

# Duct Carcinoma *in situ*: 227 Cases Without Microinvasion

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From 1979 to 1990, 227 patients with intraductal carcinomas (DCIS) without microinvasion were selectively treated; the least favourable (large lesions with involved biopsy margins) with mastectomy, the most favourable (small lesions with clear margins) with breast preservation. The preservation group was further subdivided into those who received radiation therapy (excision and radiation) and those who did not (excision alone). In the mastectomy group, there were 98 patients (43%) with an average lesional size of 3.3 cm; 41% had multifocal lesions, 15% had multicentric lesions. There has been one local invasive recurrence and no deaths. The 7-year actuarial disease-free survival is 98% with mastectomy. In the excision and radiation group, there were 103 patients (45%) with an average lesional size of 1.4 cm. 10 patients have had local recurrences (5 invasive and 5 noninvasive) one of whom has died. The 7-year actuarial disease-free survival is 84%, a statistically significant difference when excision and radiation is compared with mastectomy ( $P = 0.038$ ). In the excision alone group, there were 26 patients (11%) with an average lesional size of 1.0 cm. There have been two local recurrences (8%), one of which was invasive and no deaths. The 7-year actuarial disease-free survival is 67%, but only 3 patients have been followed for more than 4 years. A total of 163 axillary node dissections were done; all were negative. Since DCIS without microinvasion rarely metastasises to axillary lymph nodes, routine dissection should not be performed. Patients in this series with intraductal carcinoma treated with excision and radiation recurred locally at a statistically higher rate than those treated with mastectomy, in spite of the fact that those chosen for excision and radiation had clinically more favourable lesions. 6 of 12 (50%) local recurrences in conservatively treated patients were invasive. There was, however, no significant difference in overall survival in any subgroup regardless of treatment.

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## INTRODUCTION

THROUGH THE 1970s, intraductal carcinoma was a rare disease, representing less than 2% of all breast cancer [1] and generally presenting as a mass or nipple discharge. Modern mammography has converted this unusual entity into a common pathological finding with no clinical symptomatology. In the USA, more than 20 000 asymptomatic women will be given the diagnosis of intraductal carcinoma (DCIS) this year. These asymptomatic women will hear a range of confusing options from excision to mastectomy [2]. Many of them will seek consultations with multiple physicians. Currently, in Europe and the USA, there are at least seven prospective randomised studies under way comparing various forms of excision with or without radiation therapy for DCIS. As these studies are completed, they will help guide patients and physicians with treatment choices for this disease. Unfortunately, none of these studies have data available at this time.

Our study is a non-randomised retrospective analysis which stratifies all patients with intraductal carcinoma treated during the last 11 years by both treatment and histological subtype.

## PATIENTS AND METHODS

All patients presenting at The Breast Center in Van Nuys, California, from 1979 to 1990, with either a palpable mass or mammographical abnormality, diagnosed as intraductal carcinoma were included. All lesions with evidence of microinvasion (41 patients) were excluded. DCIS was divided into two main histologic categories: comedo and non-comedo (which included cribriform, micropapillary, papillary, and solid types). Multifocality was defined as additional intraductal disease 2.0 cm or more from the primary tumour and in the same quadrant. Multicentricity was defined as disease in a quadrant different from the index cancer. All mastectomy specimens were serially sectioned but only one random section was taken from each uninvolved quadrant and from the nipple and subareolar tissue unless a suspicious area was found. Multifocality and multicentricity data were available only for patients undergoing mastectomy and was not used to change the original size of the tumour which was determined at biopsy. Therefore, patients with positive biopsy margins who underwent mastectomy, in all probability, had larger lesions than recorded. A pathologist was present in the operating room during biopsy. Beginning in 1985, all surgical margins were inked or dyed with the Davidson MultiColor Marking System. All lesions were serially sectioned to determine marginal involvement and the size of the tumour. Clear margins were defined as no intraductal carcinoma within 1 mm. of any margin. Sections were taken every 2–4 mm, depending on the consistency of the unfixed tissue. Hooked-

