Breast-conserving Therapy for Macroscopically Multiple Cancers

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Of 586 unilateral stage I–II breast cancers treated with conservative surgery and radiotherapy, 61 patients were found to have two or more macroscopic tumor nodules, diagnosed either clinically (n = 20), mammographically (n = 2), or on gross pathologic examination (n = 39). After a median follow-up of 71 months, 15 of 61 (25%) of the patients with multiple tumors developed recurrence in the treated breast, compared to 56 of 525 (11%) of patients with single cancers ($p < 0.005$). Local failure occurred in 6 of 37 (16%) of bifocal tumors and in 9 of 24 (35%) of patients with 3 or more tumor foci. Recurrence was more frequent for multiplicity diagnosed clinically or mammographically (8 of 22 patients, 36%) than when it was apparent only to the pathologist (7 of 39 patients, 18%). Only 1 of 21 bifocal tumors diagnosed on gross examination recurred. Local failure occurred in only 1 of 22 cases with clearly negative resection margins; the remaining recurrences were associated with positive (n = 3) or indeterminate margins (n = 11). In contrast with recurrences of unifocal breast cancers, local failures in these patients tended to be located at a distance from the original foci, to be multifocal, or to be diffuse, including skin involvement. Only four recurrences presented as a single focus in the vicinity of the original primary tumors. This study indicates that macroscopically multiple breast cancers are at higher local failure risk, especially if multiplicity is clinically apparent, or if three or more gross nodules are seen on pathologic examination. Negative resection margins appear to be essential for satisfactory results.

ALTHOUGH MULTIPLE PATHOLOGIC studies attest to the multifocality and multicentricity of many breast cancers,[1–6] the appearance of two or more dominant tumor masses in the same breast is very uncommon.[7] Such patients are commonly excluded from breast-conserving treatment programs under the assumption that patients with macroscopically multiple tumors have a high risk of local recurrence.[8] Data to support this attitude, however, are lacking.

Supported in part by the Association Sainte Catherine, Avignon, France.

Reprints will not be available.

Accepted for publication May 15, 1989.

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At the Marseille Cancer Institute, patients with two or more tumor nodules have not been denied systematically treatment with preservation of the breast. This affords the unusual opportunity to analyze treatment results for this small subset of patients, for whom breast conservation is considered in many centers to be contraindicated.

Methods

The study group includes 586 evaluable patients with clinical stages I and II breast cancer (T1-2 NO-1, American Joint Committee,[9]) whose primary surgical treatment took place at the Marseille Cancer Institute between January 1975 and December 1983. Patients operated on outside the Cancer Institute and referred for radiotherapy, patients with clinical stage III or IV cancer, and patients treated by primary mastectomy were excluded.

Surgical and radiotherapy techniques, as well as the results of therapy, have been described in detail in previous publications.[10–12] Conservative surgery consisted of a macroscopically complete wide excision of the primary tumor, including in 486 instances a dissection of the lower two axillary levels. No particular attention was paid to microscopic resection margins, and re-excision was not used. Megavoltage radiotherapy involved treatment of the entire breast and draining lymph node areas to a basic dose of 50 Gy (5000 rad) in 5 weeks with telecobalt or 60 Gy in 6 weeks with telecesium. The tumor bed always received supplemental treatment, usually 20 to 25 Gy with an external electron beam. Adjuvant therapy did not follow a fixed protocol during the 9-year period of this study. Bilateral oophorectomy or hormone therapy was per-

formed on 212 patients, and 88 patients were treated with combination chemotherapy. In addition almost all patients treated after January 1980 received a short perioperative course of single alkylating agent.

The clinical records and pathology reports of all patients were examined and histologic slides of all primary tumors were reviewed by a single pathologist (JJ) who had no knowledge of the clinical outcome. Histologic tumor type was assigned according to the World Health Organization,[13] with infiltrating cancers classified by their predominent invasive component. Tubular carcinomas were included in the category invasive ductal carcinoma (IDC). The degree of intraductal cancer was quantified using the terminology of Schnitt et al.[14] Extensive intraductal component (EIC) was considered present only when at least 25% of the tumor mass consisted of ductal carcinoma *in situ* (DCIS), and at the same time DCIS was present in the surrounding breast tissue. Histologic grade was assigned according to a modified Bloom-Richardson system.[15]

Although no prospective India ink marking of resection margins had been performed, pathologic review included a retrospective assessment of the adequacy of excision. In addition to sections through the primary tumor, in most cases selected sections had been taken at the periphery of the excision specimen. Excision was considered to have been complete when sections through tumor showed no invasive or intraductal cancer at the margins and the peripheral sections were free of tumor. Excisions in which such a judgment could not be made, particularly when no peripheral sections were available for review, were classified as indeterminate. About 10% of cases had clearly positive margins.

