toxic *in vivo*, the effect on LAK-sensitivity reported here is achieved at lower doses of VP, which might be much less toxic *in vivo*.

Our preliminary observation that the Ca^{2+} ionofore A-23187 can reverse verapamil's effect on LAK-sensitivity of both cancer cell-lines suggests involvement of changes in intracellular Ca^{2+} levels in the determination of these effects. We are presently trying to identify the molecular mechanisms of verapamil's effects on tumour cell sensitivity to LAK cells.

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Quantitative and Qualitative Cosmetic Evaluation after Conservative Treatment for Breast Cancer

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148 consecutive patients treated by two different types of conservative surgery were objectively and subjectively evaluated for cosmetic outcome. In 73 patients, tumorectomy, axillary dissection, external radiotherapy (45 Gy) plus iridium implant (15 Gy) were performed, while in the other group of 73 patients a more extensive surgical approach was carried out: quadrantectomy, axillary dissection plus external radiotherapy (50 + 10 Gy). The appearance of the patients' breasts was analysed for symmetry by computer, and differences in symmetry were correlated with tumour location and breast size. A subjective assessment was given by a 3-member panel and the results were correlated with objective measurements. In addition, patients were asked to fill out a self-assessment questionnaire on the aesthetic result of the operated breast. Better results were generally noted in the group of patients treated by more conservative surgery. Substantial differences in the aesthetic outcome were noted between the patient's own evaluation, the computer's measurement of symmetry and the assessment of the panel of observers.
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INTRODUCTION

LOCAL CONTROL of disease is the primary objective of conservative treatment of breast cancer. In addition improvement of the patient's quality of life by achievement of an acceptable cosmetic outcome is the basis of the philosophy of breast preservation. In fact, unsatisfactory results can contribute to psychological morbidity owing to body image alteration and its effects on social functioning. The most important clinical trials [1–4] comparing mastectomy to conservative therapy have shown no differences in local recurrence rates and distant disease-free and overall survival.

So far, studies on cosmetic outcome have been small or overly subjective [6, 7]. Deformities produced by conservative surgery (quadrantectomy, lumpectomy or wide excision) are difficult to evaluate objectively and subjective assessment of cosmetic outcomes has been extremely variable [8, 9]. Asymmetry of the treated breast may occur as a result of deformities such as malposition or distortion of the nipple–areola complex, tissue deficiency, breast retraction and shrinkage. Measurement of such a symmetry may be a more objective method of evaluating the deformities and, indirectly, the cosmetic results after conservative treatment for breast cancer. [9, 10].

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Table 1. Main characteristics of 148 patients selected for symmetry study compared to all 705 patients of the Milan trial II

	Symmetry study cases	Milan trial II cases
Quadrantectomy	50.6%	51.6%
Tumourectomy	49.4%	48.4%
Age		
≤ 35	5.8%	4.4%
36–45	17.8%	26.2%
46–55	36.5%	37.7%
> 55	39.9%	31.7%
Tumour site*		
Upper outer	51.0%	48.7%
Upper inner	17.8%	24.2%
Lower outer	20.3%	17.2%
Lower inner	7.1%	7.6%
Central	3.8%	2.3%
Tumour size (cm)		
≤ 1	21.0%	25.0%
1.1–2	59.8%	56.2%
> 2.1%	14.0%	13.2%
Not evaluable	5.2%	5.6%

*No division in the subgroup "upper" or "lower" was made.

In the present study, a method to measure the asymmetry after different conservative treatments for operable breast cancer was developed and the aesthetic results of two different treatments were analysed. Results were scored by qualitative scoring by a 3-member panel and correlated with objective measurements. Self-assessment by the patients was also taken into consideration in order to verify the correlation between objective evaluation and the patients' own judgement.