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Table 1. DCIS demographics by 5 histological subtypes

Histological subtype	Number	Mean size (cm)	Involved margins*	Non-palpable	Recurrences
Comedo	108 (48)	2.5	60(56)	83(77)	8(7)
Cribriform	54 (24)	1.5	16(30)	42(78)	1(2)
Solid	25 (11)	1.6	8(32)	19(76)	2(8)
Micropapillary	26 (11)	1.9	16(62)	22(85)	1(2)
Papillary	14 (6)	1.9	7(50)	6(43)	1(9)
Total(%) or mean	227(100)	2.1	107(47)	172(76)	13(6)

(%)

\*Involved margins on initial biopsy only.

wires were used for directed biopsies of non-palpable lesions, larger lesions were bracketed, using two or more wires [3].

Treatment was not randomised. Generally, patients with lesions 4 cm or less and microscopically clear surgical margins who desired breast preservation were treated with excision and radiation therapy. Patients with larger lesions or involved surgical margins who were not thought to be good candidates for re-excision were treated with mastectomy (usually with immediate breast reconstruction). Patients with positive surgical margins who desired breast conservation were re-excised. If the new margins were clear and the cosmetic results acceptable, radiation therapy was given. The criteria were not absolute. Occasionally, patients with larger lesions were treated with breast preservation. In a small number of patients with minimally involved margins, re-excision was not carried out. During the last 6 years, 26 breast preservation patients declined radiation therapy and were treated with excision only. Level 1 and 2 axillary dissections were done routinely until 1988 and seldom thereafter.

Whole breast external beam irradiation was performed on a 4 or 6 MeV linear accelerator; a dose of 45–50 Gy was delivered utilising 18–20 Gy/fractions, 4 or 5 days per week, for 25 treatments. An 18–20 Gy boost to the tumour bed was delivered by minimum two plane iridium-192 implant to a volume encompassed by the 0.4–0.5 Gy isodose curve. The average volume implant was 148 cm<sup>3</sup>. Whenever possible, the axillary lymph node dissection and iridium-192 implant were performed simultaneously.

Interrelationships between clinical and pathological characteristics were determined by contingency table analysis. Life tables were computed using the Kaplan–Meier method [4]; comparisons of the groups were made with the Mantel–Haenszel test [5].

## RESULTS

### Overview of all patients (Table 1)

During an 11-year period, 227 patients with intraductal carcinoma without evidence of microinvasion were treated; 163 (72%) of these patients had axillary node dissections, none of which were positive. The patients ranged in age from 27 to 82 years (average 52 years). DCIS lesions ranged in size from 0.1 to 15 cm, with a mean diameter of 2.1 cm. 24% of lesions were palpable; 76% were non-palpable (discovered mammographically) and removed by wire-directed breast biopsy. During the past 4 years (1987–1990), as both mammography and our abilities improved, 87% were non-palpable. The most common

Table 2. Analysis of 227 DCIS patients by treatment: mastectomy versus excision and radiation therapy versus excision only

	Mastectomy	Excision and radiation	Excision only	Total or mean
Total no. of patients	98(43)	103(45)	26(11)	227(100)
Mean size (cm)	3.7	1.4	1.0	2.1
Non-palpable	61(62)	89(86)	22(85)	172(76)
Involved margins*	67(68)	32(31)	8(31)	107(47)
Multifocality(%)†	41	??	??	41
Multicentricity(%)†	15	??	??	15
Recurrences	1(1)	10(10)	2(8)	13(5)
7-year disease-free survival (%)	98	84	67‡	92
Deaths	0(0)	1(1)	0(0)	1(0.4)
Median follow-up (months)	59	62	18	54

(%)

\*Involved margins on initial biopsy only.

†Mastectomy specimens only.

