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Margin Width and Local Recurrence after Breast Conserving Surgery for Ductal Carcinoma *In Situ*

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ABSTRACT

Introduction

Ductal Carcinoma *in situ* (DCIS) represents 5% of symptomatic and 20-30% of screen detected cancers. Breast conserving surgery (BCS) +/- radiotherapy is performed in over 70% of women with DCIS. What constitutes an adequate margin for BCS remains unclear.

Methods

A single institution follow up study has been conducted of 466 patients with pure DCIS treated by BCS between 2000 and 2010 of whom 292 received whole breast radiotherapy and 167 did not. Patients were selected for radiotherapy based on perceived risk of in breast tumor recurrence (IBTR). Distance to nearest radial margin was measured; 10 patients had a margin width of <1mm, 94 had widths of 1-2mm and 362 had widths of >2mm. There was no association of margin width and the use of radiotherapy.

Results

At a median follow up of 7.2 years there were 44 IBTR (27 DCIS and 17 invasive). There was no evidence that margin widths >2mm resulted in a lower rate of IBTR than margin widths of 1-2mm. The actuarial IBTR rates at 5 and 10 years for margins of 1-2mm were 9.0% (95% CI +/- 5.9%) and 9.0% (95% CI +/- 5.9%) respectively and for margins of >2mm were 8.0% (95% CI +/- 3.9%) and 13.0% (95% CI +/- 3.9%) respectively, Odds Ratio for IBTR 1-2mm vs >2mm was 0.839 (95% CI 0.392-1.827) p=0.846. In a multivariate analysis only DCIS size predicted for IBTR (HR 2.73 p<0.0001).

Conclusion

1mm appears a sufficient margin width for BCS in DCIS irrespective of whether patients receive radiotherapy.

Keywords: DCIS, Margins for breast conserving surgery, Recurrence after breast conserving surgery for DCIS

INTRODUCTION

The introduction of mammographic breast screening has resulted in a dramatic increase in the number of women diagnosed with ductal carcinoma *in situ* (DCIS) [1-3]. Over 20% of screen-detected "cancers" identified through breast screening are now DCIS. In the UK 70% of women diagnosed with DCIS are treated with breast conserving surgery (BCS). The aim of BCS is to completely excise DCIS to negative margins [4-7] although the optimal margin distance (i.e. the threshold to declare a negative margin) has been a topic of debate. Guidelines for what constitutes a negative margin have varied from >0mm, >1mm, >2mm, and >10mm [8-13]. A recent systematic review investigated the association between margins and local recurrence in DCIS to determine the optimal negative margin width [14]. In this review there was heterogeneity of margin definitions across studies, and only small number of studies included margin widths of 1mm and 2mm. The authors thus had to combine >0mm and >1mm into one group. Patients with margins of ≥2mm had a significantly lower rate of local recurrence than patients with margins <2mm. This review concluded that negative margins in DCIS reduce the odds of in breast tumor recurrence (IBTR) but that margin distances above 2mm are not associated with a further reduction of odds of local recurrence compared to 2mm [14].

Given the paucity of data on distance to nearest margin in DCIS, the aim of the current study was to investigate in a large singe centre study the association of margin widths of 1-2mm and >2mm with IBTR in patients having BCS for DCIS.

