

Salvage treatment for local or local-regional recurrence after initial breast conservation treatment with radiation for ductal carcinoma *in situ*

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Abstract

The present study evaluated the outcome of salvage treatment for women with local or local-regional recurrence after initial breast conservation treatment with radiation for mammographically detected ductal carcinoma *in situ* (DCIS; intraductal carcinoma) of the breast. The study cohort consisted of 90 women with local only first failure ($n = 85$) or local-regional only first failure ($n = 5$). The histology at the time of recurrence was invasive carcinoma for 53 patients (59%), non-invasive carcinoma for 34 patients (38%), angiosarcoma for one patient (1%), and unknown for two patients (2%). The median follow-up after salvage treatment was 5.5 years (mean = 5.8 years; range = 0.2–14.2 years). The 10-year rates of overall survival, cause-specific survival, and freedom from distant metastases after salvage treatment were 83%, 95%, and 91%, respectively. Adverse prognostic factors for the development of subsequent distant metastases after salvage treatment were invasive histology of the local recurrence and pathologically positive axillary lymph nodes. These results demonstrate that local and local-regional recurrences can be salvaged with high rates of survival and freedom from distant metastases. Close follow-up after initial breast conservation treatment with radiation is warranted for the early detection of potentially salvageable local and local-regional recurrences.

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Keywords: Ductal carcinoma *in situ*; DCIS; Breast conservation treatment; Radiation therapy; Salvage treatment; Local recurrence

1. Introduction

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The increasing use of screening mammography has been associated with an increase in the detection of

smaller and earlier-staged breast cancers, including ductal carcinoma *in situ* (DCIS; intraductal carcinoma) [1–3]. Many reports have evaluated the outcome after initial treatment of DCIS using breast conserving surgery plus definitive breast irradiation. Such studies have evaluated the results of treatment in terms of survival and local control. Approximately half of all local recurrences after breast conserving surgery plus definitive breast irradiation are invasive carcinoma, and approximately half are ductal carcinoma *in situ* [4–15].

Although many studies have reported on the outcome after initial breast conservation treatment for DCIS of the breast, little information has been published on the outcome of salvage treatment after local recurrence. Initial management of DCIS using breast conservation places the patient at risk for local recurrence. As DCIS of the breast is highly curable at initial presentation, the outcome of salvage treatment for local recurrence is important for evaluating the results of the initial management of DCIS using breast conservation treatment. Successful salvage treatment is especially important for the patient with an invasive local recurrence, as this type of local recurrence, in contrast to DCIS local recurrence, places the patient at risk for subsequent distant metastases and death.

Few reports have specifically addressed the outcome after salvage treatment for local or local-regional recurrence for patients with DCIS initially managed with breast conservation treatment [7,13,14,16–18]. The present study was performed to evaluate in detail the outcome of salvage treatment for patients with local or local-regional recurrence after the initial treatment of ductal carcinoma *in situ* using breast conserving surgery followed by definitive breast irradiation.

2. Patients and methods

The present study reports the outcome for a cohort of 90 women with local failure ($n = 85$) or local-regional failure ($n = 5$) as the first and only site(s) of failure after initial treatment for mammographically detected DCIS of the breast. These 90 women were identified from a collaborative, multi-institutional database of women who had undergone initial treatment during 1973–1995 for DCIS of the breast with breast conserving surgery followed by definitive breast irradiation [4–6,16,17,19–24]. This database combines patient data from multiple institutions in North America and Europe. A detailed analysis of the outcome after initial treatment for 1003 patients presenting with newly diagnosed DCIS has recently been reported [4].

All women in the present study had American Joint Committee on Cancer (AJCC) stage Tis N0 M0 ductal carcinoma *in situ* of the breast at the time of initial presentation and treatment [25,26]. Institutions that con-

tributed patients to the present study were: (a) University of Pennsylvania, Philadelphia, Pennsylvania ($n = 5$ patients); (b) Institut Curie, Paris, France ($n = 20$ patients); (c) William Beaumont Hospital, Royal Oak, Michigan ($n = 14$ patients); (d) Mallinckrodt Institute of Radiology, St. Louis, Missouri ($n = 11$ patients); (e) Yale University, New Haven, Connecticut ($n = 10$ patients); (f) University of Texas M. D. Anderson Cancer Center, Houston, Texas ($n = 10$ patients); (g) British Columbia Cancer Agency, Victoria, Canada ($n = 9$ patients); (h) University of Michigan, Ann Arbor, Michigan ($n = 8$ patients); (i) Duke University, Durham, North Carolina ($n = 2$ patients); and (j) Netherlands Cancer Institute, Amsterdam, The Netherlands ($n = 1$ patient). Not included in the present study were patients ($n = 10$) with local or local-regional failure that occurred as an event other than isolated first failure after initial treatment.

