Conservative Treatment of Early Breast Cancer: Prognostic Value of the Ductal *In Situ* Component and Other Pathological Variables on Local Control and Survival

Long-term Results

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Abstract—*Four hundred and thirty-four patients with infiltrative ductal carcinoma were treated by limited surgery and irradiation between January 1960 and December 1980. The median follow-up was 103 months.*

Retrospective pathological analysis of the primary tumor identified a subset of pathological parameters which were predictors of local breast failure and survival.

Pathological predictors of local breast recurrence were: incomplete surgical excision (P < 0.0001), lymphatic invasion (P < 0.02) and presence of an extensive in situ component (EDISC) (P < 0.03).

Pathological predictors of survival were: incomplete surgery (P < 0.007), size of the primary tumour (P < 0.03), high histologic grade (P < 0.005), lymphatic invasion (P < 0.0001) and absence of associated in situ component (P < 0.008).

This study emphasizes the role of the in situ component in the prognosis of breast carcinoma treated with conservative management.

INTRODUCTION

THE USE OF conservative surgery combined with radiation therapy as the primary treatment of early breast cancer has gained increasing support as an alternative to mastectomy. Several retrospective series [1–4] as well as recent randomized trials [5–7] have shown no significant difference in survival between both therapeutic procedures.

However, unlike mastectomy, local excision followed by radiotherapy leaves most of the breast intact providing opportunity for local tumor relapse [2, 8, 9]. Indeed, a small percentage of patients will develop a breast failure. Recent sudies have stressed the prognostic importance of some pathological features of the primary tumor (i.e. adequacy of surgical excision, nuclear grade, histological grade,

lymphatic invasion, necrosis) in determining the risk of local recurrence [8–11]. The importance of associated intraductal carcinoma has been particularly emphasized as being highly associated with local recurrence [9, 12].

Controversies still exist, probably due to differences in the selection of cases, the extent of initial surgery and the type of irradiation.

The question to be addressed in this report is the prognostic value of pathological features of the primary tumor in identifying patients at high risk of local recurrence when treated conservatively, and the significance of these pathological variables on overall prognosis.

PATIENTS AND METHODS

Five hundred and fifty-three patients with early breast cancer were treated with conservative management at the Institut Curie between January 1960 and December 1980. Among the 553 patients, 434 had an infiltrating ductal carcinoma (Table 1). The study will focus on these 434 cases.

Histological type of the carcinoma	Number of cases
Invasive ductal	*434*
Invasive lobular	15
Medullary	19
Tubular	8
Mucinous	7
Apocrine	1
Invasive unclassifiable	34
Intraductal	32
In situ lobular	3
Total	553

The median follow-up was 103 months (range 52–301). The follow-up period ended in February 1987 or with death of the patient.

All patients were treated by limited surgery followed by external radiation therapy. This treatment was performed for patients with T1 and small T2, N0, N1a breast cancers (UICC classification) [13].

The details of treatment have previously been described [14]. All patients underwent the same type of surgery. Surgical excision consisted of a resection of the palpable tumor with 2–3 cm of surrounding grossly normal tissue.

Radiation therapy consisted of 55–60 Gy irradiation delivered to the entire breast by a CO 60 unit. A booster dose of 10–15 Gy was delivered to the tumor bed to reach a total dose of 65–70 Gy.

One hundred and fifty-six out of 434 patients had limited axillary node dissection of level I and II. This procedure was performed after 1974 with introduction of adjuvant chemotherapy. Among these 156 patients, 47 with pathologically metastatic nodes had complementary axillary irradiation.

Two hundred and seventy-eight patients without axillary surgery had their axillary and internal mammary nodes irradiated at a dose of 50 Gy with a boost of 10 Gy to the lower axillary nodes.

All pathological data were reviewed by two pathologists (B.Z., P.V.).