METHODS

Patients diagnosed with DCIS without any evidence of invasion (microinvasive cancers excluded) between 1st January 2000 and 1st January 2010 and treated with BCS with or without radiotherapy in the Edinburgh Breast Unit (EBU) were identified from the South East Scotland Cancer Network prospective database. Patients had a core biopsy to establish a diagnosis of DCIS and following full imaging assessment suitable patients underwent BCS performed by one of the specialist surgeons working in the EBU. The aim was to excise the DCIS with a 1cm macroscopic margin. In almost all patients full thickness of breast tissue from subcutaneous fat down to pectoral fascia was removed. All specimens were orientated in a standard fashion with metal clips and underwent intraoperative specimen radiography and where appropriate further tissue was removed from margins considered clinically or radiologically to be involved. It was not routine to take cavity shavings. All excision samples were fixed immediately in formalin. They were processed by specialist breast pathologists in a standard manner and standardised reports were issued and included the microscopically measured distance by the pathologist to all six margins to the nearest 0.1mm (anterior, posterior and the radial margins; medial, lateral, inferior and superior). If any radial margin (medial, lateral, inferior or superior) was less than 1mm, re-excision was advised unless the surgeon reported that he or she had excised tissue to the limit of the breast at that margin. If the pathologist reported disease less than 1mm from the anterior or posterior margin and a full thickness excision had been performed then no re-excision was performed. Patients having re-excision were considered to have clear margins if the new radial margin was ≥1mm from DCIS. A small number of patients underwent more than 1 re-excision to obtain clear margins.

Radiotherapy

After 2003 all patients with high grade DCIS were advised to have radiotherapy, although before this radiotherapy was used selectively in women with high grade DCIS. A minority of

patients with intermediate grade DCIS had radiotherapy and few patients with low grade DCIS had radiotherapy. Whole breast radiotherapy was given in a dose of 50 Gy over 25 fractions. Nine patients received a radiotherapy boost as part of a multicentre clinical trial.

Systemic Therapy

Seven patients received neoadjuvant endocrine therapy (letrozole 2.5mg or tamoxifen 20mg daily) while awaiting wide excision and therapeutic mammaplasty. Nine received post-operative tamoxifen for 5 years as part of the EORTC DCIS study. No other patient received any adjuvant endocrine treatment.

Follow up

All patients had an annual review including two-view mammography and any patient with a diagnosis of invasive or *in situ* disease which occurred anywhere in the treated breast was considered to have an IBTR.

Statistical Methods

Actuarial survival and relapse rates were calculated using the Kaplan-Meier method [15]. The log rank test was used for statistical comparison between curves [16]. A proportional hazards regression model was used to assess the independent significance of variables [17]. The odds ratio and 95% confidence intervals were calculated according to Altman [18]. Tests of significance for odds ratio were calculated according to Sheskin [19]. The analysis on margin width relates only to the distance to the nearest radial margin.

RESULTS

466 female patients with DCIS were included in this study. The median age was 60 years, with an age range of 35 to 94. The median tumor diameter was 14mm with a range of 1 to

83mm. Ten patients had a final radial margin width <1mm, 94 had a margin width of 1-2mm, and 362 had a final margin of >2mm. The 9 patients who received adjuvant tamoxifen all had margin widths of >2mm. In Table 1 the statistical associations between margin width categories and clinical, pathological, and treatment variables are shown [Table 1]. There was no significant association between margin width and whether patients received radiotherapy and no association between margin width and histological grade, comedo necrosis, age or DCIS size. Patients with margin widths of >2mm were significantly more likely (p=0.037) to have Van Nuys Prognostic Index scores of 4 – 6 than patients with margins of 1-2mm.

292 patients received whole breast radiotherapy. The statistical associations between radiotherapy and clinical and pathological variables are outlined in Table 2 [Table 2]. Patients who received radiotherapy were more likely to have high grade DCIS, and significantly more likely to have comedo necrosis and large areas of DCIS (p<0.0001). They were also more likely to have higher Van Nuys scores (p<0.0001).

Factors associated with IBTR

Median follow up time was 7.2 years. There were 44 in breast tumor recurrences in the 466 patients of which 27 were DCIS and 17 were invasive cancer. The 5year IBTR rate fell significantly from 2000-2005 to 2006-2010; hazard ratio 0.456 (P=0.021). The association between surgical margins and IBTR is shown in Figure 1 [Figure 1]. There was no evidence that patients with margin widths of >2mm had a lower recurrence rate than patients with margins of 1-2mm. Although patients with <1mm appeared to have a higher IBTR rate, there were only 10 patients and this apparent difference was not statistically significant (p=0.162). There was also no significant association between IBTR and margin width when analysed as a continuous variable. Whether patients had a re-excision did not influence IBTR. ER expression also had no statistical association with IBTR.