Tumors were considered to be macroscopically multiple when either the preoperative clinical and/or mammographic examination showed more than one discrete tumor mass or when the pathologist, on gross examination, found two or more tumor nodules separated by apparently non-neoplastic tissue. Tumors in which multifocality was apparent only on microscopic examination were classified as unifocal cancers.

Statistical analysis was based on proved recurrence in the parenchyma or skin of the treated breast, without consideration of previous events. Both direct ratios and actuarial survival functions[16] were used; differences between proportions were tested by the chi^2 test, and between survival functions by the log-rank test.[17] Multivariate analysis used the computer program Survival Analysis with Covariates—Cox Models (BMDP Statistical Software, Los Angeles, CA).

Results

Sixty-one of the 586 (11%) patients were found on review to have had macroscopically multiple tumors. In 20 patients two or more separate nodules were apparent on clinical examination and were confirmed pathologically. In 10 instances the nodules, although discrete, were in close proximity, so that a standard wedge excision could be performed.[12] In 10 patients the foci were separated by a considerable distance, so that either separate incisions or a generous partial mastectomy were required. Mammography alone detected a second focus at a distance from the primary tumor in two patients. Of the 22 multifocal tumors diagnosed clinically or mammographically, 15 were bifocal and 7 were trifocal. In the remaining 39 cases, multifocality was apparent only to the pathologist on gross examination. In 21 instances the tumor was macroscopically bifocal, and in 18 cases more than 2 separate nodules were identified (3 in 11, 4 in 4, more than 4 in 3). In all cases the nodules were in close proximity to each other.

Pathologic review showed the predominant histologic pattern of infiltrating ductal carcinoma in 54 of the 61 patients with multiple tumors (88.5%), in comparison to 442 of 525 patients with unifocal tumors (84%, difference insignificant). Of patients with IDC, 17 (31.5%) had EIC. The remaining 7 patients had infiltrating lobular cancer (n = 3), DCIS (n = 3), and colloid carcinoma (n = 1). Significant differences in histologic type between tumor nodules in individual patients were not seen.

Table 1 compares the characteristics of patients with macroscopically multiple tumors to those having grossly unifocal cancers. Although EIC was observed more frequently in multifocal tumors, no significant differences could be demonstrated in the frequency or extent of nodal

TABLE 1. *Comparison of the Characteristics of Patients with Macroscopically Multiple* Versus *Grossly Unifocal Tumors*

Characteristic	Single	Multiple	p value
Number	525	61	
Mean age (years)	52	50	NS
Histology			
Invasive ductal	442 (84%)	54 (88.5%)	NS
With EIC	89 (20%)	17 (31.5%)	0.06
Other	83	7	
Estrogen receptor			
≥10 fm/mg	308 (59%)	39 (64%)	NS
<10 fm/mg	140	12	
Unknown	77	10	
Involved nodes			
None	257 (49%)	37 (52.5%)	NS
1-3	128	15	
4+	47	7	
Unknown	93	7	
Resection margins			
Adequate	288 (55%)	22 (36%)	0.01
Inadequate	30	12	
Indeterminate	207	34	
Local recurrence	56 (11%)	15 (25%)	0.005
Contralateral cancer	22 (4%)	2 (3%)	NS
10-year survival	74%	73%	NS

NS, not significant.

