The Impact of Adding Radiation Treatment After Breast Conservation Surgery for Ductal Carcinoma In Situ of the Breast

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Ductal carcinoma in situ (DCIS; intraductal carcinoma) is most commonly detected as suspicious microcalcifications on routine screening mammography in an asymptomatic woman. As most women with newly diagnosed DCIS are eligible for breast conservation treatment, a major decision for most women is whether or not to add radiation treatment after surgical excision (lumpectomy). In four prospective randomized clinical trials, the addition of radiation treatment after lumpectomy reduced the risk of local recurrence by approximately 50%, both for overall local recurrence and for the subset of invasive local recurrence. Nonetheless, efforts have continued to attempt to identify a subset of patients with favorable DCIS who are at sufficiently low risk of local recurrence that omitting radiation treatment is reasonable. Prospective and retrospective studies have demonstrated excellent long-term outcomes at 10 and 15 years after breast conservation treatment with radiation. Careful follow-up, including yearly surveillance mammography, 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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Ductal carcinoma in situ (DCIS; intraductal carcinoma) is most commonly detected by the finding of suspicious microcalcifications on routine screening mammography in an asymptomatic woman. For the woman with newly diagnosed DCIS, the options for local treatment of the breast are 1) surgical excision (lumpectomy) plus radiation treatment; 2) lumpectomy alone without radiation treatment; or 3) mastectomy. As most women with DCIS are interested in breast conservation treatment, a major decision for these women is whether or not to add radiation treatment after lumpectomy. The need for mastectomy on the basis of extensive DCIS is relatively infrequent.

Four prospective randomized clinical trials have measured the value of adding radiation treatment after lumpectomy (1–8). Three of the four trials were designed with two arms and randomized patients after surgical excision to radiation treatment vs not (1–7). The fourth trial from the UK/ANZ (United Kingdom, Australia, and New Zealand) used a 2 × 2 factorial design to evaluate both radiation treatment and tamoxifen (8). Table 1 summarizes the data from these four randomized trials for the benefit of adding radiation treatment. In the four randomized trials, the addition of radiation treatment after lumpectomy reduced the risk of local recurrence by approximately 50%, both for overall local recurrence and for the subset of invasive local recurrence. Ten-year outcome data have been published from at least three of these randomized clinical trials (3–7). Tamoxifen does not substitute for radiation treatment after lumpectomy (3,4,8–10).

Early Breast Cancer Trialists' Collaborative Group Meta-Analysis and Overview

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis and overview of the four previously cited randomized trials of radiation treatment after lumpectomy for DCIS was presented at the National Institutes of Health State-of-the-Science Conference: Diagnosis and Management of Ductal Carcinoma In Situ (DCIS) in September 2009 (11). In this meta-analysis, a total of 3729 eligible women were randomized after lumpectomy to receive radiation treatment vs not. The 10-year rate of ipsilateral local failure (invasive carcinoma plus DCIS) was decreased by 15.2% with the addition of radiation treatment after lumpectomy (28.1% without radiation treatment vs 12.9% with radiation treatment; $P < .001$), with a ratio of annual event rates of 0.46 in favor of radiation treatment ($P < .00001$). Adding radiation treatment after lumpectomy reduced the 10-year rate of invasive local failure by 8.6% (15.4% without radiation treatment vs 6.8% with radiation treatment; $P < .001$) and the 10-year rate of DCIS local failure by 8.4% (14.9% vs 6.5%, respectively; $P < .001$). There were no differences in the 10-year rates of overall survival (8.2% vs 8.4%, respectively; $P > .1$), mortality without recurrence (5.7% vs 5.4%, respectively; $P > .1$), or cardiac mortality (1.3% vs 1.5%, respectively; $P > .1$).

All four prospective randomized trials had sample sizes between approximately 800 and 1100 patients. The primary study endpoint in all four trials was local recurrence, not survival. Given that there were only 3729 eligible patients in the meta-analysis, the ability to

Table 1. Summary of four reported prospective randomized trials that have evaluated the benefit of adding radiation treatment after lumpectomy for ductal carcinoma in situ*

Study	No. of patients	Follow-up	Outcome	Ipsilateral local recurrence, %			P
				Lumpectomy without RT	Lumpectomy with RT	Decrease with RT	
NSABP B-17 Wapnir et al. (4)	813	>12 y median	Cumulative incidence at 12 y	32.9	15.8	52	<.05
EORTC 10853 Bijker et al. (5)	1010	10.5 y median	Actuarial at 10 y	26	15	42	<.0001
Swedish Trial Holmberg et al. (7)	1046	8 y mean	Cumulative incidence at 12 y	32†	16†	50	<.05
UK/ANZ Trial‡ Houghton et al. (8)	1030	4.4 y median	Crude incidence	13.6	5.6	59	<.0001

* EORTC = European Organisation for Research and Treatment of Cancer; NSABP = National Surgical Adjuvant Breast and Bowel Project; RT = radiation treatment; UK/ANZ = United Kingdom, Australia, and New Zealand.