PATIENTS AND METHODS

A series of 148 consecutive patients treated by conservative surgery at the Istituto Nazionale Tumori in Milan from January 1985 to December 1987 was assessed for the study of post-treatment breast symmetry. 75 patients were treated with quadrantectomy and 73 with tumourectomy. These were a representative sample of the prospective trial, Milan II (comparing tumourectomy to quadrantectomy), and were under evaluation for local control of disease and survival. Patients were matched for age, tumour size and site (Table 1). A total of 705 patients, in clinical stage T1-2 (T less than 2.5 cm) N0-1, M0 entered the trial; 360 patients were randomised to quadrantectomy and 345 to tumourectomy.

These two groups of patients had the same demographic characteristics (Table 2). Quadrantectomy consisted of removal of the quadrant of the breast containing the tumour, including a skin lozenge with the major axis radial from the nipple, and removal of the pectoralis major fascia. The parenchymal resection was carried out to extend at least 3 cm from the tumour margin. An axillary clearance was performed in continuity with the tumourectomy incision when the cancer was in the upper outer quadrant, but with separate incisions for tumours in other sites, usually with an anteroposterior incision crossing the axillary fossa in a downward direction.

The defect in the breast tissue itself was closed by approximation of the two resection margins with interrupted sutures. If necessary, these were mobilised from the pectoralis fascia and the surrounding skin in order to limit skin retraction. In rare cases (5%), a drain was inserted into the breast.

Table 2. Main characteristics of the quadrantectomy and tumourectomy groups

	Quadrantectomy	(n = 75)	Tumourectomy	(n = 73)
Age				
≤ 35	5	(6.6)	3	(4.1)
36–45	16	(21.3)	14	(19.3)
45–55	26	(34.7)	28	(38.3)
> 55	28	(37.4)	28	(38.3)
Tumour site *				
Upper outer	23	(30.6)	27	(37)
Upper inner	11	(14.7)	7	(9.6)
Upper	16	(21.4)	14	(19.2)
Lower outer	14	(18.7)	16	(21.9)
Lower inner	4	(5.3)	3	(4.1)
Lower	4	(5.3)	3	(4.1)
Central	3	(4)	3	(4.1)
Tumour size (cm)				
≤ 1		(28.8)		(21.2)
1.1–2.0		54.5		57.6
> 2.1		(12.5)		(15.2)
Not evaluable		(4.2)		(6)
Breast size (radius (cm)				
≤ 9 •	17	(22.6)	13	(17.8)
9.1–11	37	(49.4)	31	(42.4)
> 11.1	21	(28)	29	(39.8)

No. (%).
*Groups not subdivided as to inner or outer.

Tumourectomy comprised a more conservative procedure, with tissue excision limited to 1 cm beyond the tumour margin, using a circular or radial skin incision. The fascia of the major pectoral muscle was usually not removed. Axillary dissection was always performed through a separate anteroposterior incision. The resection margins of the breast parenchyma were apposed with interrupted sutures.

In both groups, radiotherapy was begun 4–6 weeks after surgery and was limited to the breast, using either a 5 MeV linear accelerator, or a cobalt-60 unit, by two opposing tangential fields with an extension wide enough to cover the breast and the adjacent tissues. The fields were 16–20 cm long and 8–12 cm wide. When the breast was large and very prominent, wedge filters were used to obtain a homogeneous dose distribution. In the quadrantectomy group, the prescribed dose of 50 Gy was given over 5 weeks, with daily target dose of 2 Gy, while in the tumourectomy group, a total external dose of 45 Gy was administered, with a daily dose of 0.9 plus 0.9 Gy.

In the group of patients submitted to quadrantectomy a boost of 10 Gy was given to the breast scar during the sixth week, through a field of approximately 12 × 8 cm with Roentgen therapy or with 10 MeV electrons.

For those treated by tumourectomy, after an interval of 2 or 3 weeks, an interstitial implant with wires of ^{192}Ir was performed to give a boost of 15 Gy directly to the tumour bed using an afterloading technique. Thus, a total dose of 60 Gy was given to both randomised groups of patients, regardless of the type of surgical approach.