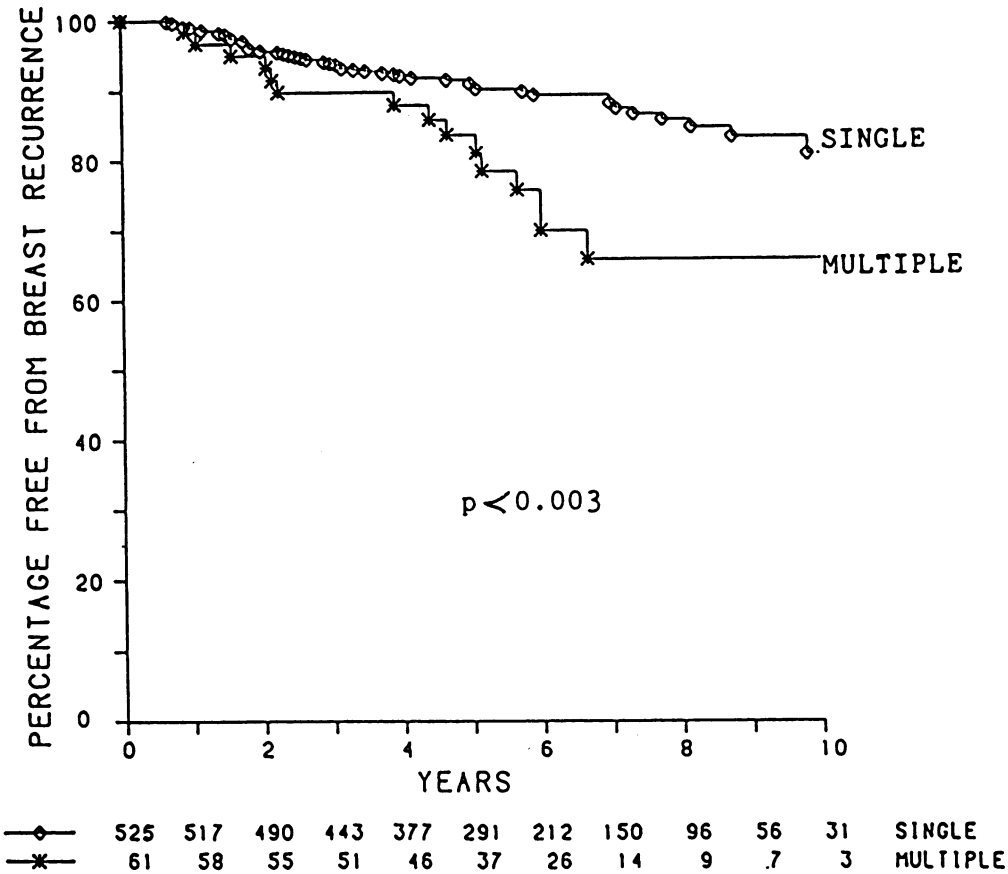

FIG. 1. Actuarial freedom from local recurrence in the treated breast for patients with macroscopically multifocal *versus* unifocal tumors. The numbers below the time axis indicate the patients at risk for each interval.

involvement or in estrogen receptor status. Microscopically adequate resection margins, however, were achieved more frequently for unifocal than for multifocal tumors. The overall survival rate was the same for both groups.

After a median follow-up of 71 months, 15 of the 61 patients (25%) with multifocal tumors developed recurrence in the treated breast, compared to 56 of the 525 (11%) patients with unifocal cancers ($p < 0.005$). Actuarial local recurrence-free survival curves for the two groups are shown in Fig. 1. Local failure occurred in 6 of 37 (16%) bifocal tumors and in 9 of 24 (37.5%) patients with 3 or more tumor foci ($p = 0.1$). When multiplicity had been apparent clinically or mammographically, local relapse occurred in 8 of 22 patients (36%), regardless of whether the tumor foci were close together (4 of 10 recurred) or far apart (4 of 12 recurred). Multifocality diagnosed only on gross pathologic examination led to local failure in 7 of 39 instances (18%, $p > 0.1$). Only 1 of 21 bifocal tumors diagnosed by the pathologist recurred in the breast. However, when 3 or more nodules were apparent on gross examination, 6 of 18 (33%) developed local failure. Based on the clinical and gross pathologic examination, therefore, excess local recurrence risk appeared to be confined to the 46 cases in which multifocality was either apparent to the clinician, or in which 3 or more gross nodules were observed by the pathologist ($p < 0.025$ compared to the 21 pathologically bifocal tumors).

The influence of the microscopic examination on local recurrence risk was investigated for the 61 patients with macroscopically multiple tumors. All but one of the 15 local failures occurred in tumors showing predominantly invasive ductal histology. Local recurrence was observed in one of three patients with invasive lobular cancers, and in none of the four patients with other histologic tumor types. For patients with IDC, multiple tumors showing EIC had a tendency to recur more frequently (6 of 17, 35%) than those without EIC (8 of 37, 22%), but this difference was not statistically significant ($p > 0.1$).