† Estimated from curves

‡ The UK/ANZ trial used a 2 × 2 factorial design evaluating excision (lumpectomy) ± radiation ± tamoxifen. The data given in table are limited to the analysis of radiation treatment.

detect a hypothetical gain in survival, if any, associated with adding radiation treatment is substantially underpowered. Thus, the absence of a survival benefit from the addition of radiation treatment cannot be considered as statistically valid evidence to support omitting radiation treatment after lumpectomy. The statistical reliability of survival analysis for DCIS is further limited because typically only half of all local recurrences show an invasive component after treatment for a primary DCIS. In contrast to DCIS, data from a different EBCTCG meta-analysis and overview of randomized clinical trials of radiation treatment after lumpectomy for primary invasive breast carcinoma demonstrated that only a very large randomized clinical trial or meta-analysis would have sufficient statistical power to detect a survival benefit, if any, from adding radiation treatment after lumpectomy (12).

In the EBCTCG meta-analysis and overview for DCIS, the absence of an effect on cardiac mortality with radiation treatment is especially important when evaluating a patient with left-sided DCIS for a potential course of radiation treatment (11). In assessing the risks vs the benefits of adding radiation treatment, complications from radiation treatment, including a hypothetical adverse impact on cardiac events, have been proposed as a rationale not to give radiation treatment after lumpectomy (13–15). The absence of an adverse impact on cardiac events in the EBCTCG meta-analysis should therefore be considered in the evaluation of the patient with a left-sided DCIS lesion for radiation treatment.

International Collaborative Study of Breast Conservation Surgery With Radiation Treatment

Long-term results from 1003 patients with mammographically detected DCIS from an international collaborative multi-institutional study have been published with 10- and 15-year outcome data (16). In this collaboration, individual patient data were combined from 10 institutions in Europe and North America. All patients were treated with lumpectomy and radiation treatment. Adjuvant tamoxifen was not used because these patients were treated in the era before the routine use of adjuvant tamoxifen. In the most recent published analysis, the median follow-up was 8.5 years (mean 9.0 years; range 0.2–24.6 years). The median patient age was 53 years (mean 54 years; range 26–86 years). In 84% of the patients, mammographic findings at presentation were microcalcifications only.

At 15 years, overall survival was 89%, and cause-specific survival was 98% (Figure 1). Thus, more patients died of causes not related to breast cancer than of causes related to breast cancer. The 15-year rate of any local recurrence (DCIS plus invasive carcinoma) was 19%. Significant factors for local recurrence were found to be the final pathology margins from the primary tumor excision (Figure 2) and patient age (Figure 3), with negative margins and older patient age each associated with a lower risk of local recurrence. For the favorable subgroups of patients aged 50 years or older or DCIS lesions with negative margins of resection, the 10-year rates of local failure were 8% or less.

A central pathology review was performed for a subset of 191 cases for which the pathology slides were available (17). Local failure was compared for patients with vs without the combination of adverse characteristics of comedo subtype plus nuclear grade 3 (Figure 4). The 5-year rate of local failure was 12% vs 3% for the two groups, respectively; however, this difference between the two groups had largely disappeared by year 10 (18% vs 15%, respectively; $P = .15$).

Breast Conservation Surgery Alone Without Radiation Treatment

Notwithstanding the substantial improvement in local recurrence associated with adding radiation treatment after lumpectomy,

Figure 1. Overall survival and cause-specific survival after breast conservation treatment with radiation for 1003 patients with mammographically detected DCIS from a collaborative multi-institutional study. Reprinted from Solin et al. (16), with permission of Wiley.

