Eur J Cancer, Vol. 27, No. 3, pp. 240–244, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Specialist Interest Articles

Is Breast Conservation after Local Recurrence Feasible?

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The feasibility of conservative salvage surgery was addressed in a clinicopathologic study of the results of wide excision for 50 selected parenchymal intramammary recurrences after standard breast conserving treatment. After median follow-up of 51 months, 16 (32%) second local failures were observed (5-year local control 62%). Cox multivariate analysis of 18 parameters indicated that only disease-free interval and resection margins significantly influenced local control. 5-year local control was 92% for recurrences occuring after 5 years vs. 49% for shorter intervals, and 73% for negative vs. 36% for positive or indeterminate margins. Local control appeared independent of morphologic features, initial tumour stage, patient age, recurrent tumour size and location. Median survival after second local failure was 33 months; tertiary therapy obtained ultimate local-regional control in 8 of 16 cases. The authors conclude that wide excision is a particularly satisfactory alternative to salvage mastectomy for late recurrences. Negative margins are essential. Further study will be required to establish additional guidelines allowing improved patient selection.
Eur J Cancer, Vol. 27, No. 3, pp. 240–244, 1991.

INTRODUCTION

BREAST-CONSERVING therapy offers not only the opportunity of avoiding surgical mutilation in most patients. In addition, preservation of the breast allows the therapeutic advantage of reserving more extensive surgery for the treatment of local recurrences, which are often difficult to manage when they occur in the skin flaps following primary radical surgery [1]. Total mastectomy has rightly been considered the treatment of choice for local failure in the breast after conservation therapy [2,3]. Nonetheless, many intramammary recurrences are small and apparently localised, and patients not infrequently continue to desire breast preservation despite local failure.

In 1988 we first reported a series of 52 selected local recurrences treated by wide excision, with total mastectomy held in reserve for second or later local failure [4]. We concluded that the preliminary results justified such alternative salvage surgery for mobile, well demarcated parenchymal recurrences 2 cm or less in diameter, without signs of rapid growth, in breasts without marked postirradiation changes. The present clinical-pathological study represents an effort to better define the oncological results of conservative salvage treatment, to determine if a multivariate analysis of risk factors might allow improved definition of the indications for wide excision, and to investigate whether subsequent local recurrences can be effectively managed.

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Revised 4 Dec. 1990; accepted 7 Dec. 1990.

MATERIALS AND METHODS

In order to facilitate review of all pathological material, this study was restricted to patients who underwent conservative salvage surgery at the Marseille Cancer Institute (Institut J. Paoli-I. Calmettes) between January 1975 and December 1987. All patients had been treated prior to December 1983 under the direction of the authors for clinical stage I–II breast cancer by breast-conserving surgery and megavoltage radiotherapy, including supplemental electron beam irradiation of the tumour bed. Treatment guidelines and techniques have been described [5, 6]. Included in the study were patients with apparently isolated parenchmal breast recurrences, with or without axillary recurrence. 4 patients with recurrence involving the skin were excluded.

Clinical records of the study patients were abstracted, and the histological slides of all recurrent tumours were reviewed by a single pathologist (J.J.), without prior knowledge of treatment outcome. Of 50 patients identified, mean age at recurrence was 50 years (range 29–74). The recurrent tumour was located within or in the immediate vicinity of the primary tumour bed in 31 (62%) and elsewhere in 19. Macroscopic diameter of the recurrence, as measured by the pathologist, was 1 cm or less in 21 (42%), 1.1 to 2 cm in 19 (38%), larger than 2 cm in 9 (18%) and unknown in 1 case.

Salvage therapy included macroscopically complete wide excision in all patients, with 1–2 cm margin of grossly normal breast tissue. Intraoperative control of resection margins or marking of the specimen with India ink was not performed, and re-excision was not used. 12 patients (24%) underwent simultaneous axillary dissection, either because the axilla had not previously been dissected, or because suspicious findings were present; nodes were positive in 4 cases. Surgical techniques have been described [4, 6].

