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Review

A review of the management of ductal carcinoma in situ following breast conserving surgery

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ABSTRACT

Ductal carcinoma in situ (DCIS) is a heterogeneous, pre-malignant disease accounting for 10–20% of all new breast tumours. Evidence shows a statistically significant local control benefit for adjuvant radiotherapy (RT) following breast conserving surgery (BCS) for all patients. The baseline recurrence risk of individual patients varies according to clinical-pathological criteria and in selected patients, omission of RT may be considered, following a discussion with the patient. The role of adjuvant endocrine therapy remains uncertain. Ongoing studies are attempting to define subgroups of patients who are at sufficiently low risk of recurrence that RT may be safely omitted; investigating RT techniques and dose fractionation schedules; and defining the role of endocrine therapy. Future directions in the management of patients with DCIS will include investigation of prognostic and predictive biomarkers to inform individualised therapy tailored to the risk of recurrence.

Background

DCIS is a non-invasive precursor to breast cancer. It is defined by the World Health Organisation (WHO) as "a neoplastic intraductal lesion characterised by increased epithelial proliferation, subtle to marked cellular atypia and an inherent but not necessarily obligate tendency for progression to invasive breast cancer" [1]. The prevalence of DCIS has increased significantly since the early 1990s, following the implementation of large-scale mammographic screening programs in the western world representing approximately 10–19% of all new diagnoses of breast tumours [2–4].

Prior to the early 1990s, DCIS was generally treated with mastectomy with excellent local control and overall survival rates in the order of 98–100% [5,6]. However, with the emergence of evidence showing survival equivalence of BCS and adjuvant RT compared to mastectomy for invasive breast cancer, there was interest in investigating treatment of DCIS with BCS and RT. This review article examines the current evidence for the management of DCIS after BCS.

The absolute mortality rates in DCIS are very low [7]. The aim of treatment for DCIS is to prevent local recurrence, both non-invasive and particularly invasive recurrence. Recurrences after BCS and RT could be salvaged with mastectomy. However, long-term outcomes of two randomised trials showed that invasive local recurrences after BCS for DCIS were associated with a 75% increase in mortality risk compared with intraductal recurrences [8]. The cumulative probability of breast cancer-related death at 10 years was 10.4% in women with an invasive recurrence (22 deaths in 263 women with invasive ipsilateral recurrence) compared with 2.7% in women with a non-invasive recurrence (8 deaths in 227 women with non-invasive ipsilateral recurrence) [8]. A study by Solin et al. [9] showed that 4 of 24 patients (17%) who had an invasive recurrence after BCS and RT developed metastatic disease while none of the patients with a non-invasive recurrence developed metastases. A study by Cutuli et al. [10] involving 195 patients who developed a recurrence after BCS with or without RT showed that 19 of the 113 patients (17%) with an invasive local recurrence developed metastatic disease at a median follow-up of 156 months. A population-based study of 1103 women with DCIS treated with BCS with or without RT reported an overall breast cancer-related mortality rate of 2% at a median follow-up of 91 months [11], representing 14% of those with ipsilateral recurrences. In a retrospective study [12] that examined 445 patients treated with BCS alone, one of the 26

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patients (4%) who had an invasive recurrence died from metastatic disease at a median follow-up of 57 months.

Adjuvant treatment following breast conserving surgery

Adjuvant radiotherapy

No randomised trials have compared mastectomy to BCS and RT for DCIS. A meta-analysis showed a summary recurrence rate of 1.4% following mastectomy, 8.9% following BCS and RT, and 22.5% after BCS alone [6]. There have been 4 randomised controlled trials with long-term follow-up comparing BCS alone with BCS and RT [8,13–15], a Cochrane review [16] and a meta-analysis [7]. The 4 randomised trials have a median follow up period ranging from 101 months to 207 months. A summary of the results for BCS alone, and BCS and adjuvant RT are shown in Tables 1 and 2, respectively. Only one of these trials required surgical margins to be free of tumour [14]. All four randomised trials showed a significant reduction in local recurrence rates with the addition of RT, with recurrence rates of 25–35% after BCS alone compared to 9–20% after BCS and adjuvant RT [8,13–15].

A Cochrane review of adjuvant RT for DCIS [16] identified a statistically significant benefit from the addition of RT for all ipsilateral breast events (hazards ratio [HR] 0.49; 95% confidence intervals [CI] 0.41 to 0.58, $P < 0.00001$); ipsilateral invasive recurrence (HR 0.50; 95% CI 0.32 to 0.76, $p = 0.001$); and ipsilateral DCIS recurrence (HR 0.61; 95% CI 0.39 to 0.95, $P = 0.03$). Benefit of RT was observed irrespective of age (<50 years vs > 50 years); tumour size (≤10 mm vs > 10 mm); whether surgical resection of DCIS was complete or not; and presence or absence of comedo necrosis.

