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## Original Paper

# Ten-year Results of Treatment of Ductal Carcinoma *in Situ* (DCIS) of the Breast with Conservative Surgery and Radiotherapy

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The optimal treatment of ductal carcinoma *in situ* (DCIS) of the breast has not yet been established. The effectiveness of adjuvant postoperative radiotherapy after conservative surgery is debated. Few data are available in Italy on the combined treatment. A collaborative multi-institutional study on this issue in 10 radiation oncology departments of the north-east of Italy was conducted. One hundred and thirty nine women with DCIS of the breast were treated between 1980 and 1990. Age ranged between 28 and 88 years (median 50 years). Surgical procedures were: quadrantectomy in 108, lumpectomy in 22 and wide excision in 9 cases. The axilla was surgically staged in 97 cases: all the patients were node-negative. Radiation therapy was delivered with <sup>60</sup>Co units (78%) or 6 MV linear accelerators (22%) for a median total dose to the entire breast of 50 Gy (mean 49.48 Gy; range 45–60 Gy). The tumour bed was boosted in 109 cases (78%) at a dose of 4–30 Gy (median 10 Gy) for a minimum tumour dose of 58 Gy. Median follow-up was 81 months. Thirteen local recurrences were recorded, 7 intraductal and 6 invasive. All recurrent patients had a salvage mastectomy and are alive and free of disease. Actuarial overall, cause-specific and recurrence-free survival at 10 years are of 93%, 100% and 86%, respectively. The results of this retrospective multicentric study substantiate the favourable data reported in the literature and confirm the efficacy of the breast-conserving treatment of DCIS employing conservative surgery and adjuvant radiation therapy. © 1997 Elsevier Science Ltd.

**Key words:** *in situ* ductal carcinoma, radiotherapy, breast cancer

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## INTRODUCTION

THE INCREASED use of mammographic screening has resulted in an increased detection of ductal carcinoma *in situ* (DCIS) of the breast [1], which currently represent approximately 10% of all newly diagnosed breast cancers and 45% of all non-palpable breast malignancies [2].

The treatment employed for DCIS of the breast varies widely, ranging from local excision alone to bilateral mastectomy with or without maxillary dissection. The best treatment option has not yet been clearly defined and the management of intraductal carcinoma remains a subject of debate.

The wide acceptance of breast-conserving treatment in the therapy of stage I–II invasive carcinomas [3, 4] has made mutilating approaches difficult to justify for a lesion such as DCIS, thought to be of lower malignant potential,

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suggesting more conservative options for intraductal tumours.

Experience with conservative management of DCIS with surgery and radiotherapy (XRT) is limited in terms of both patient numbers reported from single-institution series and length of follow-up.

In this study, an analysis of 139 women with DCIS of the breast treated in 10 Italian institutions with a conservative approach is reported.

## PATIENTS AND METHODS

A collaborative, multi-institutional retrospective study of patients affected by DCIS of the breast treated with breast-conserving therapy (excision and radiation therapy) was performed, analysing data from 10 radiation oncology departments of the north of Italy (Trento, Reggio Emilia, Varese, Treviso, Padova, Verona, Aviano, Mestre, Milano, Venezia). A detailed retrospective review of the records of all patients with DCIS referred to these institutions from 1980 to 1990 was conducted.

Table 1. Characteristics of the study population

No. of evaluable patients	139
Age (years)	
median	50
range	28–88
Menstrual status	
premenopausal	78
postmenopausal	61
Family history of breast cancer	22
Previous breast cancer	4
invasive	1
intraductal	3
Tumour location	
outer quadrants	89
inner quadrants	25
central	10
subareolar	15
Presenting symptoms	
lump	69
nipple discharge	14
none	39
lump + nipple discharge	4
unknown	13
Clinical tumour size (cm)	
median	1.5
range	1–4.5
Mammographic finding (120 cases)	
mass	45
microcalcifications	45
mass + microcalcifications	12
‘positive’ details not available	7
negative	11
Histological subtype	
comedo	49
cribriform	28
solid	7
papillary + micropapillary	28
mixed with LCIS	11
clinging	2
not specified	14

## Patient characteristics

A total of 139 sequential evaluable cases was collected. The clinical presentation of the patients is shown in Table 1. Briefly, the median age was 50 years (range 28–88 years); 61 patients had post-menopausal status; 22 of the 139 patients (16%) had a family history of breast cancer.