Figure 2. Local failure according to the final pathology margins from the primary tumor excision after breast conservation treatment with radiation for 1003 patients with mammographically detected DCIS from a collaborative multi-institutional study. Reprinted from Solin et al. (16), with permission of Wiley.

efforts continue to attempt to identify a subset of patients with favorable DCIS who are at sufficiently low risk of local recurrence that omitting radiation treatment is reasonable. Surveillance, Epidemiology, and End Results data have demonstrated that a substantial fraction of patients in the United States are treated with excision alone, without radiation treatment (18). Patients at sufficiently low risk to avoid radiation treatment after lumpectomy have not been reproducibly and reliably identified in prospective clinical trials (19). Although retrospective institutional studies have suggested the possibility of omitting radiation treatment after lumpectomy in favorable subsets of patients, retrospective studies of lumpectomy alone can serve only to generate, but not to test, such a clinical hypothesis.

In the early 1990s, Eastern Cooperative Oncology Group (ECOG) designed a nonrandomized registration study (ECOG E5194) to attempt to identify prospectively favorable patients with DCIS for treatment using local excision alone (with omission of

Figure 3. Local failure according to patient age after breast conservation treatment with radiation for 1003 patients with mammographically detected DCIS from a collaborative multi-institutional study. Reprinted from Solin et al. (16), with permission of Wiley.

Figure 4. Local failure according to central pathology review for a subset of 191 patients after breast conservation treatment with radiation from a collaborative multi-institutional study. Reprinted with permission from Solin et al. (17).

radiation treatment) (20,21). The two arms of the study were 1) low- or intermediate-grade DCIS, 2.5 cm in size or less; or 2) high-grade DCIS, 1.0 cm in size or less. A minimum negative margin width of 3 mm was required. The protocol was amended in 2000 to allow the option to take adjuvant tamoxifen.

For patients entered into the ECOG E5194 study, the median lesion size was 6 and 5 mm in the two arms, respectively (20). With a median follow-up of 6.2 years for the 565 patients with low- or intermediate-grade DCIS, the 5-year rate of ipsilateral local recurrence was 6.1% and the 7-year rate was 10.5%. With a median follow-up of 6.7 years for the 105 patients with high-grade DCIS, the 5-year rate of local recurrence was 15.3% and the 7-year rate was 18.0%. These data suggest that patients with high-grade DCIS are not suitable for treatment with excision alone (without radiation). For patients with low- or intermediate-grade DCIS, additional follow-up will be needed to determine the long-term results.

On multivariate analysis for the high-grade DCIS lesions, age was a significant variable associated with local recurrence (hazard ratio of 0.95; $P = .016$). On multivariate analysis for the low- or intermediate-grade DCIS lesions, no variable was significantly associated with local recurrence. However, the number of patients and the number of events in the many of the subsets analyzed were relatively small.

The curves for local failure in the ECOG E5194 study for the lower-risk group (low- or intermediate-grade DCIS) compared with the higher-risk group (high-grade DCIS) separated early at 5 years but tended to come together with longer follow-up at 7–8 years (20,21). The relative shape of the two curves, separating early, but coming together with longer follow-up, is similar to the data from the collaborative multi-institutional study of patients treated with breast conservation surgery plus radiation treatment (Figure 4 and *vide supra*) (17). A third study has demonstrated similar findings for a cohort of patients treated with breast conservation surgery alone (without radiation treatment) (22).

In a prospective single arm study, Wong et al. (23) reported 158 patients treated with wide excision alone (with neither radiation treatment nor tamoxifen). A minimum negative margin width of 1.0 cm or no tumor on re-excision was required. The 5-year rate of local recurrence was 12%. As this rate of local recurrence exceeded the predetermined stopping threshold for local recurrence, the study was closed early to accrual.

Margins of Resection

For patients undergoing breast conservation surgery (with or without radiation treatment), multiple retrospective studies have demonstrated that achieving a pathologically confirmed negative margin (also called margins) of resection from the primary tumor excision (lumpectomy) is associated with a decreased rate of local recurrence compared with a positive or close margin of resection. The margin of resection of course cannot be tested in a prospective randomized clinical trial. The margin of resection is one of the more interesting variables as it is one of the few clinical variables that can be controlled at least in part by physicians with the use of a wider surgical excision or with a re-excision.

The definition of a negative margin varies from study to study and from physician to physician and represents the minimum negative margin width on pathological evaluation of the lumpectomy specimen. A negative margin has been variously defined as a minimum negative margin width of 1, 2, 5, or even 10 mm. The National Surgical Adjuvant Breast and Bowel Project definition of a negative margin is no tumor cells on ink from the lumpectomy specimen (2).