‡Only 3 patients followed for >4 years in this subgroup.

mammographical finding were microcalcifications, found in 71% of patients. All lesions were classified into their predominant histological subtype; comedocarcinomas were the most common, 48%. The initial biopsy margins were involved in 47% of cases. All patients were analysed by treatment (Table 2), by histological subtype (Table 3) and by a combination of both treatment and histological subtype (Table 4). Follow-up ranged from 6 months to more than 11 years (median 56 months). There have been a total of 13 local recurrences, seven of which were invasive. The 7-year actuarial local disease-free survival for all patients regardless of treatment or histological subtype was 88%.

### Analysis by treatment (Table 2)

Mastectomy was done for 98 patients with an average lesion diameter of 3.3 cm. Initial biopsy margins were involved in 68% of patients, 41% had multifocal lesions, 15% had multicentric lesions. Axillary node dissections were done at the time of mastectomy in 88 patients (90%), none were positive. One patient with a comedocarcinoma had an invasive local recurrence

Table 3. Analysis of 227 DCIS patients by histological subtype: comedo vs. non-comedo

	Comedo	Non-comedo	Total(%) or mean
Total no. of patients	108(48)	119(52)	227(100)
Mean size (cm)	2.5	1.8	2.1
Nonpalpable	83(77)	89(75)	172(76)
Involved margins*	55(51)	44(37)	99(45)
Multifocality(%)†	38	43	41
Multicentricity(%)†	13	18	15
Recurrences	8(7)	5(4)	13(6)
7-year disease free survival	84	95	88
Deaths	1(1)	0(0)	1(0.4)

(%)

\*Involved margins on initial biopsy only.

†Mastectomy specimens only.

Table 4. Analysis of 227 DCIS patients by both treatment and histological subtype

	Mastectomy	Excision plus radiation	Excision only	Total (%) or mean
<b>Comedocarcinoma</b>				
Total no. of patients	47	52	9	108
Mean size (cm)	3.8	1.6	0.9	2.5
Involved margins(%) <sup>*</sup>	77	38	44	51
Recurrences	1(2)	7(13)	0(0)	8(8)
Deaths	0(0)	1(2)	0(0)	1(1)
<b>Non-comedocarcinoma</b>				
Total no. of patients	51	51	17	119
Mean size (cm)	2.6	1.1	1.1	1.8
Involved margins(%) <sup>*</sup>	61	24	25	37
Recurrences	0(0)	3(6)	2(12)	5(4)
Deaths	0(0)	0(0)	0(0)	0(0)

(%)

<sup>\*</sup>Involved margins on initial biopsy only.

in the suture line 2 years after mastectomy. The 7-year actuarial disease-free survival for mastectomy patients was 98% with a median follow-up of 60 months.

Excision followed by radiation therapy was done for 103 patients with an average tumour diameter of 1.4 cm; initial biopsy margins were involved in 31%. The number of patients with multifocal or multicentric lesions is unknown since the only tissue available for histopathological evaluation was the excision specimen. 75 of these patients (73%) had axillary node dissections; all were negative. 10 patients (10%) have had local recurrences; 5 invasive and 5 non-invasive. Of the 5 patients with invasive recurrences, 1 has died; the other 4 have no evidence of metastatic disease but one of them had a highly aggressive recurrence with lymphatic tumour emboli. 9 recurrences were at or near the previous biopsy site; 1 was in a quadrant different from the index cancer. In 5 patients, the margins were microscopically clear after initial biopsy; in the remaining 5, initial biopsy margins were involved. 4 patients underwent re-excision and the margins were clear in 3, leaving 2 patients with minimal marginal involvement who were treated with radiation therapy. The average initial size of the 10 recurrent lesions was 1.5 cm. The 7-year actuarial disease-free survival for all patients treated with excision plus radiation therapy was 84% with a median follow-up of 63 months.

Excision alone was done for 26 patients whose lesions averaged 1.0 cm and who declined treatment with radiation therapy. 8 (31%) patients had involved initial biopsy margins and were re-excised. There have been two local recurrences (one invasive and one noninvasive), no metastases and no deaths. Both recurrences were in the same quadrant as the index cancer. The 7-year actuarial disease-free survival is 67%, but this is an almost meaningless number since the median follow-up is just 19 months and only 3 patients have been followed for more than 4 years.