In two prior reports of salvage treatment after local or local-regional recurrence, 5-year and 8-year outcomes, respectively, were reported for 42 patients [16,17]. The present study updates these two earlier studies by reporting 10-year outcomes with a substantially larger number of patients.

Actuarial curves were calculated using the Kaplan–Meier method [27]. The time period was calculated as beginning at the time of diagnosis of local or local-regional recurrence. The log-rank test was used for statistical comparisons between groups [28]. A multivariate Cox proportional hazards regression model was used to evaluate the independent prognostic significance of the variables [29].

For analysis of overall survival, a patient was scored as a failure at the time of death, regardless of the cause of death. For analysis of cause-specific survival, a patient was scored as a failure for a death that was from carcinoma of the breast. For analysis of freedom from distant metastases, a patient was scored as a failure at the time of first evidence of distant metastatic disease. For the determination of chest wall recurrence, only patients who had undergone salvage mastectomy were included. Location of the local recurrence was scored according to the method reported by Recht and colleagues [30].

For the study population of 90 patients, the median follow-up after salvage treatment was 5.5 years (mean = 5.8 years; range = 0.2–14.2 years). For surviving patients, the median follow-up after salvage treatment was 5.8 years (mean = 6.0 years; range = 0.2–14.2 years). The numbers of patients alive and evaluable at 5 and 10 years after salvage treatment were 47 and 13, respectively. The median interval from initial treatment to local or local-regional failure was 4.7 years (mean = 5.7 years; range = 0.6–15.0 years).

Of the 10 patients with local failure excluded from the present study (see above), seven patients developed a

local failure after a contralateral breast cancer, two patients developed a local failure after a second malignant neoplasm, and one patient developed a local failure concurrent with a contralateral breast cancer. The histology of the local failure was DCIS for seven patients, and invasive carcinoma for three patients. All 10 patients were clinically node negative ($n = 6$) or pathologically node negative ($n = 4$). The median interval to local failure was 9.0 years (mean = 9.4 years; range = 3.7–17.7 years). All 10 patients were alive without evidence of disease at the time of last follow-up examination with a median follow-up after local recurrence of 4.7 years (mean = 3.5 years; range = 0–8.8 years).

3. Results

The characteristics of the 90 local or local-regional recurrences are shown in Table 1. The histology of the local recurrence was invasive carcinoma (invasive ductal, invasive lobular, or invasive not otherwise specified) for 53 patients (59%), non-invasive disease (DCIS or Paget's disease plus DCIS) for 34 patients (38%), angiosarcoma for one patient (1%), and unknown for two patients (2%). Most (76%; 68/90) of the local recurrences

were detected with mammographic findings only, and the majority (71%; 64/90) of the local recurrences were scored as a true recurrence or marginal miss (i.e., at or adjacent to the site of the original DCIS lesion). After excluding three patients with unknown information and the one patient with angiosarcoma, mammographic findings alone were the method of detection for 91% (30/33) of the non-invasive local recurrences and 68% (36/53) of the invasive local recurrences ($P = 0.024$). Of the 53 patients with invasive carcinoma, the clinical tumour size at the time of local recurrence was ≤ 1.0 cm for nine patients, 1.1–2.0 cm for six patients, 2.1–5.0 cm for four patients, > 5.0 cm for one patient, mammographically detected without specified tumour size for 28 patients, and unknown for five patients.

Treatment at the time of local or local-regional recurrence is detailed in Table 2. The surgical treatment for the majority of patients (84%; 76/90) was a mastectomy. Adjuvant systemic therapy (chemotherapy, hormones, or both) was given to 27 patients (30%).

The type of first event after salvage treatment is detailed in Table 3. Five-year and 10-year actuarial outcome data are shown in Table 4, Figs. 1 and 2. The survival status at the time of last follow-up examination was 77 patients (86%) alive with no evidence of disease (NED), 5 patients (6%) alive with disease, 3 patients (3%) dead with disease, 2 patients (2%) dead with NED, and 3 patients (3%) dead of unknown causes.

Axillary lymph nodes were evaluated at the time of salvage surgery in 45 patients (50%). The median number of lymph nodes evaluated was 9 (mean = 10; range = 1–32). Five (11%) of the 45 patients were found to have one or more pathologically positive axillary lymph node(s) at the time of salvage surgery. For these five patients, the median number of positive lymph

Table 1
Characteristics of the 90 local or local-regional recurrences

Characteristic	Number	%
Histology of the local recurrence		
Invasive ductal carcinoma ^a	50	56
DCIS	33	37
Invasive lobular carcinoma	2	2
Invasive carcinoma NOS	1	1
Paget's disease with associated DCIS	1	1
Angiosarcoma	1	1
Unknown	2	2
Method of detection of the local recurrence		
Mammography only	68	76
Physical examination only ^b	8	9
Mammography and physical examination	11	12
Bloody nipple discharge ^c	2	2
Unknown	1	1
Location of the local recurrence		
True recurrence or marginal miss ^b	64	71
Elsewhere	15	17
Diffuse or multifocal	4	4
Other	2	2
Unknown	5	6
Time (years) to local recurrence		
≤ 5.0	47	52 ^d
5.1–10.0 ^b	31	34 ^d
≥ 10.1	12	13 ^d

DCIS, ductal carcinoma *in situ*; NOS, not otherwise specified.