Adjuvant therapy at time of local failure varied greatly during the 13-year period of this study. This included hormone therapy alone in 17 patients (bilateral oophorectomy with or without tamoxifen in premenopausal, and usually tamoxifen in postmenopausal patients). Chemotherapy in various combinations, with or without hormone therapy, was administered to 15 patients, and 18 patients (36%) received no systemic adjuvant treatment. 11 selected patients, with recurrences located at some distance from the primary tumour bed, received local radiation to the excision site. In seven instances, 20–30 Gy was administered with an electron beam, and in four cases 50 Gy with an interstitial ^{192}Ir implant.

Eighteen clinical and pathological parameters were included in the analysis. Oestrogen receptor (ER) levels were determined by methods described by Martin *et al.* [7]; values of 10 fm/mg or more were scored as positive. ER was unknown in 7 patients. Microscopic resection margins were evaluated retrospectively using sections through the recurrent tumour, as well as sections taken at its periphery, as described elsewhere [8]. In 9 patients, the status of margins could not be judged with confidence; these were scored as indeterminate. Our criteria for pathological evaluation of morphologic features have been defined previously [8]. The following factors were evaluated with regard to influence on local control: age at initial therapy (less than 40 vs. 40 years or older); age at recurrence (less than 50 vs. over 50); initial T-stage (cT1 vs. T2); initial nodal status (pN^- vs. pN^x vs. pN^+); disease-free interval (less than 2 years vs. 2–5 vs. more than 5); size of recurrent tumour (1 cm or less vs. 1.1–2 vs. more than 2 cm); location of recurrence (tumour bed vs. elsewhere); microscopic excision margins (negative vs. indeterminate vs. positive); oestrogen receptor (ER^- vs. ER^+ or unknown); histological type (invasive ductal vs. other); modified Bloom–Richardson grade (1 vs. 2 vs. 3); tumour necrosis (yes vs. no); blood or lymph vessel invasion (yes vs. no); lymphocytic stromal reaction (absent to mild vs. moderate to severe); intraductal cancer within recurrent tumour (less than 25% vs. 25% or above); intraductal cancer in periphery of recurrent tumour (absent vs. present); axillary recurrence (yes vs. no); and adjuvant therapy (none vs. radiotherapy vs. hormones vs. chemotherapy).

Statistical analysis was based on actuarial survival functions, using methodology described by Kaplan and Meier [9]. Overall survival took into account all causes of death. Actuarial local control considered proven second local failure in the treated breast as endpoint, with patients not having second local recurrence treated as censored observations at time of last follow-up or at death. Differences between survival functions were tested for significance using the logrank test, between simple ratios using the χ^2 test, with appropriate modifications for small sample size [10]. Multivariate regression analysis was performed in the stepwise mode using the computer program "Survival Analysis with Covariates: Cox Models" (BMDP Statistical Software, University of California, Los Angeles).

RESULTS

After a median follow-up of 51 months following local recurrence, second failure in the treated breast has thus far been observed in 16 of the 50 patients (32%). Mean time to second local failure was 31 months. Actuarial local control in the breast was 62% at 5 years. Among 15 patients at risk for more than 5 years, one additional local failure has been observed (at 86 months). Overall survival after conservative salvage surgery was 67% at 5 and 42% at 10 years.