The sample of patients considered for the present study had completed radiotherapy for at least 3 years before evaluation of breast symmetry, in order to assure that most sequelae of radiation had stabilised [11–13].

Quantitative measurement of breast symmetry

The frontal image of the patients, while standing with arms at their sides, from neck to middle of abdomen, was symmetrically displayed by a telecamera on the computer screen, and was analysed by processing and image analysis software. Quantitative evaluation was automatically calculated by the software and consisted of the quantification of the following dimensions: (1) difference in height between the two nipples, (2) difference in height between the mammary inferior profiles, (3) difference of the distance from the median line to the nipples and (4) difference of the distance from the sternal notch to the nipples.

For the first two differences, four categories were identified: less than 1 cm, between 1 and 2 cm, between 2 and 3 cm, and more than 3 cm. The third and fourth differences were divided in two groups: 1 cm or less, and greater than 1 cm.

The size of the non-operated breast was measured as the average of two distances: from nipple to the inferior mammary profile, and from nipple to the lateral sternal margin. Three categories were identified: distance less than 9 cm, small breast; between 9 and 11 cm, medium size breast; and greater than 11 cm, large breast.

Qualitative subjective measurement

The photographs of the patients were separately submitted to a 3-member panel. Each patient was photographed from a distance of 1 metre with a 35 mm camera with a flash attachment. Photographs were obtained from neck to mid-abdomen in two positions: arms at sides and arms extended laterally at shoulder level. The three members consisted of a female surgeon involved in the study, a male surgeon from another hospital and a 24-year-old female non-physician.

The criteria used for scoring were the same as reported by other authors [8, 10, 13]. The cosmetic score was given as follows: (1) excellent, without visible treatment sequellae; (2) good, slight sequellae with minimal difference between the treated and untreated breast; (3) fair, obvious difference between the treated and untreated breast but without major distortion; and (4) poor, major aesthetic sequelae.

Patients' self-assessment

A self-assessment questionnaire was submitted to the patients. For the subjective qualitative measurement, women were asked to rate the cosmetic outcome of the breast (excellent, good, fair or poor).

A graphic representation was also used: a horizontal line graduated from 1–10 (1 = poor; 10 = excellent) was provided and patients were asked to mark on this scale their own evaluation of cosmetic outcome. Median value was calculated in both groups of patients. The statistical analysis was carried out according to the χ^2 test for trend.

RESULTS

The difference in height between the two nipples reflects upward or downward nipple displacement. Remarkable differences between the two different surgical approaches were noted (Table 3).

A difference of less than 1 cm was present in only 25% of the quadrantectomy group compared to 47% of tumourectomy patients ($P < 0.01$). Considerable asymmetry with difference greater than 3 cm was noted in 21% of the quadrantectomy patients, and only 6% of those treated by tumourectomy ($P < 0.02$).

According to the difference in height between the mammary inferior profiles 10% of quadrantectomy patients compared to 3% of the tumourectomy had significant asymmetry in height with a difference of more than 3 cm ($P < 0.10$). In considering the difference of the distances from the sternal notch to the nipples, 29% of the quadrantectomy patients compared to 13% of the tumourectomy group had a difference of less than 2 cm ($P < 0.05$) (Table 3).