A negative margin has a substantially different meaning depending on whether or not radiation treatment is to be added after lumpectomy. In the setting of definitive radiation treatment after lumpectomy, the goal of lumpectomy is to debulk the primary tumor burden to the point where radiation treatment can control microscopic residual disease in the breast, not to excise surgically every tumor cell from the breast. In contrast, in the setting of lumpectomy alone without radiation treatment, the goal of lumpectomy is to excise surgically every tumor cell from the breast. The minimum negative margin width needed from the lumpectomy specimen is substantially smaller when radiation treatment is added after lumpectomy (eg, 2 mm) compared with when radiation treatment is omitted (eg, 10 mm).

Dunne et al. (24) reported a meta-analysis of 4660 patients from 22 studies with data on margins of resection in the setting of lumpectomy and radiation treatment. Using a minimum negative margin width of at least 5 mm as the reference group, the odds ratio for local recurrence for a minimum negative margin width of no tumor cells on ink was 2.56 ($P < .05$), the odds ratio for a minimum negative margin width of 1 mm was 2.89 ($P < .05$), and the odds ratio for a minimum negative margin width of 2 mm was 1.51 ($P > .05$). Based on these data, the authors concluded that a minimum negative margin width of 2 mm was appropriate in the setting of adding radiation treatment after lumpectomy. In contrast, in the setting of lumpectomy alone without radiation treatment, a minimum negative margin width of 10 mm has been recommended (25).

Although negative margins from the primary tumor lumpectomy are preferred, some series report a small fraction of patients with close or positive margins. In these cases, the close or positive

margins typically represent limited or focal area(s) without negative margins. In the setting of a focally close or positive margin of resection, tailored re-excision is the preferred next step in management, provided that such a re-excision can be accomplished with an adequate cosmetic outcome. If a re-excision cannot be performed for a focally close or positive margin of resection, then definitive radiation treatment can be delivered, although with a slightly higher risk of local failure. The excess risk of local failure in this setting is estimated as approximately 5%–7% (16,24). In the setting of diffusely involved areas of close or positive margins from a lumpectomy specimen, further surgery of either re-excision or mastectomy is necessary.

Magnetic Resonance Imaging of the Breast

Most primary DCIS lesions in contemporary practice are detected by the finding of suspicious microcalcifications on routine screening mammography in asymptomatic women. In addition to conventional mammography, breast magnetic resonance imaging (MRI) has also been used to image DCIS (26,27). However, there are limited data on the value of breast MRI relative to local control and long-term outcomes after breast conservation treatment. No randomized trial of breast MRI has a clinical outcome (eg, local control) as the primary study endpoint.

In a retrospective study, Solin et al. (27) reported on the outcome of 756 patients after breast conservation treatment with radiation for DCIS or early-stage invasive breast carcinoma. All patients were evaluated using conventional mammography, and 215 (28%) of the patients also had undergone a breast MRI study in a nonrandomized fashion. For the overall group of patients (DCIS or invasive carcinoma), there was no significant difference in the 8-year rates of local failure (4% without a breast MRI vs 3% with a breast MRI; $P = .51$). For the subset of 136 patients with DCIS, there was also no difference in the 8-year rates of local failure (6% vs 6%, respectively; $P = .58$).

Surveillance Mammography After Breast Conservation Treatment

Routine yearly surveillance (screening) mammography is a cornerstone of follow-up care after breast conservation treatment, with or without radiation. Similar to the presentation for the primary DCIS lesion, the most common presentation of a local recurrence after breast conservation treatment is an abnormality on routine screening mammography in the asymptomatic patient. However, there are limited data on compliance with routine surveillance (screening) mammography after breast conservation treatment.

Nekhlyudov et al. (28) reported data on compliance with routine screening mammography after breast-conserving surgery in a cohort of 3037 women. Treatment was breast-conserving surgery alone in 43% (1298 of 3037) of the patients, adjuvant radiation treatment in 42% (1268 of 3037), adjuvant radiation treatment plus tamoxifen in 11% (339 of 3037), and adjuvant tamoxifen in 4% (132 of 3037). The rate of compliance with yearly screening mammography for the overall group steadily declined from 79% (2115 of 2678) in year 1 to 61% (175 of 287) in year 10. For individual patients, full compliance with yearly screening mammography

Table 2. Summary of salvage treatment for local recurrence after initial breast conservation treatment (with or without radiation) for ductal carcinoma in situ*