Table 1. Clinical-pathologic study of conservative salvage surgery: factors appearing most closely associated with local control

Factor	Second breast recurrence	*P*
Disease-free interval		
Less than 2 yr	6/13 (46%)	
2–5 yr	9/19 (47%)	
More than 5 yr	1/18 (6%)	0.01
Resection margins		
Positive or indeterminate	8/17 (47%)	
Clearly negative	8/33 (24%)	0.01
Oestrogen receptor (ER)		
Negative	10/22 (45%)	
Positive/unknown	6/28 (21%)	0.05
Extensive intraductal component (IDC only)		
Positive	6/11 (55%)	
Negative	7/30 (23%)	0.19
Adjuvant systemic therapy		
None	8/18 (44%)	
Hormone therapy (HT)	6/17 (35%)	
Chemotherapy ± HT	2/15 (13%)	0.21

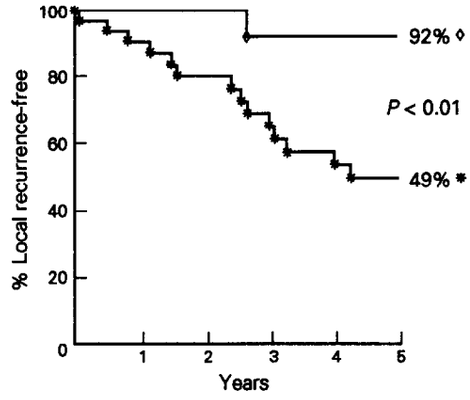
P values determined by the logrank test.
IDC = infiltrating ductal carcinoma.

The 18 clinical and pathological parameters cited above were analysed with respect to local control in the breast after conservative salvage surgery. Local control was not influenced by patient age [second local recurrence in 9/25 (36%) of patients 50 or younger at time of salvage surgery vs. 7/25 (28%) in older patients], by location of recurrent tumour [second local recurrence in 9/31 (29%) failing near the primary tumour bed, vs. 7/19 (37%) failing elsewhere in the breast], or size of the recurrent tumour [second local recurrence in 7/21 (33%) of recurrences 1 cm or smaller; 5/19 (26%) for recurrences 1.1–2 cm; vs. 3/9 (33%) for recurrences larger than 2 cm]. Local control also did not appear to correlate with initial age, initial T-stage, or initial nodal status (data not shown).

Of histomorphological features examined, none showed a significant correlation with local control. Second local recurrence occurred in 13/41 (32%) of invasive ductal cancers, and in 3 of 9 (33%) with other histological types (1 of 4 invasive lobular, 1 of 3 ductal *in situ*, 1 of 2 colloid). Local control appeared unaffected by histological grade, tumour necrosis, vascular invasion, lymphocytic stromal reaction, degree of intraductal cancer within the tumour, intraductal cancer in the periphery, and presence or absence of axillary recurrence (data not shown).

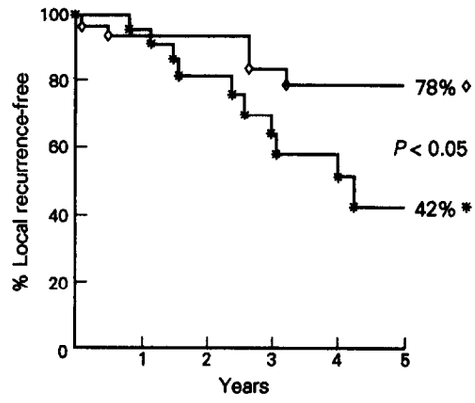
Three factors significantly correlated with local control in monofactorial analysis: disease-free interval, resection margins, and oestrogen receptor level (Table 1). Risk of second local failure was very low only for late recurrences diagnosed after 5 years. Second local failure occurred in 4 of 8 (50%) patients with positive margins, and 4 of 9 (44%) with indeterminate margins, so that the two categories were grouped together. Curves for actuarial local control as a function of disease-free interval, status of resection margins, and ER level are presented in Figs 1, 2 and 3, respectively.

Because of current interest in this risk factor, the 41 patients with invasive ductal cancers were separately evaluated according to the presence of extensive intraductal component (EIC). This



◊ 18 18 17 17 15 12 11 9 7 4 4 Interval > 5 years
* 32 31 25 24 21 20 18 14 14 11 11 Interval < 5 years

Fig. 1. Actuarial local control after conservative salvage surgery, comparing patients recurring within the first 5 years after primary treatment with those recurring later. The numbers below the time axis represent patients at risk for each interval.