Table 3. Difference of two parameters of symmetry: height between the two nipples and distances from the sternum notch to the nipples

	Quadrantectomy (n = 75)	Tumourectomy (n = 73)
Difference in height between the two nipples ($P < 0.02$)		
≤ 1 cm	18 (25)	34 (47)
1.1–2	25 (33)	21 (29)
2.1–3	16 (21)	13 (18)
> 3	16 (21)	5 (6)
Difference of the distances from the sternum notch to the nipples ($P < 0.01$)		
≤ 1 cm	30 (40)	40 (55)
1.1–2	23 (31)	23 (32)
> 2	22 (29)	10 (13)

No. (%)

For tumours located in the upper quadrants, the difference in height between the mammary inferior profiles was not significant between the two treatments (Table 4). Similar results were noted in terms of upward or downward nipple displacement, measured as difference in height between the two nipples. When the tumour was located in the inferior quadrants, a significant difference ($P < 0.10$) both in the upward or downward nipple displacement and in the mammary inferior profile was noted in the two treatment groups (Table 4).

With regard to the type of surgery, quadrantectomies and tumourectomies carried out in the inferior quadrants provided worse results in the upper quadrants, in terms of nipple and mammary ptosis asymmetry. 84% of quadrantectomy patients had a difference between the two mammary folds of less than 2 cm when the tumour was localised in the upper quadrant vs. 54.6% when the tumour was localised in the inferior quadrant ($P < 0.01$) (Table 5). In the patients submitted to tumourectomy a difference was present, but was not significant (88% of patients with difference between the mammary fold less than 2 cm in the upper quadrants, vs. 77% of patients with inferior quadrant tumours) (Table 4). Similar differences were noted in the symmetry of the two nipples by upper and inferior quadrants.

For medial or lateral tumour sites, the difference of the

Table 4. Difference in height between the mammary folds by tumour site

	Quadrantectomy (n = 72*)		Tumourectomy (n = 70*)	
	≤ 2 cm	> 2 cm	≤ 2 cm	> 2 cm
Upper quadrants	42 (84)	8 (16)	42 (87.5)	6 (12.5)
Lower quadrants	12 (54.6)	10 (45.4)	17 (77.3)	5 (22.7)

No. (%).
*Central quadrants excluded.

Table 5. Difference of the distances from the median line to the nipple by tumour site

	Quadrantectomy (n = 52*)		Tumourectomy (n = 53*)	
	<= 2 cm	> 2 cm	<= 2 cm	> 2 cm
Outer quadrants	22 (59.5)	15 (40.5)	33 (76.7)	10 (23.3)
Inner quadrants	9 (60)	6 (40)	8 (80)	2 (20)

No. (%).
*Upper and lower quadrants excluded.

distances from the median line to the nipples was considered as an index of medial or lateral nipple displacement. This was more evident in quadrantectomy than in tumourectomy patients (Table 5). When the tumour was located in the outer quadrants, differences of more than 2 cm were noted in 23% of the tumourectomy patients and in 41% of the quadrantectomy cases ($P < 0.10$). A non-significant difference was found for tumours in the inner quadrants (20% in the tumourectomy group and 40% in the quadrantectomy group).

When considering the lateral or medial displacement of the nipple, similar results were noted for tumours located in outer and inner quadrants after both tumourectomy and quadrantectomy (Table 5).

No significant difference in nipple displacement was noted in the same type of operation for different tumour locations in the outer or inner quadrants (Table 5). 23% of tumourectomies peformed in the outer quadrants resulted in difference of more than 2 cm; the result was 20% when the operation was performed in the inner quadrants. In the quadrantectomy group, a difference of more than 2 cm was found in 41% of outer quadrant tumours and in 40% of those in the inner quadrants.

When the tumour was located in the upper outer quadrants, the axillary dissection was performed in continuity with the quadrantectomy, while in the tumourectomy group it was always peformed through a separate incision. The comparison of these subgroups of patients could give an impression of the impact of "en bloc" axillary dissection on symmetry. In fact, the average upward nipple displacement, calculated as the difference of the distances from the sternum to the nipples, gave a mean difference of 1.4 cm in the upper outer tumourectomies with axillary dissection in discontinuity (19 cases) and 1.9 cm in the upper outer quadrantectomies with en bloc axillary dissection (21 cases).