All patients presented with unilateral intraductal carcinoma of the breast. The right breast was involved in 55% and the left in 45%, the lesion was in the outer quadrants in 64%, the central in 18% (subareolar in 11%) the inner in 18%. Of the 126 patients for whom the clinical presentation was known, 73 (58%) had a palpable lump. Pre-operative mammography had been performed in 120 patients, with 11 (9%) negative cases; of the remaining 109 abnormal cases, 45 (38% of the total) were due to microcalcifications alone, 45 (38%) to mass effect alone, and 12 (10%) to mass plus calcification. In 7 cases, positivity of the mammogram without a detailed description of abnormality was reported. Since most of the mammograms were not available, re-examination by a radiologist or by a panel was not possible; the description of the mammography was consequently used as a reference.

Of the 73 palpable tumours, 60 had a mammography; 56 positive cases were recorded with a mean tumour size of 1.5 cm (range 1–4.5 cm). Size was unknown in 14 cases. In 107 patients a measurement of the extent of the disease in the surgical specimen was available: the median pathological tumour was 1 cm (range 0.2–5 cm).

Fine-needle aspiration biopsy (FNAB) of a palpable mass was performed in 38 cases with negative, suspicious or positive results in 7, 12 and 19 cases respectively.

## Surgical treatment

The surgical treatment consisted of quadrantectomy in 108 cases (78%), wide excision in 9 (6%) and tumourectomy in 22 (16%). No re-excisional biopsies were performed. Postoperative mammograms were obtained in most patients to verify the completeness of the excision.

An axillary dissection was performed in 97 out of 139 cases with a median of 15 lymph nodes dissected (mean, 14; range 3–36): all were pathologically negative for metastatic disease.

## Pathology

The tumour diagnoses were reviewed and confirmed as DCIS by institutional pathologists; a central pathology review was not possible.

The cases were classified according to recognised histological criteria [5] according to dominant growth pattern; the architectural features were categorised into: comedo, solid, cribriform, papillary and micropapillary, and cases associated with lobular carcinoma *in situ* (see Table 1). In cases of mixed patterns, the predominant pattern was considered for classification. Nuclear grade and pathology margins were also studied. A complete pathology evaluation was possible for 126 of the 139 cases. In 14 cases, the original biopsy slides could not be located to be reviewed or margins were not marked (in the early 1980s), making conclusive examination impossible.

## Radiation therapy

Radiation therapy was initiated, on average 44 days after surgery (range 15–125 days). Irradiation with definitive

intent was delivered with  $^{60}\text{Co}$  (108 cases; 78%) or 6 MV photons (31 cases; 22%), by tangential fields, encompassing the entire breast up to doses of 45–60 Gy (mean 49.48 Gy; median, 50 Gy) with a dose per fraction of 2 Gy in all but 2 patients and a median duration of 45 days (mean, 42 days; range, 32–131 days). A subsequent boost to the primary site was delivered after treatment to the whole breast in 109 cases: 66 with 7–18 MeV electron beam, 40 with orthovoltage equipments and 3 with an interstitial implant for an additional median dose of 10 Gy (range 4–30 Gy). Local policy in three centres was to treat the whole breast only without an additional boost. Neither regional nodal irradiation nor adjuvant systemic treatments were used.

#### Statistical methods

Overall survival was defined as those patients eligible for initial evaluation who were alive at last follow-up. Cause-specific survival was defined as those patients who remained disease free after initial therapy, and as those ultimately salvaged after relapse. Relapse-free survival was defined as those patients who had no relapse of DCIS. Overall survival, cause-specific survival and relapse-free survival were calculated using the Kaplan–Meier method [6] with the time period beginning at the time of surgery.

Factors potentially affecting local recurrence were evaluated in univariate analysis. Fisher's exact test was used to determine the significance of different rates between patients who recurred and those who did not. All *P* values are two-sided.

