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Original Paper

Ten-year Results Comparing Mastectomy to Excision and Radiation Therapy for Ductal Carcinoma *In Situ* of the Breast

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The 10-year results of 300 patients with ductal carcinoma *in situ* (DCIS) without microinvasion are reported; 167 treated with mastectomy and 133 treated with excision and radiation therapy. There was a significant difference in disease-free survival at 10 years, in favour of those treated with mastectomy, 98% versus 81% ($P = 0.0004$). Multivariate analysis confirmed nuclear grade as the only significant predictor of local recurrence ($P = 0.02$) or invasive local recurrence ($P = 0.03$) in patients with DCIS treated with excision and radiation therapy. There was no difference in breast cancer-specific survival or overall survival between the two treatment groups.

Key words: intraductal breast carcinoma, duct carcinoma *in situ*, DCIS, non-invasive breast cancer, breast, nuclear grade, local recurrence, breast irradiation
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INTRODUCTION

WITH THE widespread use of screening mammography, ductal carcinoma *in situ* of the breast (DCIS) is being diagnosed with increasing frequency, and currently accounts for as much as 40% of screen-detected and 15% of all breast cancer in the United States. The optimal treatment of DCIS remains controversial. Management of DCIS by mastectomy cures almost all patients and remains the standard by which other treatments are measured. The role of breast conserving surgery for DCIS is currently being studied in several ongoing, prospective, randomised trials. The early results of one, the National Surgical Adjuvant Breast Project (NSABP) Protocol B-17, which show a lower local recurrence rate for patients treated with excision and radiation therapy when compared with patients treated by excision alone, has been published [1].

In spite of the limited, available, prospective randomised data, breast conserving surgery, with or without radiation therapy, for localised DCIS, has gained widespread use, despite a long-term local recurrence rate of 20–40% [2]. The identification of clinical, laboratory and pathological factors influencing local recurrence and/or survival remains an unresolved issue of great importance [3]. We report the 10-year results and an analysis of prognostic factors in 300 patients with DCIS, treated with mastectomy or excision and radiation therapy.

PATIENTS AND METHODS

300 consecutive patients with histologically confirmed DCIS, without evidence of microinvasion, treated with mastectomy or excision and radiation therapy at the Breast Center, Van Nuys, California, U.S.A., between 1979 and August 1994, were prospectively entered into the Center's computerised database. 90 additional patients treated by excision alone were not included in this report because of a short median follow-up. Treatment was not randomised. Patients with large lesions (4 cm and more), multicentricity, or involved margins not amenable to re-excision, were treated with mastectomy (usually with immediate breast reconstruction). Patients with smaller lesions (4 cm or less) and microscopically clear surgical margins (no intraductal carcinoma within 1 mm) were treated with excision and radiation therapy. 15 patients with focally involved margins, or margins that were less than 1 mm, refused re-excision and were treated with radiation therapy.

Nuclear grade was scored using previously described methods [4–6]. Essentially, low grade nuclei (grade 1) were defined as

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nuclei 1–1.5 red blood cells in diameter with diffuse chromatin and inapparent nucleoli. Intermediate grade nuclei (grade 2) were defined as nuclei 1–2 red blood cells in diameter with coarse chromatin and infrequent nucleoli. High grade nuclei (grade 3) were defined as nuclei with a diameter greater than two red blood cells, with vesicular chromatin, and one with more nucleoli. Immunostaining for HER-2/neu and p53 was performed by previously described methods [7–8].

Level 1 and 2 axillary dissections were done routinely until 1988 [9]. Thereafter, a lower axillary sampling was performed only for patients treated with mastectomy. Whole breast external beam irradiation (40–50 Gy) was performed on a 4 or 6 MeV linear accelerator with a boost of 16–20 Gy to the tumour bed by an iridium-192 implant or a linear accelerator [10].

Disease-free survival rates for each form of treatment were estimated by the Kaplan–Meier method. The statistical significance between survival curves was determined by the log-rank test for each variable studied (univariate analysis). Multivariate analysis was performed using the Cox proportional hazard model and included all significant variables found by univariate analysis. Statistical significance was determined using an alpha level of 0.05 and two-sided tests.

RESULTS

Patient and tumour characteristics for both treatment groups are compared in Table 1. Patients undergoing mastectomy had larger tumours, 39 mm versus 18 mm ($P < 0.0001$). 2 mastectomy patients, both with nuclear grade 3 comedo DCIS, suffered recurrences; both developed invasive chest wall recurrences, one 25 months after initial treatment, the other at 53 months. Both developed bone metastases, but at the time of writing were alive in remission following radiation therapy. After a median follow-up of 78 months, the 10-year actuarial disease-free survival and breast cancer-specific survival is 98 and 100%, respectively. Due to the low number of recurrences in patients treated with mastectomy ($n = 2$), none of the factors examined predict for local recurrence.