Actuarial IBTR vs Margin width

The actuarial IBTR rates at 5 and 10 years for a margin width of 1-2mm were 0.092 (95% CI +/- 0.065) and 0.092 (95% CI +/- 0.065) respectively and for a margin >2mm were 0.083 (95% CI +/- 0.031) and 0.134 (95% CI +/- 0.047) respectively. The Odds Ratio (for Overall IBTR) for 1-2mm vs >2mm was 0.776 (95% CI 0.333-1.811, P=0.558).

The rates for invasive IBTR at 5 and 10 years for margin widths of 1-2mm were 0.025 (95% CI +/- 0.033) and 0.025 (95% CI +/- 0.033) respectively and for >2mm were 0.038 (95% CI +/- 0.022) and 0.061 (95% CI +/- 0.031). The Odds Ratio of an invasive – IBTR for 1-2mm vs >2mm was 0.503 (95% CI 0.113-2.239, P=0.367)

DCIS IBTR rates at 5 and 10 years for 1-2mm were 0.068 (95% CI +/- 0.059) and 0.068 (95% CI +/- 0.059) and for >2mm were 0.048 (95% CI +/- 0.024) and 0.078 (95% CI +/- 0.039). The Odds Ratio of DCIS - IBTR for 1-2mm vs >2mm was 1.014 (95% CI 0.369-2.791, P=0.978).

IBTR and Radiotherapy

There was no significant difference in IBTR rate between patients who did and who did not receive radiotherapy (p=0.777). The rates of IBTR for patients with margin widths of 1-2 vs >2mm for patients who had or did not have radiotherapy are shown in Figure 2. No patient with a margin width <1mm (0/5) developed IBTR in the group who had radiotherapy but 3 of the 5 patients with margin width <1mm who did not have radiotherapy developed recurrence. . No patients in this series died from breast cancer.

Other Factors

There was no association between DCIS grade and IBTR (p=0.765). There was an association between the presence of comedo necrosis and IBTR. There were 20 events in 266 patients who did not have comedo necrosis, compared with 24 events in 200 patients with comedo necrosis (p=0.049). There was no significant association between IBTR and age (p=0.780). There was a significant association between size and IBTR. Patients with smaller lesions <15mm had a significantly lower rate of IBTR compared with patients with larger lesions (p=0.0001) [Figure 3]. There was also a significant association between Van Nuys Prognostic Index individual scores and IBTR (p=0.0001).

Cox Regression

The multivariate cox regression analysis included tumour grade, radiotherapy, tumour size, age, comedo necrosis, ER status, hormone treatment and margin width. Only DCIS size was found to be a significant predictor of IBTR (HR=2.731, 95% CI=1.564-4.769 p<0.0001).

DISCUSSION

The two meta-analyses performed on margin widths vs IBTR for invasive cancer and DCIS both showed that patients with involved margins have a significantly higher rate of IBTR than patients with negative margins [20, 21, 14]. A limitation of the DCIS meta-analysis was heterogeneity in margin definitions so that margin widths of >0mm and >1mm had to be combined. The aim of the current analysis was to provide data from a single-centre comparing radial margin widths of <1mm, 1-2mm and >2mm in patients having BCS for DCIS. This study concentrated on the radial margin because we have previously shown no excess of IBTR in patients with anterior or posterior margin width <1mm [23]. The current study has shown a radial margin width of 1 – 2mm was not associated with a higher rate of IBTR compared with a margin width of >2mm, odds ratio 0.776 (95% CI 0.333-1.811). This

result is important because the consensus statement that followed the meta-analysis concluded that a 2mm margin should be the standard in DCIS treated with BCS and whole breast irradiation [13]. Importantly, it states that clinical judgement should be used in determining the need for further surgery in patients with negative margins <2mm. Our study suggests that when performing BCS for DCIS there is a no need for radial margins of >2mm, but that 1mm is sufficient. Importantly, our analysis contains patients treated by BCS alone, and BCS plus radiotherapy and regardless of whether patients received radiotherapy, a 1-2mm margin produced identical rates of local recurrence to >2mm.