The adequacy of resection could be judged with confidence in 34 instances, and in 27 cases resection margins were classified as indeterminate. Whereas local recurrence occurred in 3 of 12 patients with inadequate margins and in 11 of 27 cases with indeterminate margins, only 1 of 22 patients with clearly adequate margins recurred ($p < 0.01$).

To evaluate the independent influence of different clinical and pathologic factors on local recurrence risk, a Cox multivariate analysis was performed. The following factors were entered as covariates: age (as continuous variable),

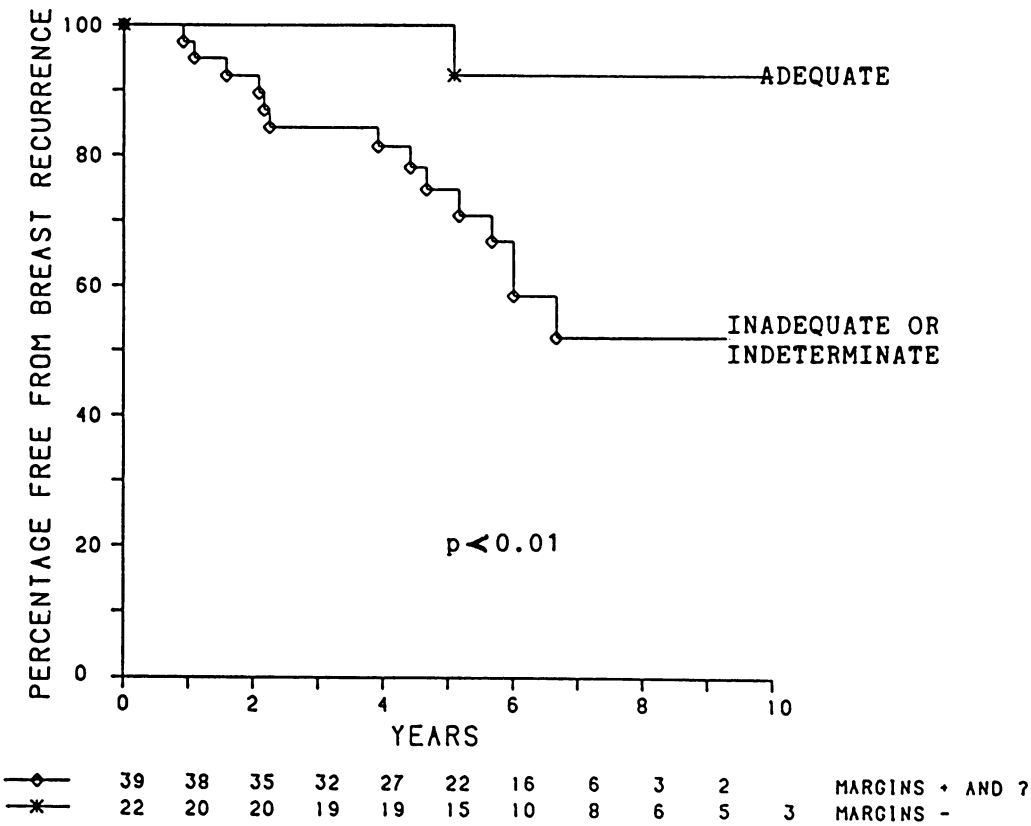

FIG. 2. Actuarial freedom from local recurrence in the treated breast for patients with macroscopically multifocal tumors, according to the retrospective review of resection margins. The numbers below the time axis indicate the patients at risk for each interval.

mode of discovery (clinical/mammographic *versus* gross pathology), number of foci (2 *versus* 3 or more), anatomic size of largest nodule (in centimeter intervals), histologic grade (1 *versus* 2 *versus* 3), EIC (absent *versus* present), resection margins (adequate *versus* indeterminate or inadequate), histologic lymph node status (negative, unknown, positive), adjuvant hormone therapy (yes, no), and adjuvant chemotherapy (yes, no). The only factor shown to have significant independent influence on the incidence of failure in the breast was the retrospective assessment of resection margins ($chi^2 = 8.32$, $p = 0.004$). Actuarial local recurrence-free survival curves according to the adequacy of excision are presented in Figure 2.

The salient clinical and pathologic features of the 15 patients suffering local recurrence are shown in Table 2. Because the mean age was 49.8 years, there was no indication that recurrence occurred preferentially in younger patients. Mean time to local recurrence was 45.1 months, with 6 of the 15 relapses having been diagnosed after the fifth year. As is apparent in Figure 1, there was a tendency for recurrences of multifocal tumors to occur later than for single tumor foci.