## RESULTS

The median follow-up for the group was 81 months from the date of surgery, with a range of 36–167 months; 102 patients (73% of the population) were followed for at least 60 months.

#### Recurrence

Local failure was recorded in 13 patients, at an interval of 30–98 months (median 54) after surgical treatment (5 cases after 5 years). Six cases were invasive carcinoma and 7 cases intraductal carcinoma. One patient, with intact axilla, developed an axillary nodal relapse after invasive local recurrence. No distant metastases were observed. Ten recurrences were detected by mammography, including 7 by mammography alone. Median interval of relapse for invasive recurrences was 53.5 months (mean, 57.5; range 30–98) and for intraductal recurrences 53 months (mean 54.1; range 38–68). Comedo lesions relapsed after a median period of 56 months (mean, 59; range 30–98) and non-comedo lesions after 51 months (mean, 53.1; range 38–74). In 8 women, either the first and the second tumours were true recurrences, occurring at the site of previous excision or on the border of the same quadrant. In three women the second tumour was located at a site different from that of the primary tumours, i.e. outside the initial quadrant; in two cases the site was not specified.

#### Treatment of recurrence

Four of the 13 relapsed patients had received a tumour bed dose of 50 Gy and 9 had had a supplemental external boost of 10 Gy. The initial surgical intervention had been quadrantectomy in 12 cases and tumourectomy in one. Salvage mastectomy was performed in all the patients. One

patient was also treated with adjuvant tamoxifen at the time of recurrence. All the patients with breast failure are alive without evidence of disease, although with limited follow-up (median, 18 months; range 7–74 months). None has subsequently failed with distant metastases.

#### Survival

One hundred and twenty-six patients survived with a preserved breast, resulting in a 5- and 10-year actuarial breast recurrence-free rate of 93% and 86%, respectively (Figure 1(a)). No patient died of her disease; 3 patients died of intercurrent disease from non-malignant causes with no evidence of recurrence at the time of their last follow-up. Five- and 10-year actuarial overall survival rates were 98% and 93%, respectively (Figure 1(b)); cause-specific survival (Figure 1(c)) and freedom from distant metastases was 100% at 5 and 10 years.

#### Second cancers

Four second malignancies occurred during the follow-up: 1 cutaneous melanoma, 1 biliary tract adenocarcinoma, 1 chronic lymphocytic leukemia, 1 cervical intraepithelial neoplasia. Four patients subsequently had a contralateral carcinoma of the breast: two intraductal after 14 and 38 months and two infiltrating after 16 and 47 months.

#### Cosmesis

The cosmetic outcome was separately assessed, with different cosmetic score systems, at the last follow-up by the physicians of every institution in 119 cases: 89% of them had an excellent or good result.

#### Toxicity

No major acute side-effects and chronic complications of the radiation treatment were noted.