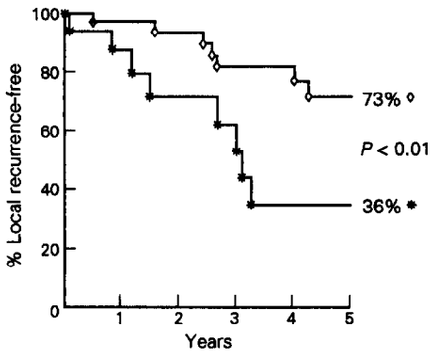
◊ 28 27 22 22 21 19 17 15 13 11 11 ER positive/unknown
* 22 22 20 19 15 13 12 8 8 4 4 ER negative

Fig. 3. Actuarial local control after conservative salvage surgery, comparing recurrences with negative vs. positive or unknown oestrogen receptors. The numbers below the time axis represent patients at risk for each interval.

was diagnosed when the recurrent tumour contained at least 25% intraductal carcinoma, and intraductal cancer was also present in the periphery [3]. There was a trend for more second local failures for recurrences with EIC (Table 1). However, 8 of 11 EIC^+ recurrences had positive or indeterminate margins, and only one of the six second local failures in EIC^+ patients occurred after histologically complete excision.

The possible effect of adjuvant therapy was also investigated. There was a non-significant trend to improved local control when adjuvant chemotherapy was employed, with or without hormone therapy, when compared to hormone therapy alone or no adjuvant systemic treatment (Table 1). However, 9 of 15 patients treated with adjuvant chemotherapy had recurrences diagnosed after 5 years. No clear benefit could be demonstrated from additional local irradiation of the excision site, second local failures having been observed in 4/11 (36%) with radiotherapy compared with 12/39 (31%) without supplemental radiation treatment.

Cox multivariate analysis revealed only 2 independently significant determinates of improved local control: disease-free interval more than 5 years (χ^2 improvement 8.2, $P < 0.004$) and negative resection margins (χ^2 improvement 4.4, $P > 0.04$).

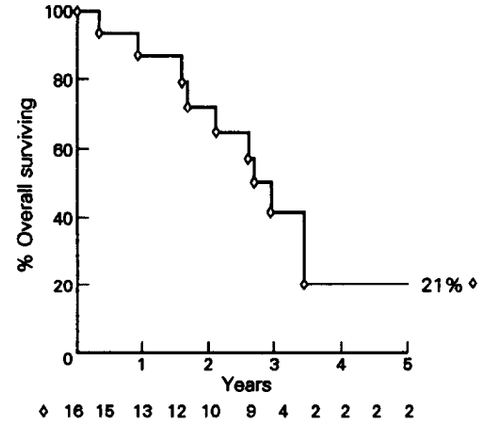


◊ 33 33 31 31 27 24 22 19 18 13 13 Margins negative
* 17 16 11 10 9 8 7 4 3 2 2 Margins positive/indeterminate

Fig. 2. Actuarial local control after conservative salvage surgery, comparing recurrences with negative vs. positive or indeterminate resection margins. The numbers below the time axis represent patients at risk for each interval.

Attention was then turned to the 16 patients suffering second local failure. In four instances (25%) the recurrence was inoperable, with extensive involvement of parenchyma and skin, resembling primary inflammatory breast cancer. In 6 patients, total mastectomy was performed, with skin or diffuse breast involvement found in 5, and apparently unifocal disease in 1 case. The remaining 6 patients were treated by further breast-conserving salvage surgery for apparently unifocal second recurrence.