Only four relapses presented as single foci in the vicinity of the primary tumors, whereas three were single recurrent tumors elsewhere in the breast, and one recurred as an apparently isolated nodule in the skin of the breast. The remaining relapses were multifocal, including diffuse involvement of parenchyma and skin in three patients. This is in contrast to the 56 local recurrences in patients with unifocal cancers, 33 (59%) of which were single foci in the immediate vicinity of the original tumor bed. Follow-up after recurrence was too short to allow comment on the salvage treatment or prognosis of this small group of patients.

Discussion

Although the multicentricity of breast cancer has traditionally been used as an argument against limited surgery,[5,6] the long-term results of breast-conserving treatment with radiotherapy suggest that the clinical relevance of multiple cancer foci documented only on pathologic examination is probably limited.[12,18-21] However the presence of more than one macroscopically apparent tumor mass has been considered to represent a contraindication for breast preservation, even by those strongly advocating this form of treatment.[8]

The present analysis represents part of a retrospective clinicopathologic study of risk factors for local recurrence, including all evaluable stage I–II patients selected for breast-conserving surgery in a single institution during a 9-year period. Although no systematic exclusion of clinically apparent multiple tumors took place, a certain selection against such cases cannot be excluded, especially

TABLE 2. *Clinical Features and Course of the 15 Patients with Macroscopically Multiple Tumors who Developed Recurrence in the Breast*

Age (yrs.)	Mode of Diagnosis	Positive Nodes	Histo	Foci	Interval (months)	Salvage Therapy	Course (months after failure)
52	Clinical (close)	?	EIC−	2	56 single, other quad.	WE	NED 74
42	Gross path	?	EIC+	4	27 multiple, skin	Chemo	DOD 17
52	Gross path	0	EIC+	3	68 multiple, same quad.	M	DOD 8
44	Gross path	?	EIC−	2	11 single, same quad.	WE + chemo	DOD 71
61	Gross path	11	EIC−	5	24 multiple, same quad.	M + Tam	LFU 13
41	Clinical (close)	0	Inv. lobular	3	25 single, same quad.	WE	NED 72
46	Mammogr. (distant)	2	EIC−	2	34 bifocal, same quad.	WE + Tam	Recur 17 AWD 55
33	Clinical (distant)	1	EIC+	3	72 single, same quad.	WE + chemo	NED 18
75	Clinical (close)	0	EIC+	2	53 bifocal, same quad.	M	NED 23
56	Gross path	3	EIC+	4+	80 single, other quad.	WE	NED 3
68	Gross path	1	EIC−	3	72 single, same quad.	WE	NED 1
54	Gross path	0	EIC−	3	19 skin, extensive	Biopsy + chemo	Meta 3 DOD 25
45	Clinical (close)	10	EIC−	3	61 skin, localized	WE	NED 1
35	Clinical (distant)	0	EIC−	2	62 single, other quad.	WE + chemo	NED 1
43	Mammogr. (distant)	0	EIC+	2	13 diffuse, inflammatory	Chemo + Tam	AWD 36

EIC, extensive intraductal component; WE, wide excision; M, total mastectomy; Chemo, chemotherapy; Tam, tamoxifen; NED, alive without active cancer; DOD, dead of cancer; AWD, alive with cancer; LFU, lost to follow-up.

given the possible technical and cosmetic difficulties associated with breast preservation in these patients and the biases of the individual surgeons involved. It is possible that some of our observations may not apply to patients with macroscopically multifocal tumors as a whole.

It is clear that macroscopic multiplicity as defined in this paper is only a facet of the spectrum of multifocality. However we have chosen to focus attention on this aspect because only those multiple foci that are apparent on clinical, mammographic, or gross pathologic examination can readily influence the pre- or intraoperative decision to proceed with conservative surgery. Using these criteria, 61 of the 586 (11%) patients in this study had macroscopically multiple tumors. In only 12 (2%) instances were the foci at a considerable distance from each other. There are very few other data in the literature pertaining to the frequency of macroscopically separate tumor masses. Fisher et al.[7] observed two clinically and pathologically distinct lesions residing in remote quadrants in only 1 of 1000 cases reviewed. In a more recent series of patients selected for breast conservation, 10 of 697 (1.4%) patients were found to have two or more separate invasive primary lesions in the treated breast, but a clear selection bias against such patients was in effect in the reporting institution.[22]