16 patients initially treated by excision and radiation therapy (12 with comedo and four with non-comedo DCIS), had a local recurrence, 8 (50%) of which were invasive. All recurrences occurred in the same quadrant, at or near the original DCIS lesion. The median time to recurrence was 58.5 months; 15 recurrences were treated with mastectomy and 1 with quadrantectomy. Two patients developed distance metastasis, 15 and 16 months after their local recurrence. Both patients died during the next 25 months. After a median follow-up of 94 months, the 10-year disease-free and breast cancer-specific survival was 81 and 97%, respectively. The disease-free survival was significantly worse for the excision and radiation therapy group ($P = 0.0004$) when compared with the mastectomy group, in spite of their significantly smaller mean size (Figure 1). There was no significant difference in breast cancer-specific survival or overall survival between the patients treated by mastectomy and those treated by excision and radiation therapy ($P > 0.2$). A total of 183 axillary node dissections were performed, all of which were negative.

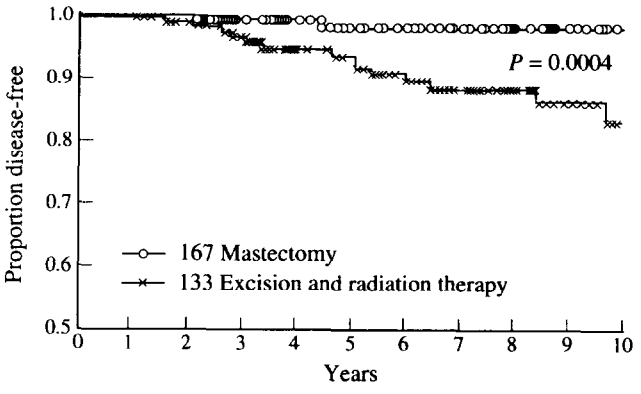

Figure 1. Ten-year disease-free survival—mastectomy versus excision and radiation therapy.

Tumour size, margin status (clear or involved), nuclear grade (1–3), the presence of comedo-type necrosis, and comedo histology were all significant predictors of local recurrence by univariate analysis (Table 2) for patients treated with excision and radiation therapy. In a multivariate analysis, using the Cox proportional hazard model with all significant univariate predictors, only nuclear grade remained a significant predictor of local recurrence ($P = 0.02$). The 8-year disease-free survival for patients treated with excision and radiation therapy stratified by nuclear grade is shown in Figure 2. In an additional multivariate analysis, in which only invasive recurrences were considered as events, nuclear grade continued to be a significant predictor of local recurrence ($P = 0.03$).

Combinations of prognostic factors, significant by multivariate or univariate analysis, may also be used to predict local recurrence in patients treated with excision and radiation therapy

Table 1. Patient and tumour characteristics

	Mastectomy	Excision + Radiation
Number of patients	167	133
Median follow-up (months)	78	94
Age (median/range)	50 (28–79)	50 (28–80)
Non-palpable	72%	89%
Mean size (mm)	39	18
Recurrences (invasive)	2 (2)	16 (8)
Local	2	16
Distant	2	2
Comedo subtype	51%	49%
Nuclear grade 3	31%	24%
Presence of necrosis	66%	71%
10-year disease-free survival	98%	81%
10-year breast cancer-specific survival	100%	97%

Table 2. Analysis of prognostic factors influencing local recurrence after excision and radiation therapy

	Univariate *P*-value	Multivariate *P*-value
Age	0.3	
Size	0.03	ns
Margins (involved versus clear)	0.05	ns
Histology (comedo versus non-comedo)	0.009	ns
Nuclear grade (1 versus 2 versus 3)	0.002	0.02
Presence of necrosis	0.003	ns
p53 ($n = 58$)	0.5	
HER-2/neu ($n = 63$)	0.09	

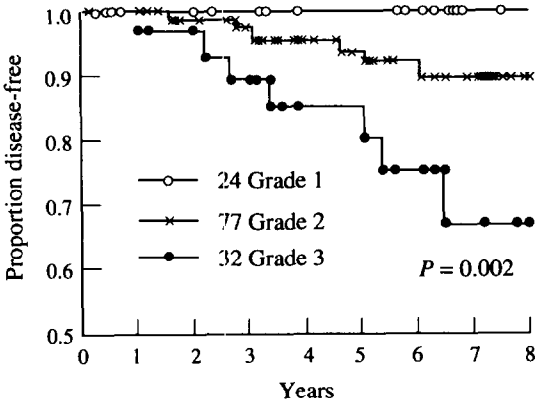

Figure 2. Eight-year disease-free survival—excision and radiation therapy patients stratified by nuclear grade. The recurrence rates were 0, 10 and 34% for nuclear grades 1, 2 and 3, respectively.