The initial pathology report was used for the gross description of the tumor: size and tumor limits were stated. Surgical excision of the tumor was assessed through the surgical pathology report in conjunction with the surgeon's note. Incomplete excision of the tumor was defined as gross incomplete excision or microscopic involvement of the surgical margins when stated in the pathology report. Complete excision of the tumor was defined as gross complete excision. As surgical margins were not routinely inked at the time of the study,

retrospective microscopic evaluation of the margins could not be made. Histologic type and grading of the carcinoma were assigned according to the WHO classification [15] and Bloom and Richardson criteria [16].

Ductal carcinoma *in situ* (DCIS) associated with infiltrating tumor was defined as absent when no ducts were involved or included less than 25% of the tumor area, and present when involved ducts included more than 25% of the tumor area. The distribution of DCIS within and/or adjacent to the infiltrative tumor was also evaluated. Four groups (A, B, C, D) were thus defined as shown in Table 2.

The presence of associated lesions of *in situ* lobular carcinoma, and lymphatic, blood vessel and perineural invasion were looked for.

Local control and survival curves were drawn using the Kaplan–Meier method [17]. Survival curves were compared using the log-rank test [18].

RESULTS

1. Local breast control

Fifty-six of the 434 patients experienced a locoregional relapse. Forty-seven relapses (84%) occurred in the ipsilateral breast, three of them being associated with an axillary recurrence. Nine patients had an isolated node recurrence (eight axillary, one supraclavicular).

Local recurrence was defined as the development of cancer anywhere in the treated breast. The actuarial local control rate in the breast was 93 ± 2.5% at 5 years, 89 ± 3.5% at 10 years and 83 ± 7% at 15 years.

Univariate analysis of pathological characteristics influencing local control in the breast is shown in Table 3. Three pathological factors were found to be associated with a statistically significant increase in the risk of local failure: adequacy of surgical excision ($P < 0.0001$), lymphatic invasion ($P < 0.02$) and presence of extensive DCIS component (EDISC) associated with the primary tumor ($P = 0.03$).

Patients were stratified according to amount and distribution of associated DCIS component. Local

Table 2. *Amount and distribution of ductal* in situ *component associated with the infiltrative tumor: definition of four groups*

Adjacent to the tumor	Within the tumor	
	Absent*	Present†
Absent*	A	B
Present†	C	D

*Absent: DCIS <25% of the invasive tumor.
†Present: DCIS ≥25% of the invasive tumor.

Table 3. Pathological factors influencing local breast control

	No. of patients*	No. of BR	10 year LCB rate†	P value‡
Adequacy of surgical excision				
Incomplete	59	15	76%	<0.0001
Complete	374	31	91%	
Lymphatic invasion				
Presence	25	6	74%	<0.02
Absence	401	39	90%	
DCIS component				
Extensive	63	12	77%	= 0.03
Non-extensive	361	33	95%	

*This study being retrospective, complete pathological analysis could not be performed for all patients.
†Kaplan–Meier estimates.
‡Log-rank test.
BR: breast recurrence, LCB: local control in the breast.

relapse risk did not differ in group A (166 patients) without DCIS component, in group B (33 patients) with DCIS component within the primary tumor and in group C (162 patients) with DCIS component adjacent to the tumor mass.

However, group D (63 patients) with DCIS component within the primary tumor and adjacent to it (defined as extensive DCIS component—EDISC), had significantly more local failure when compared to the three other groups ($P = 0.03$) (Fig. 1).

The relationship between adequacy of surgical excision and presence of extensive DCIS component was studied. No correlation was found between these two factors. When adjusted to adequacy of surgical excision, extensive DCIS no longer contributed to predict local recurrence in the breast ($P = 0.10$).

All other pathological variables (size and circonscription of the tumor, grade of the carcinoma, associated *in situ* lobular carcinoma, perineural

Fig. 1. Local breast control according to DCIS component. (1) Non-extensive (groups A, B, C); (2) extensive (group D).

invasion, axillary nodal metastases) were not found to be correlated to an increased risk of local relapse.

2. *Survival*

Overall survival was 93 ± 2.5% at 5 years, 86 ± 4% at 10 years and 79 ± 6% at 15 years.