^a With or without associated DCIS.

^b Includes the one patient with angiosarcoma.

^c Includes one patient also with a positive mammogram.

^d The sum does not equal 100% because of rounding.

Table 2
Treatment at the time of local or local-regional recurrence for the overall group of 90 patients

Treatment	Number	%
Mastectomy ^a		
No adjuvant systemic treatment ^b	40	44
Adjuvant tamoxifen	10	11
Adjuvant chemotherapy	9	10
Adjuvant chemotherapy plus tamoxifen	3	3
Adjuvant hormones – NOS	1	1
Unknown	13	14
Excision ^c		
No adjuvant systemic treatment	4	4
Adjuvant tamoxifen	3	3
Adjuvant chemotherapy	1	1
Unknown	1	1
Unknown	5	6

NOS, not otherwise specified.

^a With or without axillary lymph node staging.

^b Includes the one patient with angiosarcoma.

^c Excisional biopsy or wide local resection.

Table 3

Type of first event after salvage treatment for the overall group of 90 patients

Type of first event	Number	%
None	68	76
Chest wall failure ^a	2	3
Regional failure	0	0
Distant metastases	7	8
Contralateral breast cancer	6	7
Second malignant neoplasm	3	3
Death		
From cause other than breast carcinoma	2	2
From unknown cause	2	2

^a Scored only for the 76 patients treated with salvage mastectomy.

Table 4

Actuarial outcome data after salvage treatment for the overall group of 90 patients

	At 5 years % (95% CI)	At 10 years % (95% CI)
Overall survival	90 (80–96)	83 (66–92)
Cause-specific survival	95 (86–99)	95 (86–99)
Freedom from distant metastases	91 (82–96)	91 (82–96)

CI; confidence interval.

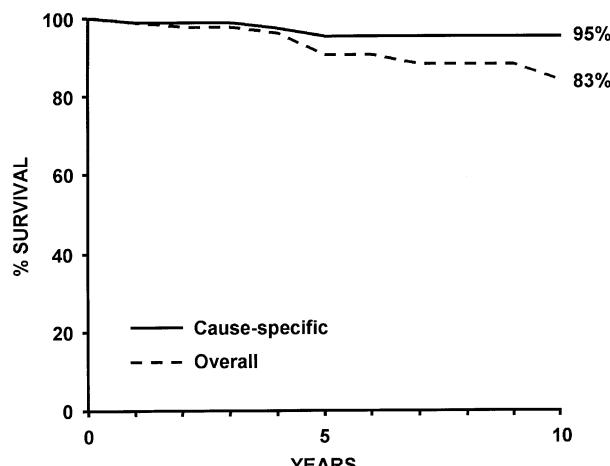


Fig. 1. Actuarial overall survival and cause-specific survival for the overall group of 90 patients after local or local-regional recurrence.

nodes was 6 (mean = 12; range = 1–30). The clinical course for these five patients is detailed in Table 5. Excluding the five patients with pathologically positive axillary lymph nodes, none of the remaining 85 patients developed a subsequent regional nodal recurrence.

At the time of recurrence, invasive histology and the presence of pathologically positive axillary lymph nodes were adverse prognostic factors for the subsequent development of distant metastatic disease on both univariate and multivariate analyses (both $P < 0.001$) (Table 6 and Fig. 3). Method of detection of the local recurrence (mammography alone vs. other) was signifi-

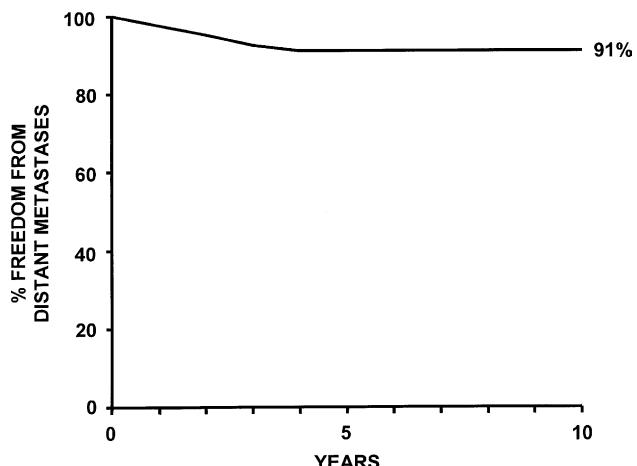


Fig. 2. Actuarial freedom from distant metastases (FFDM) for the overall group of 90 patients after local or local-regional recurrence.

cant on univariate analysis ($P = 0.04$), but not on multivariate analysis ($P = 0.18$). Interval to local recurrence (≤ 5 years vs. > 5 years), patient age (≤ 49 years vs. ≥ 50 years), mastectomy for salvage surgery (yes vs. no), and use of systemic therapy (yes vs. no) were all not correlated with the development of distant metastatic disease (all $P \geq 0.10$).