Comparison of patient-related and tumor-related characteristics yielded very little to distinguish macroscopically multiple from unifocal tumors (Table 1). Both patient groups had a similar average age and comparable rates of estrogen-receptor positivity and lymph node involvement. Contralateral breast cancers were observed with similar frequencies and overall survival was identical. The most notable morphologic feature was a higher prevalence of EIC in patients with multiple tumors. A correlation between EIC and multiple primary lesions has also been noted by Leopold et al.[22]

Our experience confirms the hypothesis that macroscopically multiple tumors have an inherently greater tendency to local failure after conservation therapy than do grossly unifocal cancers. Our attempts to identify subgroups of patients at high recurrence risk must be viewed with some degree of skepticism, given the small number of events for analysis. Patients suffering local recurrence, however, were almost exclusively confined to those in which the multiple lesions were apparent to the clinician, or in which the pathologist identified three or

more nodules on gross examination. Tumors that were close together did not tend to recur less often than those that were far apart. There appeared to be a tendency for tumors with EIC to recur more frequently, although this difference was not statistically significant. Extensive intraductal commponent has previously been identified as an important risk factor for local recurrence in the breast[14,21] and has been postulated by Leopold et al.[22] as being responsible for the higher recurrence rate observed in patients with multiple primary tumors. Our study neither confirms nor refutes this hypothesis.

The major weakness of this study concerns the issue of microscopic resection margins. The surgical approach in this series was based on a 'complete' wide excision of the gross lesion, with a margin of about 1 cm of macroscopically normal surrounding tissue, as judged by the operating surgeon.[12] It is likely, however, that improved local results might be achieved in these high-risk patients if intraoperative control of microscopic resection margins were to take place, with judicious use of re-excision to assure adequacy of resection.[23] The potential value of this close collaboration between surgeon and pathologist is suggested by our study of resection margins. Although it is recognized that adequacy of excision is best assessed prospectively,[20,24] our retrospective analysis yielded interesting results, despite the substantial number of margins that were classified as indeterminate. First the surgical approach used in this series attained adequate margins significantly less often for multiple than for single tumors (Table 1). Second local failure was, with one exception, observed only in patients with inadequate or indeterminate margins. The status of resection margins proved to be the only significant predictor of local recurrence risk in the Cox multivariate analysis (Fig. 2).

As might be expected, analysis of local failures suggests that such recurrences tend to be multifocal and sometimes extensive for patients having had macroscopically multiple primary lesions (Table 2). This is in contrast with recurrences in patients with grossly unifocal cancers, which tend to be single and confined to the vicinity of the tumor bed.[21,25] In addition recurrences in patients with multiple tumors have a tendency to occur later than in patients with single lesions (Fig. 1), raising the possibility that some of these local failures might represent previously unrecognized 'new' primary tumors in the retained breast. The possible importance of new tumor formation has been discussed in previous publications.[21,25]

The limited scope of this study precludes firm conclusions regarding the treatment and prognosis of recurrence in these patients. However, as only 3 of the 15 local failures were treated with total mastectomy, it is likely that the extent of recurrence was underestimated in some cases. Despite the fact that two patients survived relapse free more than 6 years after wide excision of their recurrences, conservative salvage surgery should be used with particular caution in this subgroup of patients.[26]

It appears justified to consider patients with grossly recognizable multiple tumor foci to be at greater risk when treated with conservation therapy. This is reflected in a higher risk for local recurrence and in a tendency toward multifocal, more extensive recurrences as compared to patients with macroscopically unifocal cancers. Nonetheless retrospective review of resection margins suggests that satisfactory results can be achieved if particular attention is paid to the adequacy of excision in these high-risk patients. It is apparent that close collaboration between surgeon, pathologist, and radiation oncologist is especially important in this situation. Under these conditions, we do not consider the presence of macroscopically multiple tumor foci alone to represent a contraindication to breast-conserving surgery with radiotherapy.

Whether a conservative operation should be undertaken in the face of macroscopically multiple tumors depends, to some extent, on the degree with which the particular patient desires breast preservation. Because resection of a larger portion of the breast is sometimes necessary, it is possible that the cosmetic result may, in some cases, not meet with the expectations of the patient. It is apparent that such a judgment can best be rendered by a surgeon who has a considerable personal experience with conservative breast operations.

Acknowledgment

The authors thank Jakob Roth, Ph.D., for his invaluable contribution to the statistical analysis.

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