Median follow-up after second local failure was 33 months. Tertiary surgery resulted in local control up to the last follow-up or death in 8 patients (50%), including 5 of 6 patients treated with a third conservative operation. At last follow-up, 5 patients remain alive without relapse at 6, 13, 33, 35 and 84 months after tertiary surgery, 1 patient is alive with active disease at 117 months, and 10 patients (63%) are dead of breast cancer. The median survival after second local failure was 33 months, 4-year overall survival 21% (Fig. 4).



◊ 16 15 13 12 10 9 4 2 2 2 2

Fig. 4. Overall survival after tertiary therapy for 16 patients having had second recurrence in the breast after conservative salvage surgery. Median survival was 33 months. The numbers below the time axis represent patients alive at each interval.

DISCUSSION

When we first resorted to conservative surgery in the early 1970s for recurrent disease in the irradiated breast, there were neither clinical nor pathological data supporting its use in this setting. Even since our first report [4], we are unaware of subsequent publications by other groups reporting results of such treatment in significant numbers of patients. However, other authors have gone on record as employing conservative salvage surgery frequently [11, 12], occasionally [13] or only very rarely [2, 3].

In recent years pathological studies of salvage mastectomy specimens have pointed out the anatomical constraints of the use of wide excision in the treatment of recurrence in the breast. Using routine pathological examination, cancer foci outside the quadrant of reference were found by Schnitt *et al.* [14] in only 4 of 18 (22%) and by Fowble *et al.* [2] in only 16 of 51 (31%) salvage mastectomy specimens. The largest study was reported by Fisher *et al.* [15], who described the pathological anatomy of 110 intra-mammary recurrences. The authors found only 14 (13%) cases with cancer foci outside the quadrant of the primary tumour. However, in this study the great majority of local recurrences analysed had occurred in patients having received no radiation therapy. It is possible that recurrences tend in some instances to be less localised in irradiated patients, in whom local failures tend to be diagnosed later, than in unirradiated patients.

Although none of the above studies utilised serial sectioning methods, the reports suggest that surgical treatment directed at the quadrant of recurrence has the potential to locally control up to 69–87% of parenchymal breast failures. When used after standard breast-conserving treatment, the unselected use of wide excision for recurrence would thus be followed by second local failure in at least one-fourth to one-third of patients, since full-dose radiation therapy can no longer be administered to the remainder of the breast. Conservative salvage surgery can gain recognition as a viable alternative to total mastectomy only if indications can be better defined to reduce second local failures to an acceptable minimum, and if second local recurrences can to a great degree be successfully treated.

In the present favorably selected series, in which 80% of recurrent tumours were 2 cm or less in diameter, the relatively high rate of second local failure (37% at 5 years) is probably explained in part by the lack of satisfactory resection margins in 17 cases. Negative margins, demonstrated by careful pathological examination of an inked resection specimen [15], should be viewed as an indispensible element of conservative salvage surgery. Re-excision should be resorted to in the event of positive or uncertain margins, and if clearly negative margins cannot be achieved, total mastectomy should be performed. Our limited experience suggests that local irradiation to the excision site, which cannot always be safely employed, should not be expected to compensate for inadequate excision. The recurrence rate in patients with clearly negative margins (27% at 5 years) is consistent with the pathological studies cited previously and is similar to local recurrence rates observed after complete local excision without radiotherapy for early primary breast cancer [11, 15].

The attempt of the present study to define additional risk factors for second local failure must be viewed as disappointing. The only subgroup of patients with a very low failure rate after conservative salvage surgery were those with late recurrences diagnosed after 5 years. Although wide excision appears to provide excellent results for late recurrences, it is possible that more second local failures will be diagnosed in these patients with longer follow-up. Otherwise, there was no conclusive indication how local control could be improved for patients with early failures having negative margins, of whom 7 of 19 patients (37%) in this series suffered second local recurrence. It is possible that oestrogen receptor, extensive intraductal component or other morphological features will prove useful in this regard. The scope of this study was apparently inadequate to allow identification of further significant factors.