For the two patients with chest wall recurrence after salvage mastectomy (Table 3), the sequence of events was as follows. Both patients had invasive ductal carcinoma at the time of local failure in the breast that occurred 7.3 and 2.2 years, respectively, after initial definitive radiation treatment. Both patients underwent salvage mastectomy, and had pathologically negative axillary lymph nodes. At the time of local recurrence, one patient received systemic chemotherapy consisting of doxorubicin plus cyclophosphamide, and the second patient did not receive systemic therapy. Chest wall recurrence developed 3.8 and 7.6 years, respectively, after salvage mastectomy. One of the two patients had uncontrolled recurrence on the chest wall at the time of last follow-up examination. Neither patient had developed distant metastatic disease, although with very short follow-up of 7 and 4 months, respectively, after chest wall recurrence.

One patient developed an angiosarcoma as local recurrence (Table 1). At the time of local recurrence, this patient presented with a positive physical examination 6.2 years after initial definitive radiation treatment. She was treated with a salvage mastectomy without adjuvant systemic therapy, and was alive without further evidence of disease 7.3 years after salvage treatment.

4. Discussion

The present study has documented the results of salvage treatment for local or local-regional recurrence

Table 5
Clinical course for the five patients with local-regional recurrence

Patient	Age at initial diagnosis and treatment (years)	Interval to recurrence (years)	Method of detection for the recurrence	Histology of the recurrence	Clinical tumour size of the recurrence (cm)	Location of the recurrence	Salvage surgery	Pathologic axillary lymph node status ^a	Salvage systemic therapy	Subsequent distant metastases	Interval to distant metastases (years)	Survival status	Follow-up after salvage treatment (years)
1	52	12.4	Mass on mammography	Invasive ductal carcinoma	0.9	Elsewhere	Mastectomy with ALND	1/17	Adjuvant tamoxifen	No	N/A	Alive NED	2.1
2	39	5.8	Mass on P.E. and mass on mammography	Invasive ductal carcinoma	5.0	TR/MM	Mastectomy with ALND	5/6	Preoperative FAC chemotherapy	Yes	0.8	AWD	1.4
3	40	9.0	Mass on P.E. and microcalcifications on mammography	Invasive lobular carcinoma	7.9	Diffuse	Mastectomy with ALND	6/7	Adjuvant chemotherapy	Yes	1.1	AWD	2.9
4	58	2.8	Palpable axillary lymph node	Invasive ductal carcinoma	Unknown	Other	Mastectomy with ALND	18/18	NOS	Yes	1.0	DOD	4.9
5	45	7.4	Mass on mammography	Invasive ductal carcinoma	1.0	TR/MM	Mastectomy with ALND	30/32	Adjuvant CAF	Yes	2.1	AWD	10.1

ALND, axillary lymph node dissection; N/A, not applicable; NED, no evidence of disease; P.E., physical examination; TR/MM, true recurrence or marginal mass; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; AWD, alive with disease; NOS, not otherwise specified; DOD, dead of disease; CAF, cyclophosphamide, doxorubicin, and 5-fluorouracil.

^a Number of positive axillary lymph nodes/total number of axillary lymph nodes evaluated.

after the initial treatment of mammographically detected ductal carcinoma *in situ* using breast conserving surgery followed by definitive breast irradiation. The high 10-year rates of overall survival, cause-specific survival, and freedom from distant metastases demonstrate the efficacy of salvage treatment for the majority of patients (Table 4, Figs. 1 and 2).

Few reports have specifically addressed the issue of salvage treatment for local or local-regional recurrence after initial management for DCIS of the breast using breast conservation treatment, either with or without radiation [7,13,14,16–18]. For patients with DCIS of the breast initially managed with breast conservation treatment, the results after salvage treatment for local or local-regional recurrence are summarised in Table 7. These studies show that approximately half of the local recurrences were invasive carcinoma, and approximately half were ductal carcinoma *in situ*. The crude rate of successful salvage treatment was high (>90%) in most studies, including the current study. However, other than the current study, limited information on actuarial outcome after salvage treatment has been reported [14,18].

Mastectomy has been the historical standard local treatment for the patient with local or local-regional recurrence after breast conservation treatment [15,31]. The majority of patients (84%; 76/90) in the present study were treated with salvage mastectomy at the time of local or local-regional recurrence (Table 2). Cutuli and colleagues [13] reported that the rate of salvage mastectomy was 74% (49/66) for patients initially treated with lumpectomy plus radiation, and 58% (34/59) for patients initially treated with lumpectomy without radiation. In the NSABP (National Surgical Adjuvant Breast and Bowel Project) B-17 study, the rate of salvage mastectomy was 62% (29/47) after initial treatment with lumpectomy plus radiation, and 48% (50/104) after lumpectomy without radiation [7].

