international randomised trial, comparing traditional Halsted mastectomy with Halsted mastectomy plus dissection of the internal mammary nodes, showed that the more aggressive approach had no advantage over the traditional surgery.

The objectives in conserving the breast are to achieve effective local control and at the same time produce a good cosmetic result. To this end we developed an extensive surgical excision called "quadrantectomy", whose main characteristic was a radially directed incision by which the resection encompassed the whole ductal tree from the retro-areolar region downwards and to the periphery. We were convinced that intraductal permeation was an important mechanism of tumor spread, and that therefore all branches to the involved duct had to be removed. The main duct and its associated tree is often referred to as a breast lobe and the operation could have been designated "lobectomy"; however we chose the name quadrantectomy since the quadrant concept was simpler to explain. After quadrantectomy we planned radiotherapeutic treatment consisting of 50 Gy delivered to two tangentially opposed fields, using high energy equipment, plus a

boost of 10 Gy on the scar with orthovoltage equipment. The procedure was completed by total axillary lymph node dissection (all three levels). We considered that this intervention, which we called QUART, was radical, although at the beginning we applied it only to T1 tumors (less than 2 cm).

In 1973 we began a randomized trial (the *Milan I Trial*) to compare small size breast cancer patients treated by Halsted mastectomy with those receiving QUART. The trial was concluded by the beginning of 1980, after 701 cases had been recruited: 349 underwent mutilating surgical intervention while in 352 the breast was conserved. The preliminary results<sup>1</sup> indicated similar survival in both groups. After 20 years this trend was confirmed,<sup>2</sup> and also demonstrated that local recurrences treated by salvage mastectomy did not affect the prognosis. The thirteen year survival data showed that QUART gave identical results as Halsted mastectomy, and that subdivision of patients by tumor size, site and age still did not reveal any difference between the treatments. Subdivision by lymph node involvement showed that QUART was superior to Halsted, although the difference was not statistically significant. Furthermore, the fear that radiotherapy might entail a late oncogenic effect was not confirmed. There were nine new ipsilateral cancers in patients with heavily irradiated breasts, and 19 new cases in the contralateral breasts, the same number that occurred in the contralateral non-irradiated breasts of Halsted patients. It appeared therefore that breast irradiation, at the doses we used, might protect the breast, either by destroying occult foci of *in situ* lesions or by inactivating any proliferative precancerous lesions.

The conclusion that breast conservation is as safe a procedure as traditional mastectomy in small breast carcinoma was confirmed in subsequent publications.<sup>3-6</sup>

Correspondence to: Prof. Umberto Veronesi, MD, European Institute of Oncology, Via Ripamonti 435, 20141 Milano, Italy.

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The question arose, however, as to whether better cosmetic results could be achieved by an even less aggressive surgical approach. Following a number of second generation trials implemented in various centers,<sup>7,9</sup> studying different surgical approaches and types of radiotherapy, we initiated a new trial which compared classic quadrantectomy, axillary dissection and radiotherapy with a more limited surgical treatment consisting of a lumpectomy ("tumorectomy") plus axillary dissection, followed by external radiotherapy and a boost with <sup>192</sup>Ir implantation (TART). Lumpectomy consisted of excision of the primary tumor with a 1 cm margin of normal breast tissue, without including the overlying skin except for a very small portion for histologic confirmation. Axillary dissection was always total, and was performed by separate incision, as defined. Radiotherapy was both external and interstitial. External irradiation began four weeks after surgery and the technique was the same as that used after quadrantectomy, with the difference that the total dose (45 Gy) was given over five weeks. After 2-3 weeks <sup>192</sup>Ir wires were implanted interstitially to give a boost of 15 Gy directly to the tumor bed. A total of 60 Gy was thus given to both groups of patients. Radiation was never applied to the axillary or supraclavicular regions. Seven hundred five patients were admitted, 360 received QUART and 345 received TART, the groups being comparable clinically and in terms of the adjuvant treatment received. Local failures in the area of the previous surgery (i.e. cutaneous, subcutaneous and parenchymal lesions) appearing three to five cm from the quadrantectomy/lumpectomy scar were considered true local recurrences. At the time of last review there were 15 local recurrences in the QUART group and 34 in the TART group. Survival was the same in both groups.

The results of this trial will pose a very delicate dilemma to the surgeon as he has to decide whether the better cosmetic result obtained by tumorectomy and radiotherapy could counterbalance the greater incidence of local recurrences taking into account the fact that recurrences are traumatic for patients, in whom intense anxiety often appears or reappears. Since local recurrences are in some cases treated by mastectomy, an excessive number of salvage operations would compromise the original objectives of the procedure.

In more recent years new trials have been undertaken in an attempt to verify whether radiotherapy is necessary after breast conservative procedures. In Sweden, the Uppsala-Örebro Breast Cancer Study

Group<sup>10</sup> showed that women who underwent conservative surgery without radiotherapy had a significantly higher rate of local recurrences than those in whom radiotherapy was used.

Between 1987 and 1989 in Milan we randomly assigned 567 women with small breast cancers to quadrantectomy followed by radiotherapy or to quadrantectomy without radiotherapy.<sup>11</sup> As usual, all patients underwent total axillary dissection and regular follow-up (for a mean period of 39 months). Two hundred ninety nine patients received QUART and 280 received quadrantectomy plus axillary dissection without radiotherapy (QUAD). There was no significant difference between the two groups with respect to age, site and size of the primary, histological characteristics, or level of axillary invasion; neither was there any difference with regard to level of nodular involvement broken down by adjuvant treatment administered. We did, however, observe a marked difference between the two groups with respect to recurrences. Only three of the 294 QUART patients (1%) developed a local recurrence, compared with 28 local recurrences among the 280 patients (10%) of the QUAD group.