When considering breast size, the best symmetry (64% of the patients having a difference between the mammary folds of less than 1 cm) was noted in patients with mid-sized breasts who had undergone tumourectomy (Fig. 1). Patients with small breasts treated by tumourectomy had inferior results, i.e. 30% with a difference of more than 2 cm between the mammary folds. In the quadrantectomy group, the difference between the mammary folds was lower in medium and small sized breasts, while the larger breasts had a higher percentage of asymmetry (Fig. 1). Similar results were noted when the asymmetry between the nipples was considered.

In terms of subjective cosmetic scores, several differences were noted in the evaluation of the 3 panel members (Fig. 2). These differences were less marked in the judgement of the two extreme categories (excellent and poor), while most difference was seen in the mid categories (good and fair). Better cosmetic scores were given by the male surgeon from another hospital.

75% of the patients treated by quadrantectomy considered their results excellent or good compared to 89.5% of those tested by tumourectomy. The median value on the self-assessment scale was 7.0 (range 1.6–10) in the quadrantectomy group and 8.5 (range 4.3–10) in the tumourectomy group.

DISCUSSION

The results show that the extent ot surgical resections is an important factor in the production of breast asymmetry after conservative treatment for breast cancer. Wider breast resection, as in quadrantectomy, was shown in our study to result in greater breast deformity.

Upward and downward displacement of the nipple was a more common cause of breast asymmetry after quadrantectomy than after tumourectomy, while medial or lateral nipple displacement occurred less frequently in both groups.

The deformity of the breast contour, expressed as a difference between the level of the mammary folds, was slightly evident in the quadrantectomy group in which 10% of patients had height asymmetry with a difference of more than 3 cm compared to the non-operated breast. Resections performed in the inferior quadrants appeared to be the main cause of this deformity, in particular producing the downward nipple displacement, while resections carried out in the superior quadrants provided good nipple and breast contour symmetry with only a slight difference between the two surgery groups. Inferior cosmetic results of resections in the lower quadrants justify study of quadrantectomy performed with more aesthetic incisions in order to improve cosmetic outcome [14].

Some authors [12, 13, 15–17] have related breast deformity to radiation dose, and have considered it the most important cause of distortion. They have shown that tissue fibrosis is related to radiation dose, and high dose (70 Gy in 35 fractions) was identified as the predominant factor. For patients receiving a lower radiation dose, other factors were more important in determining cosmetic outcome. These included type of surgery, tumour site and breast size. In our series, the standard radiation doses delivered were similar in both groups; the different external beam radiation dose and the different boost administered could have had an impact on the cosmetic results, but this is difficult to evaluate, due to the predominant impact of the type of surgery in the analysis.

The volume of the breast is another important factor in breast symmetry. In the present study, the size of the breast was indirectly calculated as the average of the distance between the nipple and the inferior profile of the non-operated breast, and the distance between the nipple and the lateral margin of the sternum. These measurements provide a reliable parameter of the breast size. We noted that breast size had an influence on symmetry, both in tumourectomy and quadrantectomy patients (Fig. 1). However, this impact seems to be of a different nature in the two groups: in the tumourectomy group, medium and large size breasts had better symmetry compared to small ones, while in the quadrantectomy group, large breasts seemed to be less symmetrical compared to the small ones. In small breasts, quadrantectomy seems to achieve a better symmetry with respect to tumourectomy. This could be a bias due to the small difference in these parameters between small and larger breasts. However, we cannot exclude that for small breasts, quadrantectomy achieves a better result in terms of breast restoration compared to tumourectomy.