Only a small number of reported patients have been treated at the time of local recurrence with a second attempt at breast conservation using repeat (or secondary) lumpectomy, with or without radiation. Nine patients (10%) in the present study were treated with secondary breast conservation surgery (Table 2). After initial treatment using lumpectomy plus radiation, Cutuli and colleagues [13] reported that 29% (4/14) of the patients treated with a repeat lumpectomy (including four patients also treated with limited re-irradiation) developed a second local recurrence, and Fisher and colleagues [7] reported that 22% (4/18) of the patients treated with a repeat lumpectomy (number of patients also treated with re-irradiation not specified) developed a second local recurrence. In contrast, after initial treatment using lumpectomy without radiation, Cutuli and colleagues [13] reported that 16% (4/25) of the patients treated with a repeat lumpectomy (including 20 patients also treated

Table 6

Development of distant metastases according to the histology of the local recurrence and axillary lymph node status^a

Histology of the local recurrence	Axillary lymph node status	Number of patients	Subsequent development of distant metastases (crude)	Freedom from distant metastases at 5 years (actuarial)	P value
Non-invasive	Node negative ^b	34 ^c	0% (0/34)	100%	<0.001 ^d
Invasive	Node negative ^b	48	6% (3/48)	92%	
Invasive	Pathologically node positive	5	80% (4/5)	N/A	

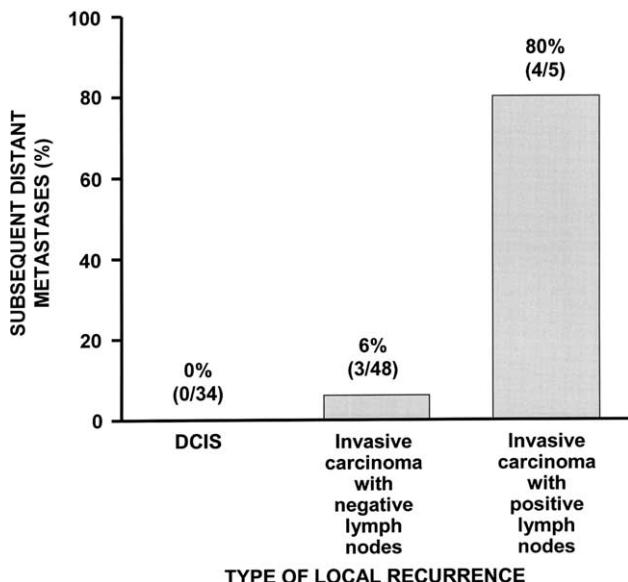
N/A, not applicable (i.e., too few patients at risk to perform an actuarial calculation); DCIS, ductal carcinoma *in situ*.^a Analysis excludes two patients with unknown histology at the time of local recurrence and the one patient with angiosarcoma.^b Includes patients with clinically negative axillae without pathologic axillary lymph node staging and patients with pathologically negative axillary lymph node staging.^c Includes 33 patients with DCIS and the one patient with Paget's disease plus associated DCIS.^d Comparison of the non-invasive group (*n* = 34) to the group with invasive carcinoma and negative axillary lymph nodes (*n* = 48).

Fig. 3. Development of distant metastatic disease after salvage treatment according to the histology of the local recurrence and axillary lymph node status. The DCIS (ductal carcinoma *in situ*) group includes 33 patients with DCIS and the one patient with Paget's disease plus associated DCIS. The negative axillary lymph node group includes patients with clinically negative axillae without pathologic axillary lymph node staging and patients with pathologically negative axillary lymph node staging. Excluded from analysis were two patients with unknown histology and the one patient with angiosarcoma.

with radiation) developed a second local recurrence, and Fisher and colleagues [7] reported that 6% (3/54) of the patients treated with repeat lumpectomy (number of patients also treated with radiation not specified) developed a second local recurrence. Given the success of salvage mastectomy and the small number of reported patients treated with repeat (or secondary) breast conservation after local recurrence, salvage treatment should include a mastectomy for the patient treated initially with breast conserving surgery plus definitive breast irradiation.

In the current study, invasive histology of the local recurrence and pathologically positive axillary lymph nodes were noted to be adverse prognostic factors (Table 6 and Fig. 3). However, given the small total number of patients (*n* = 90) and the small number of distant metastatic events (*n* = 7), the results of the univariate and multivariate analyses should be interpreted cautiously. Compared to the 85 patients with local only first failure, the five patients with local-regional first failure appeared to have a different pattern of recurrence (Table 5). The interval to recurrence was relatively long (>5 years) for four of the five patients. Recurrence was detected as a positive physical examination finding and/or a mass on mammography for all five patients. The location of the recurrence in the breast was a true recurrence or marginal miss for only two of the five patients. The four patients with local-regional recurrence who developed subsequent distant metastases appeared to have had relatively advanced disease at the time of recurrence; all four patients had ≥ 5 pathologically positive axillary lymph nodes at the time of local-regional recurrence, and the clinical tumour size was ≥ 5 cm for two of the four local recurrences.