A life-table analysis of the probability of local disease-free survival for mastectomy versus excision plus radiation versus excision alone is shown in Fig. 1. There is a significant difference in favor of mastectomy when mastectomy is compared with

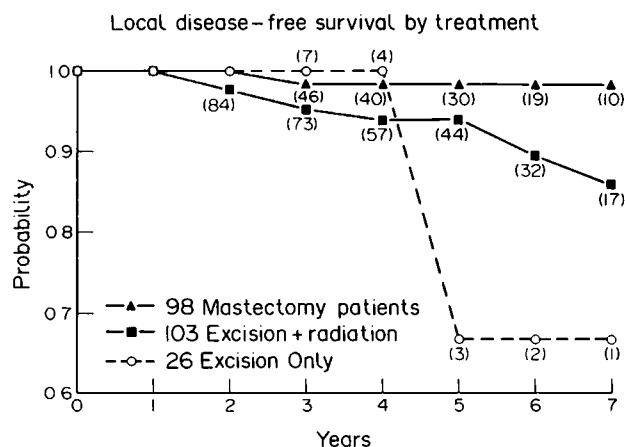


Fig. 1. Life-table analysis showing the probability of remaining free of local recurrence for patients treated with mastectomy, excision plus radiation therapy, or excision only. The number of patients at risk for each data point are shown in parentheses. Excision only patients are represented by a dotted line since they are few in number and with short follow-up. Only 3 excision only patients have been followed for more than 4 years.

excision plus radiation therapy ( $P = 0.038$ ). The difference in local recurrence is not significant when excision alone is compared with either excision plus radiation or mastectomy. Since, there has been only one death, there is no significant difference in overall survival among the three treatment subgroups.

#### Analysis by histological subtype (Table 3)

There were 108 comedocarcinomas, averaging 2.5 cm in diameter; initial biopsy margins were involved with microscopical tumour 51% of the time. 119 non-comedo lesions were smaller, averaging 1.8 cm; biopsy margins were involved in 37% of the cases ( $P = 0.185$ ). The average age for both comedo and non-comedo patients was the same, 52 years. 83 of 108 (77%) patients with comedocarcinomas underwent axillary lymph node dissection; 80 of 119 (67%) patients with non-comedo lesions underwent axillary dissection, as noted in the analysis by treatment, all 163 node dissections were negative.

There have been 8 local recurrences in patients with comedocarcinomas, 5 of which (57%) showed invasion. There have been 5 local recurrences in patients with noncomedo lesions, 2 of which (40%) showed invasion. The 7-year actuarial disease-free recurrence rate for comedocarcinomas is 84%, for non-comedo lesions it is 95%. This difference is not significant ( $P = 0.47$ ) nor is there any significant difference in the likelihood of a recurrence to be invasive based on histological subtype. The mean disease-free interval for all patients who recurred was 46 months. 1 patient with a comedocarcinoma has died; no patients with non-comedo lesions have died. The difference in overall survival is not significant.

#### Analysis by treatment and histological subtype (Table 4)

**108 comedocarcinomas by treatment.** Mastectomy was the treatment for 47 patients with comedocarcinomas averaging 3.8 cm in diameter. This subgroup had the largest lesions and 77% had involved biopsy margins. There was no statistical difference in multifocality (38 vs. 43%) or multicentricity (13 vs. 18%), when mastectomy specimens were evaluated by histological subtype (comedo versus noncomedo). The single invasive local recurrence in a mastectomy patient as mentioned above

was a comedocarcinoma. There have been no deaths in this subgroup.