Study	Salvage BCS for local recurrence		Salvage mastectomy for the overall study cohort		Follow-up (y) after initial treatment
	Initial BCS alone (without RT)	Initial BCS plus RT	Initial BCS alone (without RT)	Initial BCS plus RT	
NSABP B-17 Fisher et al. (1)	52% (54/104)	38% (18/47)	12% (50/403)	7% (29/411)	7.5 mean
ECOG E5194 Hughes et al. (20)	44% (29/66)	—	6% (37/670)	—	6.2 median
Solin et al. (16,29)	—	11% (9/85)	—	8% (76/1003)	8.5 median
Cutuli et al. (30)	42% (25/59)	21% (14/66)	18% (34/190)	10% (49/515)	7.0 median

* BCS = breast-conserving surgery (ie, excision, lumpectomy); ECOG = Eastern Cooperative Oncology Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; RT = radiation treatment.

was only 34% (361 of 1077) through the first 5 years of follow-up after treatment and only 15% (43 of 287) through the first 10 years of follow-up.

Salvage Treatment After Local Recurrence

One of the arguments advanced in favor of omitting radiation treatment after lumpectomy at the time of initial presentation is the hypothetical ability to use salvage (secondary) breast conservation treatment, typically with radiation treatment, at the time of local recurrence. However, little or no data have been reported to support this argument. Local recurrence is most commonly detected as an abnormality on routine screening mammography in the asymptomatic patient and should potentially be amenable to secondary breast conservation treatment.

Relatively few studies have reported data on salvage treatment after primary (initial) breast conservation treatment, with or without radiation (Table 2). In three studies reporting salvage treatment after initial lumpectomy alone (without radiation treatment), the rate of salvage breast conservation treatment was only 42%–52%. This relatively low rate suggests that some patients may be rejecting secondary breast conservation treatment in favor of mastectomy for non-medical reasons (eg, fear and anxiety of further

recurrence). Thus, preventing local recurrence by adding radiation at the time of initial treatment may be a more important long-term strategy than the alternative strategy of reserving radiation treatment for use after salvage (secondary) breast conservation surgery at the time of local recurrence.

In the collaborative multi-institutional study of patients treated for DCIS with a lumpectomy plus radiation treatment, there were 90 patients with local or local-regional recurrence as the site of first failure (29). At the time of local or local-regional recurrence, salvage surgery was mastectomy for 84% (76 of 90) of the patients, and adjuvant systemic therapy (chemotherapy, hormonal therapy, or both) was given to 30% (27 of 90) of the patients. The median follow-up after salvage treatment was 5.5 years (mean = 5.8 years; range = 0.2–14.2 years). After salvage treatment, the 10-year rate of overall survival was 83%, and the 10-year rate of cause-specific survival was 95% (Figure 5). The 10-year rate of freedom from distant metastatic disease was 91%. Adverse prognostic factors for the subsequent development of distant metastatic disease after salvage treatment were invasive histology at the time of the local

Figure 5. Overall survival and cause-specific survival after salvage treatment for 90 patients with local or local-regional recurrence from a collaborative multi-institutional study. At initial presentation of DCIS, all patients had undergone breast conservation treatment with radiation. Reprinted from Solin et al. (29), with permission of Elsevier.

Figure 6. Development of subsequent distant metastatic disease after salvage treatment for patients with local or local-regional recurrence from a collaborative multi-institutional study. At initial presentation of DCIS, all patients had undergone breast conservation treatment with radiation. Reprinted from Solin et al. (29), with permission of Elsevier.

recurrence and pathologically positive axillary lymph nodes (Figure 6). These results demonstrate that local and local-regional recurrences can be salvaged with high rates of survival and freedom from distant metastases and that careful follow-up after initial breast conservation treatment with radiation is warranted for the early detection of potentially salvageable local and local-regional recurrences.

Summary

Prospective and retrospective studies have demonstrated excellent long-term outcomes at 10 and 15 years after breast conservation treatment with radiation. Adding radiation treatment after lumpectomy reduces the rate of local recurrence by about half in randomized clinical trials. In the ECOG E5194 nonrandomized registration study, the rate of local recurrence after excision alone (without radiation treatment) for low- or intermediate-grade DCIS was 6.1% at 5 years and 10.5% at 7 years, although longer follow-up is warranted. After initial breast conservation treatment with radiation, careful follow-up including yearly surveillance mammography is indicated. Local and local-regional recurrences after initial breast conservation treatment with radiation can be salvaged with high rates of survival and freedom from distant metastases.

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