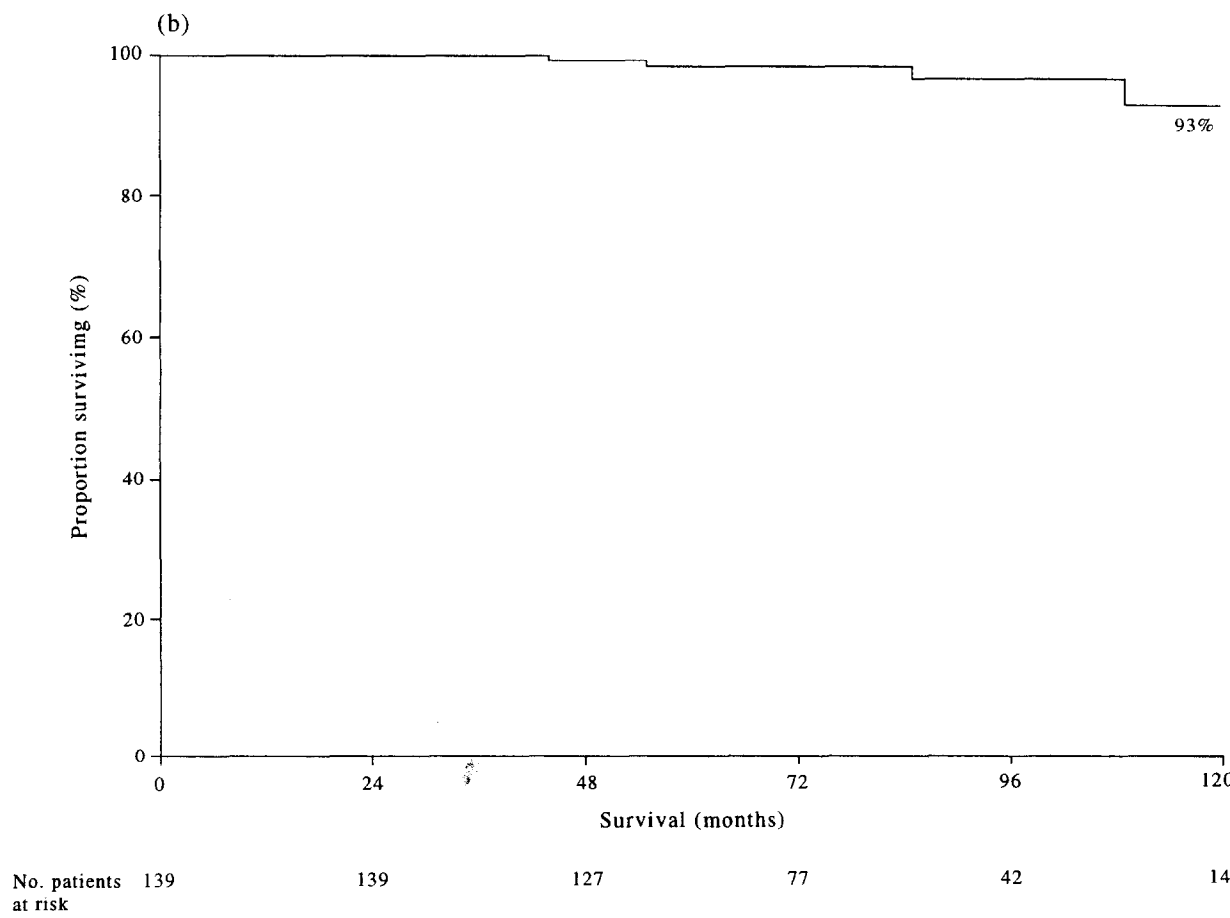
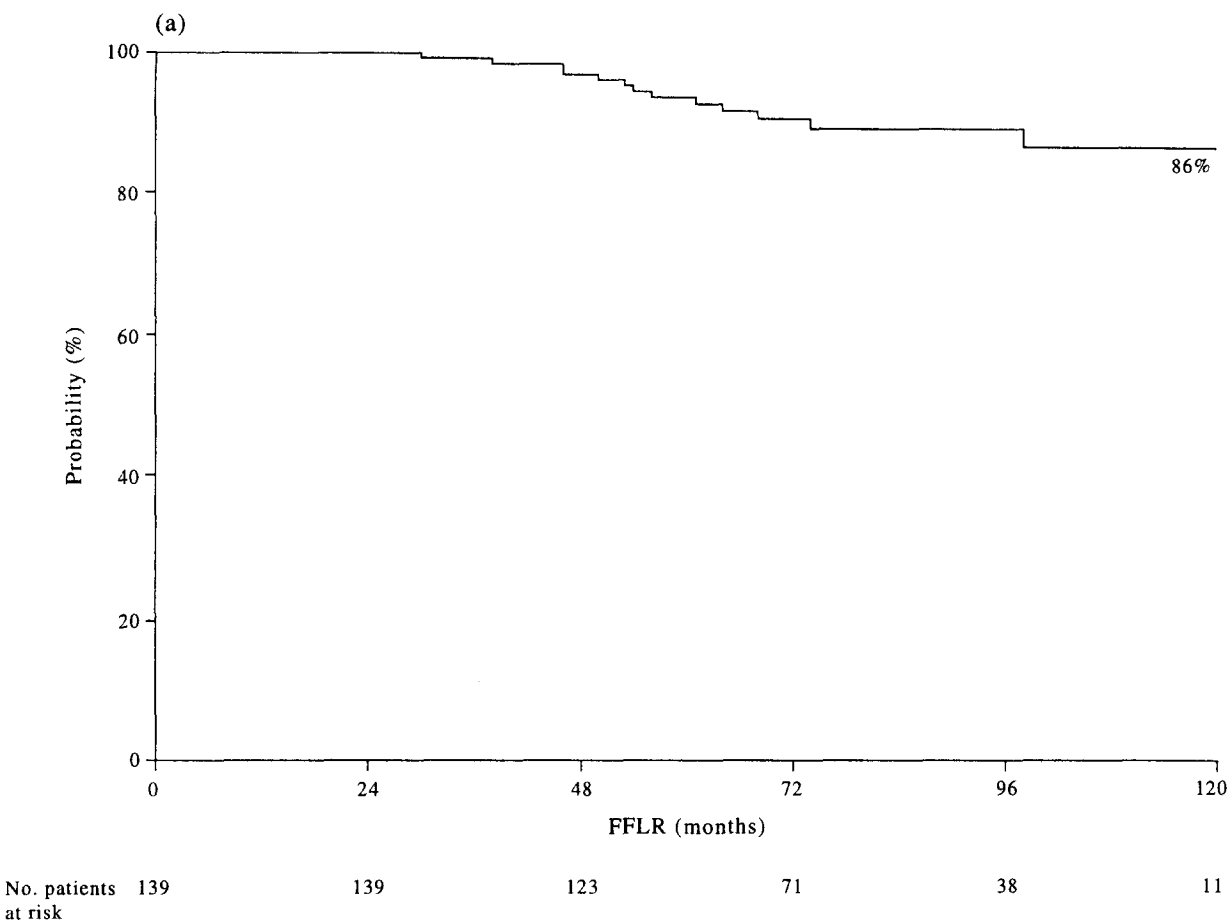
#### Statistical analysis