The present study did not take into consideration the effect of chemotherapy, which is considered by many authors to

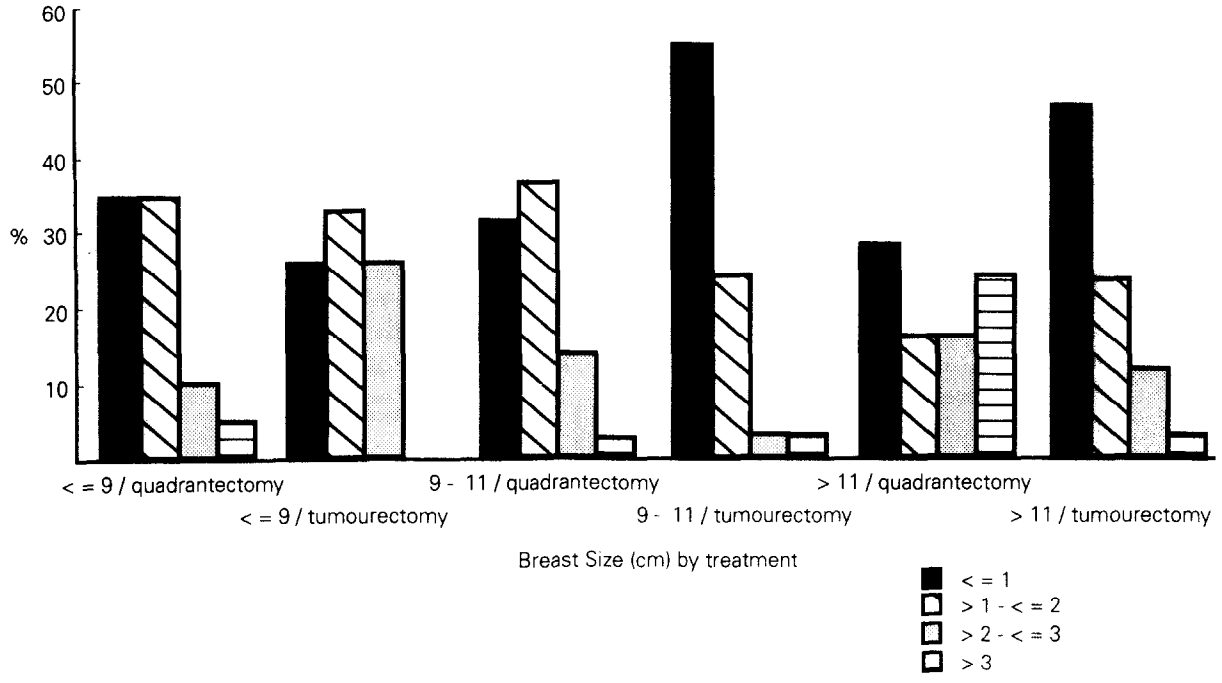

Fig. 1. Differences in height between the mammary folds by breast size.