This trial clearly showed that postoperative radiotherapy administered directly after quadrantectomy has a protective effect against local recurrences and new primary carcinomas. That there was a difference between the two groups did not surprise us; what was a surprise was the magnitude of the difference between them: 28 local recurrences and four new carcinomas after quadrantectomy alone, compared with three recurrences and no new tumors when quadrantectomy was combined with radiotherapy. In the QUAD group local recurrences occurred mainly in patients under 55 years of age, but rarely in patients older than that. The presence of an extensive intraductal component was also confirmed as an important predictor of local recurrences. This trial definitively established quadrantectomy plus axillary dissection and radiotherapy as an effective conservative treatment that does not expose patients to increased risk of local recurrence, notwithstanding the fact that in older women conservative surgery without radiotherapy may result in a low rate of local recurrences, provided that the surgery is an extensive one, removing two to three cm of normal tissue around the primary carcinoma.

In a more recent analysis of breast cancer patients uniformly treated by quadrantectomy, axillary dissection and subsequent radiotherapy, we evaluated local and distant recurrences according to

demographic, biological and pathological variables in 2233 women.<sup>12</sup> Young age was an important risk factor for recurrence, with peritumoral lymphatic invasion also predictive for local and distant events. Tumor size and axillary lymphnode involvement were not related to local recurrences but were important predictors of distant metastases. Extensive intraductal component was only a risk factor for local recurrence. Finally, women up to the age of 35 at first diagnosis, who had initial peritumoral lymphatic invasion and local recurrence within two years of surgery, were at high risk for distant spread.

More recent developments of the conservative approach to breast cancer are directed to the avoidance of the axillary dissection in cases with clinically negative nodes.<sup>13</sup> In fact, the axillary dissection is presently performed for staging purposes and any method that would identify the presence of occult metastases without the need of such an extensive total axillary dissection, would greatly improve the quality of life of breast cancer patients. Following this line of thought we developed the "sentinel node" technique, consisting in an injection of a minimal quantity of colloid albumin labelled with <sup>99</sup>Tc around the primary carcinoma which would be captured via the lymphatic route by the first axillary node (sentinel node) which would drain the lymph from that area. In a series of 163 patients we discovered that the predictive value of the sentinel node histology is very high, superior to 95%. When the sentinel node is negative for metastases the chances that other axillary lymph nodes are involved by metastatic cancer cells are very low. We hope that if the data will be confirmed by larger case-series, the axillary dissection would be avoided in all cases without clinical nodal involvement.

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# Conservative surgery of the breast: Ten years of experience at the University Hospital for Tumours, Zagreb, Croatia

Vladimir Orešić, Zrinko Petrincec, Mladen Stanec and Danko Velemir Vrdoljak

Department of Surgery, University Hospital for Tumours, Zagreb, Croatia

*In this presentation we tried to show the evolution of breast conserving surgery in our Department. The first breast conserving operations were done in 1982. In 1986 the number of patients undergoing these procedures started to increase. The break point was the year 1993 when we started our breast cancer screening program, and since then the number has been increasing rapidly.*

**Key words:** breast neoplasms; mastectomy-methods; treatment outcome

## Introduction

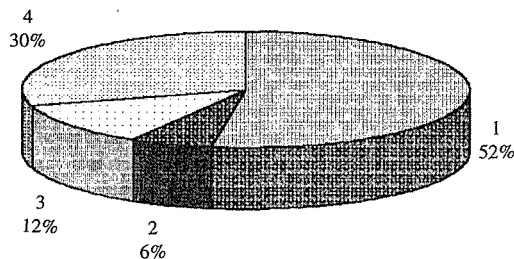
This survey of ten-year experience is aimed at pointing out the number of changes that breast cancer surgery has undergone and is still going through. Over 35% of all breast carcinomas registered in Croatia are treated at the University Hospital for Tumors in Zagreb. The first conservative surgical procedure for breast cancer was performed in 1981, and up to 1987, a modest number of segmentectomies was registered at our Hospital, starting to increase thereafter. An actual increase was achieved only by 1993.

## Patients and methods

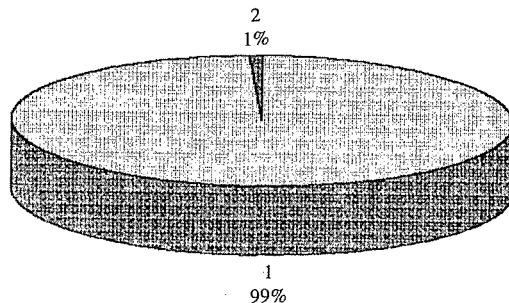
In the period between 1986 to March 1997, 7875 patients underwent surgery for breast tumors, of which 4627 were diagnosed as carcinoma of the breast. Other types of breast surgery were applied for various breast diseases (Figure 1). From the total number of breast carcinoma registered in that period, there were 4133 modified radical mastectomies and 494 segmentectomies including dissection of the axilla. Conservative surgery for breast cancer accounted for 10% (Figure 2).

Correspondence to: Dr. Danko Velemir Vrdoljak, Department of Surgery, University Hospital for Tumours, Ilica 197, 10000 Zagreb, Croatia

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**Figure 1.** Breast surgery in total performed from 1986 to March 1997 (total 7805). 1. MRM; 2. segment.; 3. fibroaden.; 4. negative biop.



**Figure 2.** MRM and segmentectomies ratio in 1986. 1. MRM; 2. segment.

Following the protocol of the University Hospital for Tumors in Zagreb, all patients were submitted to postoperative irradiation and, if necessary, adjuvant chemotherapy or hormone therapy, which depended on the axillary status.<sup>1-4</sup>