Few other reports have attempted to evaluate prognostic factors after salvage treatment for local or local-regional recurrence (Table 7). In the NSABP B-17 study, distant metastatic disease developed in 50% (3/6) of the patients after local-regional recurrence, including 50% (2/4) of the patients with local-regional recurrence after initial treatment using lumpectomy plus radiation [7]. Distant metastatic disease developed in 4% (3/70) of the patients with invasive local recurrence without regional nodal involvement (including two of 17 patients initially treated using lumpectomy plus radiation), and in 4% (3/81) of the patients with DCIS local recurrence (including two of 30 patients initially treated using lumpectomy plus radiation). Silverstein and colleagues [14] reported that the 10-year rate of subsequent distant metastatic disease was 16% for patients with invasive local recurrence, but none of the patients with DCIS local

Table 7

Results of salvage treatment after the initial management of ductal carcinoma *in situ* of the breast using breast conservation treatment with or without radiation

Study	Treatment	Number of patients with local recurrence	% Invasive local recurrence	Outcome after salvage treatment		Adverse prognostic factor(s) after local recurrence
				Crude salvage	10 year FFDM	
Fisher [7]	Exc ± RT	157 ^a	48% (76/157)	96% (151/157)		Local-regional recurrence
Fisher [9]	Exc + RT ± Tam	172	44% (76/172)			
Bijker [10]	Exc ± RT	137	48% (66/137)			
Houghton [12]	Exc ± RT ± Tam	258 ^b	42% (108/258 ^b)			
Cutuli [13]	Exc ± RT	125 ^a	57% (71/125)			
Silverstein [14]	Exc ± RT	109	43% (47/109)	95% (104/109)	93% Overall	Invasive local recurrence
					84% Invasive 100% DCIS	
Current study	Exc + RT	90 ^a	61% (53/87 ^c)	91% (82/90)	91% Overall	Invasive local recurrence and pathologically positive axillary lymph nodes
					92% Invasive, node negative 100% Non-invasive	

FFDM, freedom from distant metastases; Exc, excision; RT, radiation treatment; Tam, tamoxifen.

^a Includes patients with local or local-regional recurrence.

^b Includes all breast cancer events (223 ipsilateral local recurrences and 35 contralateral breast cancers).

^c Excludes two patients with unknown histology and the one patient with angiosarcoma.

recurrence developed distant metastatic disease. Cutuli and colleagues [13] reported that the risk of developing distant metastatic disease after invasive local recurrence was 18% for patients treated initially with lumpectomy plus radiation, and 16% for patients treated initially with lumpectomy alone. Other potentially important prognostic factors that could not be identified in the present study might emerge with a larger number of patients and longer follow-up.

Regional lymph node involvement is an uncommon finding at the time of local recurrence. In the present study, 6% (5/90) of the patients presented simultaneously axillary lymph node involvement and local recurrence, including 9% (5/53) of the patients with invasive local recurrence. Similar findings have been noted in other studies. In the NSABP B-17 study, 4% (6/157) of the patients had local-regional recurrence, including 8% (6/76) of the patients with invasive local recurrence [7]. Cutuli and colleagues [13] reported that 20% of the patients with invasive local recurrence had simultaneous axillary recurrence.

For the patient with an apparently isolated local recurrence in the breast, the management of the axilla remains unresolved. Given the small but real incidence of simultaneous axillary lymph node involvement for the patient with an invasive local recurrence, and given the strong adverse prognostic significance of pathologically positive lymphadenopathy at the time of local recurrence, pathologic axillary lymph node staging

should be considered for the patient with an invasive local recurrence and a clinically negative axilla. Whether sentinel lymph node biopsy can replace axillary lymph node dissection at the time of salvage surgery in this setting is not certain. In view of the absence of subsequent regional or distant metastases for the patient with DCIS local recurrence, axillary lymph node staging does not appear to be indicated at the time of local recurrence. Although axillary staging is not indicated for the patient with DCIS of the breast at the time of initial treatment, some authors have advocated using sentinel lymph node biopsy at the time of initial treatment for selected patients with DCIS [32–34]. The management of the axilla at the time of invasive local recurrence for the patient who had previously undergone sentinel lymph node biopsy at the time of initial management is not certain, although repeat (or reoperative) sentinel lymph node biopsy has been reported as technically feasible [35].

