The Breast 31 (2017) 181–185

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Factors influencing local control in patients undergoing breast conservation surgery for ductal carcinoma *in situ*

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ARTICLE INFO

Article history:
Received 28 June 2016
Received in revised form
9 October 2016
Accepted 3 November 2016

Keywords:
Ductal carcinoma *in situ*
Local recurrence
Prognostic factors

ABSTRACT

Background: The aim of our study was to assess various predictors for local recurrence (LR) in patients undergoing breast conservation surgery (BCS) for ductal carcinoma *in situ* (DCIS).
Materials and methods: An audit was performed of 582 consecutive patients with DCIS between Jan 1975 to June 2008. In patients undergoing BCS, local guidelines reported a margin of ≥10 mm during the above period. Guideline with regard to margin of excision changes soon after this period.
We retrospectively analysed clinical and pathological risk factors for local recurrence in patients undergoing BCS. Statistical analysis was carried out using SPSS version 19, and a cox regression model for multivariate analysis of local recurrence was used.
Results: Overall 239 women had BCS for DCIS during the above period. The actuarial 5-year recurrence rate was 9.6%. The overall LR rate was 17% (40/239. LR was more common in patients ≤50 years: (10/31 patients, 32%) compared to patients > 50 years (30/208, 14%, P = 0.02). Forty three per cent of patients (6/14) with <5 mm margin developed LR which was significantly higher compared to patients with 5–9 mm margin (12%, 3/25) and with ≥10 mm margin (14%, 27/188, P = 0.01). On multivariate analysis age ≤50 years, <5 mm pathological margin were independent prognostic factors for local recurrence.
Conclusion: Our study shows that younger age (≤50 years) and a margin < 5 mm are poor prognostic factors for LR in patients undergoing breast conservation surgery for DCIS.

1. Introduction

Ductal carcinoma *in situ* (DCIS) represents 10% of all breast carcinomas and 20–45% of all mammographically detected cancers [1–5]. It is a heterogeneous disease rather than a single entity and given that patients have a wide variant of personal needs and preferences, no single approach is appropriate for all patients [6]. With the introduction of screening mammograms in UK in 1988, approximately 90% of DCIS diagnosed are asymptomatic small lesions (<4 cm), and most of these lesions could be excised surgically by breast conserving surgery [7]. Based on historical reports mastectomy could virtually guarantee a cure in these subjects with DCIS with 98%–99% survival reported after 10 years. However, mastectomy would be 'over treatment' for many of these small lesions. On the other hand breast conservation surgery is not without risks as approximately 50% of subsequent local recurrence are an invasive cancer from which they may die [8–10].

Various risk factors have been analysed and based on this patients have been stratified into different sub sets for treatment decision making [3]. In patients undergoing breast conservation surgery, there is no clear data to provide guidance on the margin of excision in patients undergoing breast conservation surgery for DCIS. The EORTC DCIS trial reported a high local recurrence rate of 36% at 10 years in patient with close or involved margins (<1 mm or frankly involved) compared to those with clear margin (15% at 10 years) regardless of the use of radiotherapy [11]. A survey done in UK demonstrated that approximately half of surgeons aim for a margin of more than 2 mm, where as the other half accept a margin of 2 mm or less [12]. A recent consensus by the Society of Surgical

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http://dx.doi.org/10.1016/j.breast.2016.11.002
0960-9776/

Oncology and American Society of Radiation Oncology suggest a negative margin (no ink on tumour) as a standard for invasive breast cancer [13]. In DCIS patients, Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma *in situ* suggest a margin of 2 mm [14]. The Association of Breast Surgery suggests units to adhere to local guidelines regarding acceptable margin width for DCIS [15]. At Nottingham City Hospital) a margin of ≥10 mm was the preferred margin in those patients undergoing breast conservation surgery for DCIS until June 2008. The aim of our audit study was to assess various predictive factors for local recurrence including margin of excision in patients undergoing breast conservation surgery for DCIS.

2. Materials and methods

This retrospective audit involved 582 consecutive patients with DCIS undergoing surgical treatment (mastectomy and breast conservation surgery) +/− radiotherapy between Jan 1975 to June 2008 at the City Hospital Nottingham. The mammographic screening program started in 1988. Patients with the diagnosis of DCIS who underwent surgical treatments were identified from databases kept at the Breast Institute. Patients with a history of invasive cancer treated previously and subsequently developing subsequent DCIS were excluded. Each patient's data was extracted from the paper case notes and IT pathology system.

Data extracted included: microscopic final margins, tumour size, tumour grade, evidence of micro-invasion and adjuvant treatment.