[8, 11–12]. For example, the combination of higher nuclear grade and comedo-type necrosis yielded a group of 29 patients with an 8-year disease-free survival (DFS) of 65% compared with 92% for 104 patients without both of these factors ($P = 0.001$). Similarly, the combination of high nuclear grade and comedo histology yielded a group of 21 patients with an 8-year DFS of only 56% compared with 93% for 112 patients without both of these factors ($P = 0.0002$).

DISCUSSION

The treatment of DCIS with mastectomy is associated with a 1–2% local recurrence rate at 10 years in this and other series [13]. Patients in this series treated with excision and radiation therapy had a local recurrence rate of 7 and 19% at 5 and 10 years, respectively, demonstrating the necessity for long-term follow-up in patients with DCIS treated with breast conservation. Our findings are comparable to the results of the randomised NSABP B-17 trial (10% local recurrence rate at 5 years for DCIS patients treated with excision and radiation therapy) [1] and to a multi-institutional trial reported by Solin and associates (16% at 10 years) [14].

A strong correlation between higher nuclear grade and local recurrence for patients with DCIS treated with excision only was described by Lagios in 1989 [15]. In the present study, we were able to demonstrate, by multivariate analysis, that nuclear grade is the most significant predictor of local recurrence or invasive local recurrence in patients with DCIS treated with excision and radiotherapy.

1. Fisher B, Constantino J, Redmond C, *et al.* Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *N Engl J Med* 1993, **328**, 1581–1586.
2. Frykberg ER, Bland KI. Overview of the biology and management of ductal carcinoma in situ of the breast. *Cancer* 1994, **74**, 350–361.
3. Recht A, van Dongen JA, Peterse JL. Ductal carcinoma in situ. *Lancet* 1994, **343**, 969.
4. Bloom HJG, Richardson WW. Histologic grading and prognosis in breast cancer: A study of 1409 cases of which 359 have been followed for 15 years. *Br J Cancer* 1957, **11**, 369–377.
5. Page DL, Anderson TJ, Rogers LW. Carcinoma in situ (CIS). In Page DL, Anderson TJ, eds. *Diagnositic Histopathology of the Breast.* Edinburgh, Churchill Livingstone, 1988, 157–192.
6. Lagios MD. Duct carcinoma in situ: Pathology and treatment. *Surg Clin N Am* 1990, **70**, 853–871.
7. Slamon DL, Godolphin W, Jones LA, *et al.* Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989, **244**, 707–712.
8. Silverstein MJ, Poller DN, Waisman JR, *et al.* Prognostic classification of breast ductal carcinoma *in situ*. *Lancet* 1995, **345**, 1154–1157.
9. Silverstein MJ, Gierson ED, Colburn WJ, *et al.* Axillary lymphadenectomy for intraductal carcinoma of the breast. *Surg Gynecol Obstet* 1991, **172**, 211–214.
10. Silverstein MJ, Waisman JR, Gamagami P, *et al.* Intraductal carcinoma of the breast (208 cases): clinical factors influencing treatment choice. *Cancer* 1990, **55**, 102–108.
11. Tavassoli FA. Intraductal carcinoma. In Tavassoli FA, ed. *Pathology of the Breast.* Norwalk, Connecticut, Appleton and Lange, 1992, 229–261.
12. Solin LJ, Yeh IT, Kurtz J, *et al.* Ductal carcinoma in situ (Intraductal carcinoma) of the breast treated with breast conserving surgery and definitive irradiation. *Cancer* 1993, **71**, 2532–2542.
13. Kinne DW, Petrek JA, Osborne MP, *et al.* Breast carcinoma in situ. *Arch Surg* 1989, **124**, 33–36.
14. Solin LJ, Recht A, Fourquet A, *et al.* Ten-year results of breast-conserving surgery and definitive irradiation for intraductal carcinoma (ductal carcinoma in situ) of the breast. *Cancer* 1991, **68**, 2337–2344.
15. Lagios MD, Margolin FR, Westdahl PR, Rose MR. Mammographically detected duct carcinoma in situ. Frequency of local recurrence following tylectomy and prognostic effect of nuclear grade on local recurrence. *Cancer* 1989, **63**, 619–624.