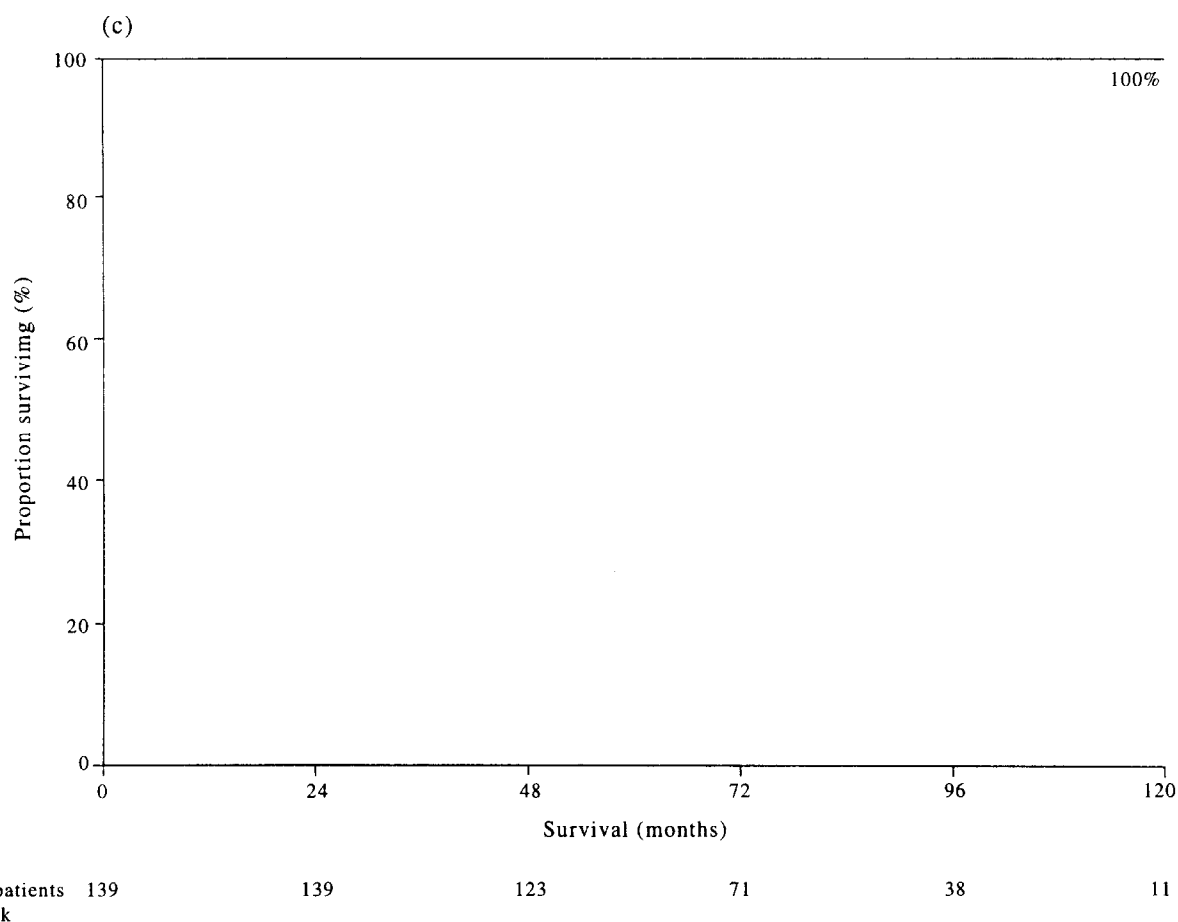
No variables demonstrated significance in the univariate analysis of recurrence (Table 2), for this reason multivariate analysis was not done.