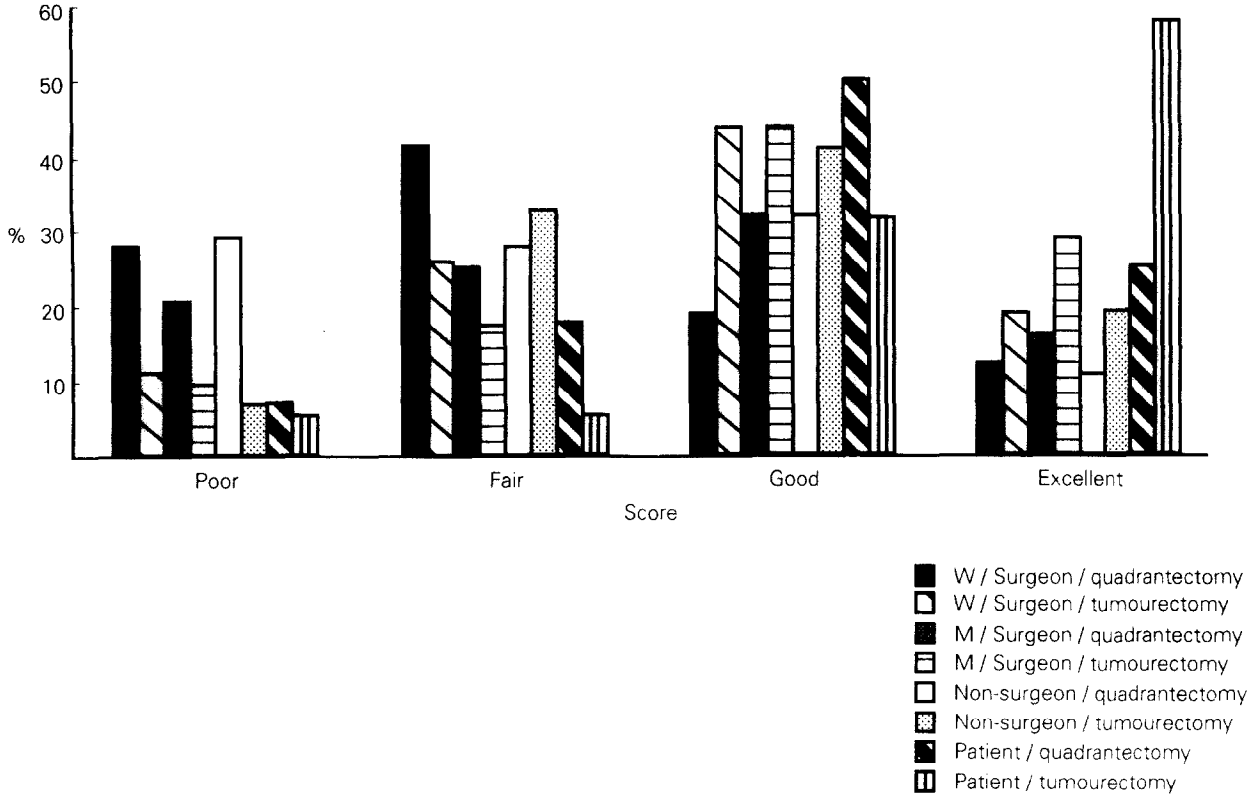

Fig. 2. Qualitative cosmetic assessment by the 3-member panel and the patients. 3-member panel: female surgeon involved in study ($\bar{W}$), male surgeon from another hospital (M), and a female non-surgeon.

influence aesthetic results [18–20], with other factors such as age and menopausal status. The small number of cases in each subgroup would not have allowed for valid comparisons.

In this study, the qualitative subjective assessment showed diversity in the judgements of the 3 panel members. This emphasises that assessment scales are subject to observation bias and cannot be considered as reliable methods for assessing cosmetic results after conservative treatment for breast cancer. The patients' self-assessment questionnaire showed better results in the tumourectomy group, revealing the same trends as the objective assessment.

Nevertheless, differences in cosmetic score point out that the

patient's judgement is based not only on the pure aesthetic results, but also on more complex elements, e.g. physical appearance, breast appearance, age and environmental factors [21].

In conclusion, the amount of breast tissue removed appears a determinant in the cosmetic result of operated breasts. Nevertheless, the width of the resection seems to be important for local breast control of the disease. Studies performed by Holland *et al.* [22] quantified the risk of residual disease at different distances from a primary tumour. For tumours less than 2 cm in diameter, the risk is 59% at a distance of 1 cm; 42 % at 2 cm and 17% at 3 cm. The probability of radicality of surgery increases with the increase of the width of resection.

Clinical support for Holland's histological studies is provided by the results of our trial, Milan II [23], comparing two conservative procedures using different widths of resection. In fact, in the group of patients submitted to tumourectomy, the number of local breast failures was three times greater than in the quadrantectomy group (24 local recurrences for tumourectomy vs. 8 for quadrantectomy). Considering these data, the choice of a less favourable cosmetic result in order to achieve better local control may be reasonable.

Although it is difficult to quantify the morbidity of aesthetic failure of primary treatment, it is our impression that this is less serious than the morbidity of local relapse, both oncologically and psychologically.

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