Individual patient data from all four trials were analysed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [7]. A total of 3729 patients were analysed and the result showed a significant absolute reduction in 10-year risk of any ipsilateral breast event of 15.2% (28% vs. 12.9%).

Is there a group of patients in whom radiotherapy can be safely omitted?

Given the heterogeneity of DCIS and the perceived overtreatment of some patients, several studies have attempted to identify prospectively or retrospectively subgroups of women who are at sufficiently low risk of recurrence that RT may be safely omitted.

Wong et al. [17] prospectively studied 158 women with low-risk DCIS. The tumours were grade 1 or 2, ≤2.5 cm in mammographic dimensions, and treated by BCS with margins of ≥1 cm (or no residual DCIS on re-excision). Tamoxifen use was not permitted. The median follow-up was 40 months (3.3 years). The study was closed to accrual early because the number of local recurrences reached the predetermined stopping rules. There were 13 patients with ipsilateral breast recurrence occurring 7–63 months after study enrolment. This corresponded to a 5-year local recurrence rate of 12%, despite the favourable prognostic features. It is expected that this recurrence rate would increase over time given the long natural history of low-risk DCIS.

The Eastern Cooperative Oncology Group (ECOG E5194) [18] prospectively studied patients with low-risk DCIS from 1997 to 2002. The patients had low or intermediate grade DCIS measuring ≤2.5 cm (558 patients), or high-grade DCIS measuring ≤1 cm (103 patients), which were resected with microscopic margins of ≥3 mm, and no residual calcifications on post-operative mammograms. The use of tamoxifen was permitted for patients recruited after 2000, but was not mandatory. The 5-year ipsilateral breast tumour recurrence rates were 6.1% in the low or intermediate grade group at a median follow-up of 74 months; and 15.3% in the high grade group at a median follow-up 80 months. Hughes et al. concluded that patients with a small, low or intermediate grade DCIS resected with clear margins could be adequately treated with BCS alone. However, patients with high-grade DCIS had a high rate of recurrence, and BCS alone was inadequate. It is noteworthy that the median tumour size was 6 mm in the low or intermediate grade group, and 5 mm in the high grade group. The patients had a median age of 60 years. Thus, although the inclusion criteria for the study were broader, these were highly selected patients, and caution should be used in applying these results to the general patient population.

The Radiation Therapy Oncology Group (RTOG) 9804 study is a randomised controlled trial comparing observation to RT after BCS for patients with low-risk DCIS. The low-risk group was comparable to ECOG E5194 study [18]. The tumours were mammographically detected, low or intermediate nuclear grade, ≤2.5 cm in diameter, and resected with surgical margins of ≥3 mm. Tamoxifen was permitted, but not mandatory. This study has closed to accrual, and results are pending.

In the overview of randomised controlled trials of adjuvant RT for DCIS, the EBCTCG showed that adjuvant RT halved the rate of ipsilateral breast events [7]. The benefit from RT persisted regardless of age, extent of resection and use of tamoxifen. The overview identified 291 women with small (1–20 mm), low nuclear grade tumours resected with negative margins. Their 5-year and 10-year risks of an ipsilateral breast event after BCS alone were 20.6% and 30.1%, respectively. RT reduced these risks to 7.1% at 5 years, and 12.1% at 10 years, which were highly significant.

Given the long natural history of low grade DCIS, long-term data are required to determine if RT may be safely omitted in selected patients. The current evidence shows a significant benefit for

Table 1
Outcome of treatment for DCIS with BCS alone.

Study	Period	No. patients	% Screen detected	% Negative margins	Median follow-up (months)	Local recurrence rate (%)	% Local recurrences being invasive
Bijker et al. [13] EORTC[a]	1986–96	503	71%	84%	126	26%	50%
Cuzick et al. [14] UK/ANZ DCIS[b]	1990–98	544	>90%	100%	152	25%	38%
Holmberg et al. [15] SweDCIS[c]	1987–99	520	79%	80%	101	27%	45%
Wapnir et al. [8] NSABP B-17 and B-24[d]	1985–90	403	81%	87%	207	35%	56%

[a] European Organisation for Research and Treatment of Cancer.
[b] United Kingdom, Australia and New Zealand DCIS study.
[c] Swedish Breast Cancer Group DCIS trial.
[d] National Surgical Adjuvant Breast and Bowel Project B-17 and B-24.