## DISCUSSION

The therapeutic management of DCIS remains one of the most controversial issues in primary breast care. Historically, mastectomy has been considered the appropriate treatment for intraductal carcinoma of the breast for several years. An overall local recurrence rate of 1% and an overall mortality rate of 1.3% has been reported in 1411 published cases [7], showing that mastectomy, viewed as a prophylactic intervention, is not a complete guarantee of curability. The results of limited surgery alone are quite unsatisfactory: local recurrence has been reported at a cumulative average rate of 18.3%, ranging from 10% to 63% [8]. Studies of carefully selected patients treated with excision alone show recurrence rates of 15–20% at 10 years or more [9, 10].

The results obtained with conservative surgery plus irradiation compare well with those obtained with mastectomy; this treatment seems as curative as mastectomy in terms of the percentage of patients dying of their disease [11]. In comparison with reported results of conservative surgery alone, postoperative radiotherapy can reduce the breast recurrence rate to an acceptable level, but does not





**Figure 1. Kaplan–Meier representation of the probability of (a) freedom from local relapse (FFLR), (b) crude survival and (c) cause-specific survival for 139 patients with DCIS of the breast treated with conservative surgery and radiotherapy.**

eliminate it. Independent single and multi-institutional studies document that excision and radiotherapy provided acceptable local control while achieving excellent survival and cosmetic results [12–23].

The only published randomised study, the NSABP B-17 trial [24], compared limited excision followed by irradiation or observation: the addition of radiation decreased the risk of a breast recurrence to 7% from 16.4% in those women treated with lumpectomy alone, and decreased the risk of

subsequent development of an ipsilateral invasive breast cancer by 77%.

In some reports, a marked difference in local recurrence rate has been observed between 5 and 10 years or more in patients treated with surgery plus irradiation [13, 19, 21]. It is possible that irradiation could delay the appearance of further breast disease, but the risk remains low compared to the incidence in patients conservatively treated without irradiation [19, 22, 25].

**Table 2. Correlation between local recurrence and various clinical, pathological and treatment parameters potentially influencing outcome**

Parameter			Univariate <i>P</i> -value
1.	Patient-related		
	patient age	<35 years versus ≥35 years	0.9123
	menstrual status	premenopausal versus postmenopausal	0.195
	presentation	clinical versus mammographic	0.342
	familial history of breast cancer	yes versus no	0.3878
	nipple discharge	yes versus no	0.1564
2.	Tumour-related		
	size	<2 cm versus ≥2 cm	0.0678
	histologic subtype	comedo versus non-comedo	0.5794
	nuclear grade	grade 1–2 versus grade 3	0.2322
	comedo subtype + nuclear grade	comedo + grade 3 versus other	0.8121
3.	Treatment-related		
	surgery	tumorectomy versus quadrantectomy	0.3275
	total radiation dose	≤50 Gy versus > 50 Gy	0.3978