The same pathological variables were analyzed and correlated to overall survival. Analysis of pathological factors influencing overall survival is shown in Table 4.

Five factors were found to influence survival: adequacy of surgery ($P < 0.007$), size of the tumor ($P < 0.03$), histologic grade of the carcinoma ($P < 0.005$), lymphatic tumor emboli ($P < 0.0001$) and absence of DCIS component ($P < 0.008$).

Tumor size could be recorded in only 314 cases. Information was missing from the gross description in 120 cases. The histological grade according to Bloom and Richardson criteria could be evaluated in 387 cases. The quality of retrospective material precluded reliable grading in all other cases.

Analysis of the influence of associated DCIS component on overall survival revealed a significantly higher mortality rate in the group A patients who did not have DCIS component compared to the three other groups of patients (B, C, D) (Fig. 2).

DISCUSSION

After discussing briefly the pathological parameters influencing local control and survival we will focus on the value of the DCIS component as a prognostic factor.

In agreement with other authors [9], our study outlines the importance of complete excision of the tumor: patients whose tumors were not completely excised had a much higher local failure rate than
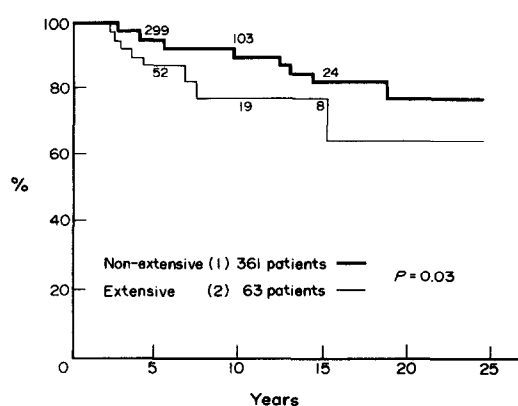
Table 4. Pathological factors influencing survival

	No. of patients*	No. of deaths	10-year survival rate†	P value‡
Adequacy of surgical excision				
Incomplete	59	16	75%	<0.007
Complete	374	43	88%	
Lymphatic invasion				
Presence	25	12	60%	<0.0001
Absence	401	45	89%	
DCIS component				
Absence	166	31	79%	<0.008
Presence	258	27	90%	
Tumor size				
>1 cm	193	26	83%	<0.03
≤1 cm	121	7	95%	
Histologic grade				
I	104	4	98%	
II	250	39	84%	<0.005
III	33	6	79%	

*This study being retrospective, complete pathological analysis could not be performed for all patients.
†Kaplan–Meier estimates.
‡Log-rank test.
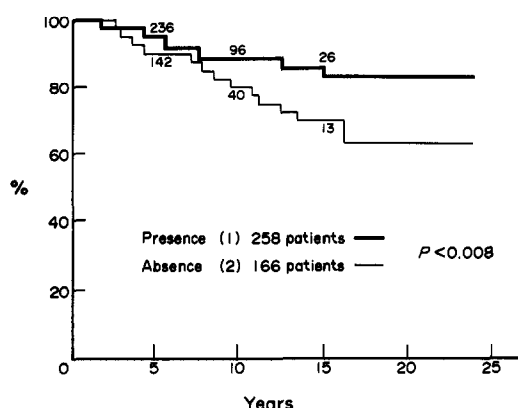BR: breast recurrence, LCB: local control in the breast.

Fig. 2. Survival according to DCIS component. (1) Presence (groups B, C, D); (2) Absence (group A).

patients whose tumors were adequately removed. The extent of excision must take in consideration on the one hand for a complete removal of the tumor mass and on the other for a good cosmetic result. Two other pathological factors significantly influenced local control in the breast: the presence of lymphatic invasion which is in accordance with Fisher et al. [10] and the presence of extensive DCIS which will be examined later.

In order to assess the general prognostic significance of the histological parameters studied, we correlated them with survival.