The role of systemic therapy as a component of treatment for local or local-regional recurrence is not resolved at the present time. No data has demonstrated that the use of systemic therapy improves outcome after local or local-regional recurrence. The patients in the present study were treated largely in the era before adjuvant tamoxifen was routinely used as a component of the initial management for DCIS of the breast. Adjuvant tamoxifen may be considered for the patient who has a DCIS local recurrence that is hormone receptor

positive and who was not treated with tamoxifen at the time of initial treatment for DCIS. The role of using an aromatase inhibitor for postmenopausal patients is not known. Adjuvant systemic therapy may be considered for the patient with invasive local recurrence, as the presence of invasive carcinoma places the patient at higher risk for developing metastatic disease, particularly when axillary lymph nodes are pathologically involved at the time of local recurrence (Table 6 and Fig. 3).

Patients with local or local-regional only first failure comprise only a small fraction of the women initially presenting with ductal carcinoma *in situ* of the breast [4–15]. The 91% rate of freedom from distant metastatic disease at 10 years and the 95% rate of cause-specific survival at 10 years in the present study (Table 4, Figs. 1 and 2) are seen only for this subset of 90 patients with local or local-regional recurrence, not for the overall group of initially treated patients. After initial treatment with breast conserving surgery and definitive irradiation for DCIS of the breast, the risks of distant metastatic disease and death from breast cancer for the overall group of patients are small [4–15].

After the initial management of DCIS using breast conservation treatment, a long and careful follow-up surveillance program is warranted for the early detection of potentially salvageable local and local-regional recurrences [36]. The time course for the development of local or local-regional recurrence is prolonged. In the present study, 48% (43/90) of these recurrences were detected more than 5 years after initial treatment, and 13% (12/90) more than 10 years after initial treatment (Table 1). Similar results have been observed in other studies [7,9,11–13,18].

In summary, the present study has reported 10-year outcomes after salvage treatment for local or local-regional recurrence after the initial treatment of mammographically detected DCIS using breast conserving surgery followed by definitive breast irradiation. These recurrences were salvaged with high rates of overall survival, cause-specific survival, and freedom from distant metastases. Adverse prognostic factors after salvage treatment were invasive carcinoma at the time of recurrence and the presence of pathologically positive axillary lymph nodes. As local and local-regional recurrences are generally salvageable with further treatment, prolonged and careful follow-up is warranted after the initial treatment of ductal carcinoma *in situ* using breast conserving surgery and definitive breast irradiation.

Conflict of interest statement

None declared.

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References

1. Baxter NN, Virnig BA, Durham SB, et al. Trends in the treatment of ductal carcinoma *in situ* of the breast. *J Natl Cancer Inst* 2004, **96**, 443–448.
2. Burstein HJ, Polyak K, Wong JS, et al. Ductal carcinoma *in situ* of the breast. *N Eng J Med* 2004, **350**, 1430–1441.
3. Ernster VL, Barclay J, Kerlikowske K, et al. Incidence of and treatment for ductal carcinoma *in situ* of the breast. *JAMA* 1996, **275**, 913–918.
4. Solin LJ, Fourquet A, Vicini FA, et al. Long-term outcome after breast conservation treatment with radiation for mammographically-detected ductal carcinoma *in situ* of the breast. *Cancer* 2005, **103**, 1137–1146.
5. Solin LJ, Kurtz J, Fourquet A, et al. Fifteen-year results of breast-conserving surgery and definitive breast irradiation for the treatment of ductal carcinoma *in situ* of the breast. *J Clin Oncol* 1996, **14**, 754–763.
6. Solin LJ, McCormick B, Recht A, et al. Mammographically detected, clinically occult ductal carcinoma *in situ* treated with breast-conserving surgery and definitive breast irradiation. *Cancer J Sci Am* 1996, **2**, 158–165.
7. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol* 1998, **16**, 441–452.
8. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet* 1999, **353**, 1993–2000.
9. Fisher B, Land S, Mamounas E, et al. Prevention of invasive breast cancer in women with ductal carcinoma *in situ*: an update of the National Surgical Adjuvant Breast and Bowel Project experience. *Semin Oncol* 2001, **28**, 400–418.
10. Bijkir N, Peterse JL, Duchateau L, et al. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-*in-situ*: analysis of European Organization for Research and Treatment of Cancer Trial 10853. *J Clin Oncol* 2001, **19**, 2263–2271.
11. Julien JP, Bijkir N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma *in situ*: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *Lancet* 2000, **355**, 528–533.
12. Houghton J, George WD, Cuzick J, et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma *in situ* of the breast in the UK, Australia, and New Zealand: randomised controlled trial. *Lancet* 2003, **362**, 95–102.
13. Cutuli B, Cohen-Solal-le Nir C, de Lafontan B, et al. Breast-conserving therapy for ductal carcinoma *in situ* of the breast: the French Cancer Centers' experience. *Int J Radiat Oncol Biol Phys* 2002, **53**, 868–879.
14. Silverstein MJ, Waisman JR. Outcome after invasive local recurrence in patients with ductal carcinoma *in situ* of the breast. In Silverstein MJ, Recht A, Lagios MD, eds. *Ductal Carcinoma in situ of the Breast*. second ed. Philadelphia, PA, Lippincott Williams & Wilkins, 2002. pp. 545–553.
15. Fowble B. Overview of conservative surgery and radiation therapy ductal carcinoma *in situ*. In Silverstein MJ, Recht A, Lagios MD,

eds. *Ductal Carcinoma in situ of the Breast*. second ed. Philadelphia, PA, Lippincott Williams & Wilkins. pp. 287–302.