Excision and radiation therapy was the treatment for 52 comedocarcinomas averaging 1.6 cm; 38% had involved biopsy margins which required re-excision. There have been 7 (13%) local recurrences and 1 death in this subgroup. Excision alone was the treatment for 9 patients with comedocarcinomas averaging 0.9 cm; 44% had involved margins requiring re-excision. There have been no local recurrences, metastases or deaths in this group but median follow-up is short (19 months).

The 7-year actuarial disease-free survival for patients with comedocarcinomas treated with mastectomy was 97%; for patients treated with excision and radiation, it was 75%. The difference was not significant due to the smaller sample size ( $P = 0.088$ ).

**119 non-comedocarcinomas by treatment.** Mastectomy was the treatment for 51 non-comedo lesions averaging 2.6 cm; 61% had initially involved biopsy margins. There have been no recurrences or deaths in this subgroup. Excision and radiation therapy was the treatment for 51 additional non-comedo lesions averaging 1.1 cm; 24% of initial biopsy margins were positive and required re-excision. There have been 3 local recurrences, no metastases and no deaths in this subgroup. Excision alone was the treatment for 17 patients with noncomedo lesions averaging 1.1 cm. 4 patients (24%) required re-excision because of initially involved margins. 2 patients have recurred locally. No patient has developed metastatic disease and there have been no deaths.

The 7-year actuarial disease-free survival for patients with noncomedo lesions treated by mastectomy was 100%; for those treated with excision and radiation therapy, it was 96%. There is no significant difference in disease-free or overall survival for non-comedo lesions regardless of treatment.

## DISCUSSION

Treatment for breast cancer can be divided into three general categories based on anatomic considerations: local (the breast), regional (the surrounding lymph nodes) and systemic (the whole body). Fisher has popularised the paradigm that breast cancer is a systemic disease when diagnosed and that local/regional variations in treatment have no effect on survival [6]. This paradigm, while not accepted by everyone, applies to infiltrating breast carcinomas and not to non-palpable noninvasive disease. Fisher readily admits that there is no paradigm for DCIS [6]. In fact, if there is any disease where local nuances in treatment are likely to effect outcome, it is DCIS.

The need for systemic and regional treatment in DCIS can be quickly dismissed. Since intraductal carcinoma seldom metastasises, there is no indication whatsoever for systemic chemotherapy. The National Surgical Adjuvant Breast Project (NSABP) is currently studying the addition of tamoxifen to excision plus radiation therapy but this is not systemic therapy in the classical sense. Rather, the NSABP is testing to see whether tamoxifen will decrease the rate of local recurrence in the treated breast along with preventing the *de novo* development of contralateral breast cancer.

Regional treatment, such as axillary lymph node dissection, is not required either. In this study, none of 163 patients had axillary metastases. Ashikari *et al.* [7] reported one positive node dissection out of 113, Fisher *et al.* [8] reported none out of 78 dissections, and numerous other researchers report a rate of axillary metastases in the range of 0–4% [1, 9–11]. It is neither

in the patients best interest nor cost effective to perform 100 or more axillary dissections to find a single positive case. Axillary dissection carries with it a potential for arm swelling, loss of arm function to various degrees, and sensory change. Although these risks are slight, there is only minimal potential for gain.

Since 1988, we have abandoned routine axillary node dissection, only performing it for large intraductal lesions (greater than 5.0 cm) where foci of invasion might have been missed or for lesions demonstrating microinvasion. In a previous publication [12] which included 184 patients in this report and 29 additional patients with microinvasion, we reported 49 cases meeting these criteria, there was only one positive node dissection (2%), raising the question of whether it is indicated even for this select subgroup.

The major controversy is the treatment of the breast [2]. Can the breast be preserved? When does DCIS become too big for breast preservation? How do you measure DCIS? Is radiation necessary? Must the margins be clear? How do you define clear margins? Will residual DCIS progress to invasive cancer? If not always, how often? Is multicentricity important? Numerous prospective randomised studies are underway comparing various forms of excision with and without radiation therapy. But they will not answer all of these questions nor many others that we have not asked.