The meta-analysis of BCS in invasive cancer showed an odds ratio for IBTR of 1.74 (95% CI 1.42-2.15) for close margins compared with negative margins [20]. The odds of local recurrence was higher for >0 mm (i.e. no tumor on ink) relative to 5 mm (p=0.021) [20]. The consensus panel, having considered data from this meta-analysis and other expert advice concluded that margins of >0mm are sufficient to determine a negative margin when performing BCS for invasive cancer [8]. The disease that is most often closest to the margin in patients undergoing BCS for invasive disease is DCIS [22]. Having different margins for BCS for invasive cancer and for DCIS thus makes little biological sense. A 1mm radial margin for invasive cancer was confirmed as being sufficient in our recent study in invasive cancer [23]. The meta-analysis of BCS for invasive cancer also showed that 1mm is a sufficient margin for BCS in invasive cancer [20]. It makes biological and clinical sense to have a single margin width definition for BCS irrespective of whether the disease is invasive or *in situ.* Based on our data from the current and our earlier study [23] this margin width should be 1mm.

The current study is unique in that the distance from the DCIS to each margin was measured microscopically and treatment was consistent during study period. A potential weakness but also a potential strength of this study is that it is a single-centre study and although this study is small compared to the numbers in the meta-analysis the confounders of heterogeneity of definitions, margin measurement and variable treatments are not an issue in our study. Another potential advantage is that few patients received any systemic therapy so any effect of surgical margins on IBTR is likely to be amplified. Another strength is the consistent method of data collection and completeness of follow-up.

Patients were selected for radiotherapy based on known prognostic criteria such as grade and size so patients whose cancers were high grade, and were larger were significantly more likely to receive radiotherapy [Table 2]. It is well-known that radiotherapy reduces local recurrence by over 50% [24]. The current study shows that with selective use of radiotherapy it is possible to abrogate the known effect of DCIS grade and IBTR. A large US study showed advantages for radiotherapy in high risk lesions [25], and the benefits in terms of reducing IBTR and in particular invasive cancer development are clear in this study. Less than 40% of recurrences in our study were invasive and there have been no breast cancer deaths. This supports the concept of avoiding radiotherapy in lower risk women [26, 27].

Despite more women with larger lesions being treated with radiotherapy [Table 2], women with larger lesions were still more likely to develop IBTR. The relationship of size and IBTR is well recognised [28-30]. There were 21 patients who had DCIS >41mm treated by breast conserving surgery, but these patients did not do any worse than patients with DCIS measuring between 16 and 40mm. In our series of patients having mammaplasty for large

areas of DCIS there have been no recurrences [31]. BCS even for large areas of DCIS is thus an option and not all patients with large areas of DCIS require mastectomy. The current study confirms that individual Van Nuys Scores (even in the presence of selective radiotherapy) predict for IBTR [30]. As margin width grade and age did not predict for recurrence in the current study, it is likely that the presence or absence of comedo necrosis and size explains why in this dataset Van Nuys scores were significantly associated with IBTR.

In conclusion this study has shown no increase in local recurrence rates for radial margins of 1 – 2mm compared with margins >2mm. A radial margin width of 1mm appears sufficient for BCS for both invasive cancer and DCIS. There is no need for re-excision after BCS for invasive cancer or DCIS if the radial margin width is ≥1mm.

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TABLES AND FIGURES