16. Solin LJ, Fourquet A, Vicini FA, et al. Salvage treatment for local recurrence after breast-conserving surgery and radiation as initial treatment for mammographically detected ductal carcinoma *in situ* of the breast. *Cancer* 2001, **91**, 1090–1097.
17. Solin LJ, Fourquet A, McCormick B, et al. Salvage treatment for local recurrence following breast-conserving surgery and definitive irradiation for ductal carcinoma *in situ* (intraductal carcinoma) of the breast. *Int J Radiat Oncol Biol Phys* 1994, **30**, 3–9.
18. Silverstein MJ, Lagios MD, Martino S, et al. Outcome after invasive local recurrence in patients with ductal carcinoma *in situ* of the breast. *J Clin Oncol* 1998, **16**, 1367–1373.
19. Solin LJ, Fourquet A, Vicini FA, et al. Mammographically detected ductal carcinoma *in situ* of the breast treated with breast-conserving surgery and definitive breast irradiation: long-term outcome and prognostic significance of patient age and margin status. *Int J Radiat Oncol Biol Phys* 2001, **50**, 991–1002.
20. Solin LJ, Yeh I-T, Kurtz J, et al. Ductal carcinoma *in situ* (intraductal carcinoma) of the breast treated with breast-conserving surgery and definitive irradiation: correlation of pathologic parameters with outcome of treatment. *Cancer* 1993, **71**, 2532–2542.
21. 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.
22. Solin L, Fourquet A, McCormick B, et al. Intraductal carcinoma of the breast: long-term results with breast-conserving surgery and definitive irradiation. *Eur J Cancer* 1993, **29A**(Suppl. 6), S66. (Abstract).
23. Solin LJ, McCormick B, Fourquet A, et al. An international collaborative study: a 15-year experience. In Silverstein MJ, Recht MD, Lagios MD, eds. *Ductal Carcinoma in situ of the Breast*. second ed. Philadelphia, PA, Lippincott Williams & Wilkins, 2002. pp. 359–366.
24. Solin LJ, Haffty B, Fourquet A, et al. An international collaborative study: a 15-year experience. In Silverstein MJ, Lagios MD, Poller A, Recht A, eds. *Ductal Carcinoma in situ of the Breast*. first ed. Philadelphia, PA, Williams & Wilkins, 1997. pp. 385–390.
25. Greene FL, Page DL, Fleming ID, et al., eds. *AJCC Cancer Staging Manual*. 6th edn. New York, NY, Springer-Verlag, 2002. pp. 223–236.
26. Singletary SE, Allred C, Ashley P, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol* 2002, **20**, 3628–3636.
27. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
28. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966, **50**, 163–170.
29. Kalbfleisch J, Prentice R. *The Statistical Analysis of Failure Time Data*. New York, NY, Wiley, 1980., 70–141.
30. Recht A, Silver B, Schnitt S, et al. Breast relapse following primary radiation therapy for early breast cancer. I. Classification, frequency and salvage. *Int J Radiat Oncol Biol Phys* 1985, **11**, 1271–1276.
31. Recht A. Salvage of local-regional failure. In Silverstein MJ, Recht A, Lagios MD, eds. *Ductal Carcinoma in situ of the Breast*. second ed. Philadelphia, PA, Lippincott Williams & Wilkins, 2002. pp. 539–544.
32. Klauber-DeMore N, Tan LK, Liberman L, et al. Sentinel lymph node biopsy: is it indicated in patients with high-risk ductal carcinoma-*in-situ* and ductal carcinoma-*in-situ* with microinvasion? *Annal Surg Oncol* 2000, **7**, 636–642.
33. Pendas S, Dauway E, Giuliano R, et al. Sentinel node biopsy in ductal carcinoma *in situ* patients. *Annal Surg Oncol* 2000, **7**, 15–20.
34. McMasters KM, Chao C, Wong SL, et al. Sentinel lymph node biopsy in patients with ductal carcinoma *in situ*: a proposal. *Cancer* 2002, **95**, 15–20.
35. Port ER, Fey J, Gemignani ML, et al. Reoperative sentinel lymph node biopsy: a new option for patients with primary or locally recurrent breast carcinoma. *J Am Coll Surg* 2002, **195**, 167–172.
36. Schwartz GF, Solin LJ, Olivotto IA, et al. Consensus conference on the treatment of *in situ* ductal carcinoma of the breast, April 22–25, 1999. *Cancer* 2000, **88**, 946–954.