2.1. Treatment protocol

Prior to surgery all patients were discussed at the multidisciplinary meeting comprising of surgeon, radiologist, pathologist and oncologist. A clear superior, inferior, lateral and medial pathological margin on ≥ 10 mm is considered adequate clearance [15].

Until 2003 if a pathological margin of ≥10 mm was achieved, no further treatment was deemed necessary in these patients. However, since 2003 certain patients were offered radiation treatment following discussion at the multidisciplinary team meeting: this was based on the grade of the DCIS and the size of the histological margin. Histological grade of the tumour was categorised into grades 1–3 by the modified Scarf-Bloom-Richardson criteria. Patients were followed-up every year until death or their last clinic visit on or before June 2008.

Based on the histopathology of the surgical specimen, patients were divided into three groups (<5 mm margin, 5–9 mm margin and ≥10 mm margin). Cox regression model for multivariate analysis of local recurrence was used with variables with significant P values (<0.05) in the univariate analysis carried out using SPSS version 19.

3. Results

Two hundred and thirty nine patients out of the total of 582 (41%) had breast conservation surgery during this period (1975–2008). The median age was 59 years (40–86) as shown in Table 1. The median follow-up was 76 months (1–308). The actuarial 5-year recurrence rate was 9.6%. Sixty five percent of the recurrences were invasive recurrences (26/40).

Significantly higher incidence of local recurrence was associated with patients ≤50 years, excision margin less than 5 mm (Table 2) and presence of micro-invasion. Tumour size and histological grade were not associated with LR. Seventy five patients were reported to have comedo necrosis, however this was not associated with any significant increase in the incidence of local recurrence when compared to those without comedo necrosis (P = 0.231).

Although only a small number of patients had radiation treatment, it did reduce the incidence of local recurrence by half as shown in Table 3. The numbers were too small to show statistical significance.

Multivariate analysis showed that age at diagnosis (≤50 years), margin of excision (<5 mm) and presence of micro-invasion were all independent prognostic factors for local recurrence as shown in Table 4.

4. Discussion

This audit reports a local recurrence rate of 9.6% at 5-years. This is within the quality outcome measures described by the Association of Breast Surgery during this period for local recurrence rates of less than 20% at 10 years with a target 10% at 5 years [16]. More recent guidelines have removed the higher 20% figure and left the lower 10% figure as the guideline 5 year recurrence rate [17].

Margin of excision is an important prognostic indicator. A recent consensus by the Society of Surgical Oncology and American Society of Radiation Oncology suggest a negative margin (no ink on tumour) as a standard for invasive breast cancer [13]. This was following a meta-analysis of margin width and ipsilateral breast tumour recurrence (IBTR) from a systematic review of 33 studies including 28,162 patients. Positive margins were associated with a two-fold increase in the risk of IBTR compared with negative margins. There was no statistically significant evidence that more widely clear margins reduce IBTR although there were inherent limitations to the data included in the meta-analysis (eg 32/33 studies were retrospective, significant missing data, only studies reporting positive and negative margins included, no SOPs for surgical margins). Society of surgical oncology- American society of radiation oncology- American society of clinical oncology consensus guidelines on margin of excision in patients undergoing breast conservation surgery in patients with DCIS suggest the use of 2 mm margin as standard for adequate margin of excision. Systematic review and meta-analysis of 20 studies showed that negative margins halve the risk of IBTR compared with positive margins defined as ink on DCIS. A 2 mm margin minimizes the risk of IBTR compared with smaller negative margins [14]. In our study, patients with a clear margin of excision of 5 mm or more had a significantly lower rate of local recurrence compared to with a clear margin of less than 5 mm. DCIS is different biology compared to invasive disease and margin may be more important than those for invasive cancers.

Although only a small number had radiation treatment (RT) in our case series, it did show a 50% reduction in the incidence of local recurrence in spite of the fact that patients selected for radiotherapy had more adverse prognostic factors (younger patients with larger tumours) as shown in Table 5. None of the patients who had RT following breast conservation surgery with clear margin developed local recurrence (Both the patients who developed LR following radiation treatment had unknown margins). Recent Oxford review, a meta analysis of 4 randomised controlled trials involving over 3700 women showed that radiotherapy following breast conservation surgery versus breast conservation surgery alone reduced the absolute 10-year risk of any ipsilateral breast event (ie, either recurrent DCIS or invasive cancer) by 15.2% (12.9% vs 28.1% 2 $P < 0.00001$), and it was effective regardless of the age at diagnosis, extent of breast-conserving surgery, use of tamoxifen, method of DCIS detection, margin status, focality, grade, comedo necrosis, architecture, or tumour size [18].

Clear margin of excision and use of radiation treatment following breast conservation surgery have been reported to be