An important finding in this study was the poor prognosis of second failure in the treated breast, with overall survival of 21% four years after tertiary therapy (Fig. 4). One-quarter of second local recurrences were inoperable, and another 31% of patients had extensive recurrence at mastectomy. Ultimate local control could be achieved by tertiary treatment in only half of the 16 patients failing locally after conservative salvage surgery.

It is possible that patients recurring a second time after breast-conserving salvage surgery represent a more aggressive subgroup of tumours, who might have done poorly regardless of the type of surgical therapy applied. However, our data suggest that a small decrement in ultimate local control may result from the use of wide excision in this setting. With a median follow-up of 51 months, 8 of 50 (16%) patients in this selected series had uncontrolled local disease. In contrast, 5-year local failure rates after salvage mastectomy of 8–12% have been reported [2, 16]. Since only less extensive local recurrences are selected for wide excision, it is likely that the apparently increased risk of uncontrolled local disease associated with the use of conservative salvage surgery is real, although probably small.

In summary, wide excision is a practicable alternative to total mastectomy for small, well-demarcated parenchymal recurrence in patients desiring continued retention of the diseased breast. This strategy allowed 39 of 50 patients (78%) in this study to retain their breasts while obtaining local control of recurrent disease, in five instances with the aid of a third breast-conserving operation. In this sense one might conclude that breast conservation after local failure is a feasible goal for the majority of patients with apparently limited recurrences.

Nonetheless, even with negative margins, it is likely that a risk of second local failure of at least 25% can be expected. Other than long disease-free interval, we have been unable to define factors which would allow selection of patients with a minimal risk of second failure. Since second local recurrence carries with it an unfavorable prognosis, greater experience and further study will be required to minimise the apparent risks associated with conservative salvage surgery.

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Acknowledgement—The authors thank Jakob Roth for his contribution to the statistical analysis.

Eur J Cancer, Vol. 27, No. 3, pp. 244–248, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Association Between Breast Cancer and Family Malignancies

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In a case-control study, the relationship between a family history of cancer of the breast, ovary, colon, uterus or prostate and the risk of breast cancer was investigated. The data consisted of family histories from 495 breast cancer cases and 785 controls aged 20–56 years. A positive association was found between the occurrence of breast cancer and a history of breast cancer in the families of the subjects affected. This relationship increased linearly with both the degree of kinship of the affected relatives and with their number. The risk of breast cancer associated with other types of cancer in the family was not significantly different from unity.
Eur J Cancer, Vol. 27, No. 3, pp. 244–248, 1991.

INTRODUCTION

THE RELATIONSHIP between breast cancer and other epidemiologically linked types of cancers has mainly been studied at population level by examining the geographical variations in incidence rates, and at individual level by evaluating the individual risk of a second primary cancer [1]. To our knowledge, only two case-control studies have been performed to determine the association between a family history of cancer and the risk of breast cancer in a large population [2, 3].

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Revised 17 Oct. 1990; accepted 3 Dec. 1990.

SUBJECTS AND METHODS

The data were obtained from a case-control study performed in five French public hospitals. The details of the methods used to select the cases and controls and to collect data were those described elsewhere [4] and are only summarised here. Cases had to be 20–56 years old, with a histologically defined breast cancer, confirmed within the past 7 months. All histological types were accepted. For every case, three types of controls could be selected: friends or colleagues of the case, and patients hospitalised for a malignant tumour or for a non-malignant condition. The diseases for which these controls were hospitalised had to be diagnosed within the past 12 months. The criteria for matching controls to cases were age at interview (within 5 years), years of birth (within 5 years), date of interview (within 14 months) and interviewer. Hospital controls had to be hospitalised in the same hospital as the case. 495 cases and 896 controls were interviewed. More than 99% of all the subjects agreed to be interviewed. Information was recorded on a structured questionnaire and concerned the following characteristics: basic demographic details, current and past medical history, menstrual and reproductive experience, life style factors, contracep-