Several prospective randomized studies have shown that survival following conservative treat-

ment for early breast cancer is equivalent to that of mastectomy [5, 6]. Reported factors in the series of patients treated by mastectomy are: tumor size [19, 20], histological grade [19, 20], lymphatic invasion [19] and presence of axillary node metastases [20].

Our data indicate that the major pathological predictors of long-term prognosis for women with infiltrating ductal carcinoma of the breast treated with primary radiotherapy are the same as those for mastectomized patients.

Nodal status did not appear to have any effect on prognosis in our series. Axillary dissection was performed in one-third of the cases and 47 (31%) patients had axillary nodes involved. It is likely that this group is too small to yield significant results.

Our study emphasizes the role of intraductal component in the prognosis of breast carcinoma treated with tumorectomy and irradiation.

We found that extensive DCIS influenced local control in the breast. Although we did not find such a high risk as Schnitt [9, 12], who reported a 24% risk of local recurrence at 5 years for patients with extensive intraductal component compared to only 2% for other patients ($P < 0.0001$), we did note a statistically significant rate of breast failure at 5 years for patients with extensive DCIS component compared to other patients (11.3 ± 3% vs. 5.9 ± 8%).

Differences in the risk of local relapse, related to extensive intraductal component in the two series,

could be explained by differences in surgical technique. The Boston group's patients have an excisional biopsy under local anesthesia [3]. Our patients had a wide surgical excision consisting of resection of the tumor mass surrounded by 2–3 cm of grossly normal tissue. Moreover, the importance of extensive DCIS in our study is lessened when adjusted to adequacy of surgical excision.

For patients treated with a much wider excision (quadrantectomy) as in the Milan trial [7], an extensive intraductal component does not seem to constitute a risk for local relapse. It is likely that in lesions that exhibit associated intraductal tumor, occult tumor burden which remains after surgical excision is related to the width of surgical removal.

Indeed, Holland *et al.* [21] have found the expected rate of local recurrence after a breast-conserving surgical procedure to be related to the extensiveness of the excision. Holland *et al.* estimated that, for tumors measuring 2 cm or less, removed with a 2 cm margin of grossly normal tissue, remaining tumor foci would be present in the breast in about 42% of the cases. If the same series of tumors (<2 cm) were removed with a 4 cm margin, which is on average equal to a whole breast quadrant, the remaining tumor foci would drop to 10%.

It must be stressed also that our definition of extensive DCIS component (EDISC) is slightly more restrictive than the Boston group's definition. Tumors regarded as having an extensive DCIS component must have the combination of DCIS within the tumor comprising 25% or more of the invasive component and DCIS outside the tumor comprising 25% or more of the invasive component of the tumor. Therefore, we differ from Schnitt *et al.* [9] in the definition of DCIS present in the adjacent tissue: they define it as any amount of DCIS in breast tissue adjacent to the invasive component.

Our previously reported data on a smaller series of 263 patients [2] did not demonstrate any correlation between pathological variables and the risk of breast recurrence. However, the previous study included all histological types of carcinoma and did not focus on infiltrative ductal carcinoma. Moreover, the adequacy of surgical excision was not evaluated previously.

The number of patients in the present study has doubled and, since the local recurrence rate is low in these early stages of breast cancer, we believe that significant statistical differences can appear only with a very large series of patients.

It is noteworthy that our study confirms the findings of Silverberg and Chitale [22]. They had correlated the amount of intraductal carcinoma associated to the infiltrative tumor with prognosis and found a progressive decrease in survival rate with decreasing proportions of the associated intraductal component.

More recently, Rosen *et al.* addressed the issue of the significance of reported pathological predictors of local control in breast-preserving therapy [23]. In a consecutive series of women treated with mastectomy for early breast cancer, he correlated these histological parameters with prognosis. Beside the well-established parameters (nodal status, nuclear grade and histological grade), he also confirmed a poorer survival rate in patients without an associated intraductal component.

Our data need to be confirmed with other proliferative parameters and validated through multivariate analysis.

The prognostic value of clinical parameters is under investigation. A multivariate analysis of pathological and clinical prognostic factors will be the subject of another report [24].

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