**Title:** Importance of margin width and re-excision in breast conserving treatment of early breast cancer; a Danish breast cancer cooperative group study of 11,900 women

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**Body:** Background: The majority of women with invasive breast cancer are treated surgically by breast conserving surgery (BCS). A significant proportion subsequently undergo re-excision to obtain clear margins. However what constitutes a sufficient negative margin continues to be subject of controversy. The purpose of the study was to investigate the association between margin width and ipsilateral breast tumour recurrence (IBTR) as well as identifying factors associated with residual disease after repeat surgery, and to determine the effect of re-excision on IBTR in a population-based nationwide cohort.

Method: 11,900 patients treated with breast conserving therapy for unilateral invasive cancer in Denmark between 2000 and 2009 were included. All patients received whole breast irradiation and were offered systemic adjuvant treatment according to the guidelines of the Danish Breast Cancer Cooperative Group.

Results: The median follow-up was 4.9 years. The cumulative incidence of IBTR at 5 and 9 year was 2.4% and 5.9%, respectively. No decrease in IBTR with a wider negative margin compared to a narrow but negative margin was seen in adjusted analysis (>0-1 mm vs. 2-4 mm vs. ≥5 mm (reference): HR 1.54 (CI 95% 0.81-2.93) vs 0.95 (CI 95% 0.56-1.62) vs. 1). A final positive margin did however increase the risk of IBTR (HR 2.51; 95% CI 1.02-6.23). Other factors associated with increased IBTR were young age (HR 3.10; 95% CI 1.89-5.10), more than 4 positive lymph nodes (HR 1.80; 95% CI 1.24-2.62), and re-excision (HR 1.53; 95% CI 1.16-2.02). Receiving chemotherapy (HR 0.45; 95% CI 0.33-0.61) or boost (HR 0.43; 95% CI 0.31-0.60) reduced risk of IBTR as did being oestrogen receptor positive treated with (HR 0.35; 95% CI 0.25-0.49) or without (HR 0.43; 95% CI 0.31-0.60) adjuvant endocrine therapy.

Within two months of initial BCS 1342 women (11%) had a re-excision. Residual disease was found in 20% of re-excisions. In adjusted analysis DCIS outside the invasive tumour (OR 2.69; 95% CI 1.99-3.63), positive initial margin (OR 2.26, 95% CI 1.70-2.99, p<0.001), and age <50 years (OR 1.53; 95% CI 1.00-2.31) was associated with increased risk of residual disease. Patients with residual disease after re-excision had in the adjusted analysis an increased risk of ipsilateral breast tumour recurrence (IBTR), regardless of whether residual findings were invasive carcinoma (HR 2.97, CI 95% 1.57-5.62) or DCIS (HR 2.58, CI 95% 1.50-4.45). However no difference was seen for overall survival comparing one procedure with repeat surgery with or without residual disease (p=0.96).

Conclusion: An overall low rate of IBTR was seen. While a final positive margin was associated with a more than two-fold risk of IBTR, no evidence of improved local control was found with wider negative margins compared to narrow. However the finding of residual disease at re-excision was associated with an increased risk of IBTR.