The current study is the largest series of DCIS treated with conservative surgery and irradiation reported in Italy. Surgical and radiotherapeutic treatment policies used in our centres were very similar, allowing the examination of a homogeneous population. Our results are in keeping with reported series with similar follow-up [13, 15, 19, 22]. Median time to local recurrence was 54 months, similar to other comparable reports [22, 23] showing a probability of breast preservation at 10 years of 86%. In our series cause-specific survival was 100% at 10 years, all the 13 patients with local recurrence being salvaged by mastectomy, although with a limited median follow-up of 18 months. Adjuvant radiotherapy at a dose of approximately 50 Gy to the whole breast plus a boost of 10 Gy in the majority of cases was administered without particular morbidity allowing good cosmetic results.

Unfortunately, we were unable to find any of the studied tumour-, patient- or treatment-related risk factors statistically predictive for local recurrence, although size of tumour was of borderline significance ( $P = 0.0678$ ). Similar negative results were observed in a multi-institutional retrospective study by Solin and associates [23]: many clinical and pathological factors which potentially could affect local recurrence were evaluated and none were predictive of local recurrence.

The majority of breast recurrences in our study were observed at or near the site of primary DCIS, suggesting a persistence rather than a new second tumour: 8 of the 11 known sites of recurrence were in the same quadrant as the first lesion.

The failure rate has been reported as being greater for palpable than for radiographically detected *in situ* cancers [2]. The clinical size of the measurable palpable primary tumours in our series was relatively small, with 88% of lesions smaller than 2 cm, and 39 patients with non-palpable, mammographically discovered lesions. Recently, White and associates reported a low rate of local recurrence in patients treated by surgery and irradiation for mammographically detected lesions [18].

The importance of nuclear grade, comedo histology, or both, as predictive factors for recurrence in patients treated with conservative surgery and radiation has been observed [17, 18, 20, 22]. Data from a recent comparative study [25] showed an irradiation benefit for disease-free survival and local control for patients with high-grade DCIS; in contrast, patients with low-grade DCIS did not benefit from the use of radiation therapy. Low-grade DCIS seems to be more indolent, recurring at a much lower percentage and after a much longer disease-free interval [10, 26]. Neither nuclear grade nor comedo histology statistically correlated with local recurrence in our series.

We observed no difference in local recurrence rate between patients who received irradiation to the whole breast only (50 Gy) or with a supplemental boost (60 Gy). No dose volume effect has been shown to exist for DCIS, but some authors [12, 14] have suggested a minimum dose  $\geq 60$  Gy or  $\geq 65$  Gy if residual disease is left in the biopsy site. An axillary dissection was performed in 97 patients: all the cases were pathologically negative, confirming the results reported in patients treated with mastectomy [27].

There are still some uncertainties regarding both the case selection and the ultimate outcome of patients treated with radiotherapy and surgery. Available data indicate breast-

conserving treatments as a valid alternative to mastectomy for the majority of patients. Our retrospective study, even though it involved numerous institutions and spanned a long period of time, indicates that clinically or mammographically detected DCIS can be successfully treated with conservative surgery and definitive irradiation. Due to limited sample size and the low recurrence rate, no specific characteristics associated with local relapse were identified. Currently, breast irradiation appears to be an integral part of breast-conserving treatment in patients with DCIS; results of ongoing prospective randomised trials addressing this issue should further clarify whether radiation therapy should be added to conserving surgery.

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## APPENDIX

The following centres and clinicians participated in the survey:

Trento, Dr Lucia Busana; Varese, Dr Roberto Luraghi; Reggio Emilia, Dr Luigi Serra; Padova, Dr Ornella Lora; Mestre, Dr Rolando Polico; Aviano, Dr Mario Roncadin; Treviso, Dr Pierluigi Zorat; Milano, Dr Paolo Montanaro; Venezia, Dr Guglielmo Fila; Verona, Dr Giovanna Cavazzini.