We know that mastectomy for DCIS achieves long-term survival rates approaching 100% [10, 13, 14]. In this series and other radiotherapy series [8, 15–17], the overall survival rate is almost as good but DCIS is a slow disease, requiring an extended follow-up period. The average patient in this series has been followed for just under 5 years, an inadequate period of time for DCIS. Even with this relatively short follow-up, there is a statistically higher local recurrence rate when excision and radiation is compared with mastectomy. More than half of the recurrences are invasive and therefore have the potential to metastasise. We currently do not know whether there may be an appreciable death rate due to invasive recurrences in patients with breast preservation.

In this series, DCIS existed in other quadrants in 15% of the cases, in spite of the fact that only one random section was taken from each non-involved quadrant. When multiple sections are taken, the rate of multicentricity increases to 32–36% [9, 18] in some series. However, Holland and associates [19], using the most accurate of all techniques, the serial subgross method with radiographical/histological correlation found that most DCIS lesions were larger than expected but involved only one region of the breast. They found true multicentricity in only one of 82 mastectomy specimens. In this series, 11 of 12 recurrences in conservatively treated patients were in the same quadrant as the index cancer, multicentricity playing a role in only one case. With longer follow-up time, however, multicentricity could become a more important factor.

It is commonly thought that comedocarcinomas have a poorer prognosis when compared with non-comedo lesions. They are often poorly differentiated, aneuploid [20], exhibit high tumour labeling indices with thymidine [21], overexpression of Neu protein [22], and may recur at a higher rate than non-comedo lesions [9, 23]. In this series, there is no statistical difference in recurrence rate by histological subtype. However, a year before we compiled the data for this paper, when this series had only 8 recurrences, 7 were comedo, a statistically significant difference with a  $P$  value of  $<0.05$  [12]. During the last year, there have been 5 recurrences, 4 of which were non-comedo, tipping the scales back, converting significance to insignificance. We must

be cautious. In spite of what our biostatisticians tell us about *P* values, there are simply too few events (recurrences or deaths) and the follow-up too short for us to make definitive conclusions about the treatment of DCIS.

When intraductal carcinoma is suspected on mammography, the initial biopsy should be carefully planned. We generally use two or three bracketing hooked-wires to localise the larger lesions [3]. In spite of this, 47% of the lesions in this series had microscopically involved margins on initial biopsy. This results, in part, from the fact that the entirety of the intraductal tumour is not always marked with microcalcifications [19] and since it is neither palpable nor visible, it is extremely difficult to excise completely. The actual percentage of marginal involvement may, in fact, be even higher than 47%. The evaluation of margins is somewhat random in spite of serial sections and the marking of margins. We do not perform frozen sections on non-palpable lesions; the entire specimen is submitted for microscopic evaluation. If DCIS is found, additional histochemical studies are done on the blocks.

In this series, we have selected the clinically most favourable patients for breast preservation. As a group, they have the smallest lesions, the highest percentage of initially clear surgical biopsy margins, and the highest percentage of non-palpable lesions. In spite of this, the breast preservation patients have a statistically higher local recurrence rate. With this in mind, we feel that mastectomy is the best choice for patients who demand the highest local disease-free and overall survival rate. It is the procedure of choice for those patients who are unwilling to assume any increased risk, no matter how small.

Excision and radiation therapy is appropriate for patients who are interested in preserving their breast, whose lesions meet the clinical criteria used in this study, who feel strongly about staying whole, who are willing to assume a small, but not absolutely quantifiable, increased risk of local recurrence and an even lower risk of metastatic disease.

Our series of excision only patients is too small and has been followed for too short a time period for us to draw any conclusions about this limited procedure. However, we are impressed by the results of Lagios [9, 24] and we will perform this procedure for those patients who meet Lagios' strict criteria, who understand the limited experience with this procedure, and who are willing to accept a theoretically increased risk.

A small decrease in disease-free and possibly overall survival rate may be a small price to pay for staying whole. We believe that this is a decision the patient is entitled to make and when this decision is made, we strongly support it.

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