Material and Methods: Patients underwent tumorectomy followed by whole breast irradiation of 50 Gy with 2 Gy per fraction. Patients having a microscopically complete excision (N = 5318) received no boost or a 16-Gy boost, while patients with a microscopically incomplete excision received a boost dose of 10 or 26 Gy (N = 251). In a subgroup of 1725 patients with central pathology review, clinical and pathologic characteristics were evaluated in relation to final margin status (FMS) including age, tumor size, volume of excision, receptor status, histology, and use of adjuvant systemic therapy. In the study population, the FMS was negative in 73% (n = 1162), positive in 6% (n = 102), and close (<2 mm) in 21% (N = 332) of patients respectively.

Results: The 10 year cumulative risk of ipsilateral breast tumor recurrence (CR-IBTR) was 10.2% vs. 6.2% for the no boost and the boost group, respectively (P < 0.0001). The hazard ratio for local recurrence was 0.59 (0.46−0.76) in favour of the boost. The absolute risk reduction at 10 year per age group was the largest in patients 40 years or less: 23.9% to 13.5% (P = 0.0014). In a subgroup analysis of patients with central pathology review, the 10 year CR-IBTR was 6%, 8% and 11% for negative, close and positive margin involved with invasive carcinoma (IC) respectively (P = 0.24). For margins involved with ductal carcinoma in situ (DCIS) the 10 year CR-IBTR was 8%, 10%, 14% for negative, close and positive margin groups respectively (P = 0.02). The 10 year CR-IBTR was 4% vs. 13% for the no boost vs the boost groups for patients with margins involved with IC (P = 0.0001). For margins involved with DCIS the 10 year CT-IBTR was 6% vs. 15% for the no boost vs. boost groups (P = 0.0001). In a multivariable analysis of local control, an IC tumor of grade 3 (P = 0.0004, HR2.01) and presence of DCIS (P = 0.05, HR 1.40) were associated with an increased risk of local failure.

Conclusions: Young age is the most important risk factor. High grade of invasive tumor and/or DCIS is a more significant risk factor than margin status. A boost dose of radiation ameliorates the effects of involved margins and significantly lowers the risk of IBTR in patients with high risk features.

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DCIS with close or focally involved margins following breast-conserving surgery (BCS): reexcision or radiotherapy with boost?

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Background: In patients (pts) treated with BCS and radiotherapy for DCIS, additional surgery (reexcision or mastectomy) is recommended when margins are narrow or involved. We investigated whether, in patients with DCIS and close (<2 mm) or focally/minimally involved margins, an additional radiation dose to the tumor bed could avoid secondary surgery.

Patients and Methods: This study included 208 women with DCIS of the breast treated with BCS between 1992 and 2002 and found to have close (<2 mm) (89 pts) or involved margins (119 pts). Only cases with focally (<1 mm) or minimally (1−15 mm) involved margins were included. Sixty-one pts (29%) underwent a re-excision (REEX) followed either by whole breast irradiation (55 pts) or by mastectomy for persistent margin involvement (6 pts). The other 147 pts (71%) received breast irradiation (RT) with a boost to the tumor bed, without re-excision. Comparisons of clinical and histological features were done using a chi-square or Fisher's t-test. Event rates were determined with Kaplan–Meier estimates, and comparisons of outcome were performed with a log-rank test.

Results: Median age of the whole group was 53 yrs (28−82). Only 7 pts (3.4%) had less than 41 years. The rate of involved margins was lower in the RT group than in the REEX group (50% vs 74%, respectively, p = 0.0019). All other clinical and histological features were comparable between both groups. Median whole-breast radiation dose was 50 Gy in both groups. Median total doses to the tumor bed were 67 Gy (45−77) in the RT group and 60 Gy (46−74) in the REEX group (p < 0.0001). Among the 61 re-excised pts, 56% had residual DCIS and 6% had invasive cancer. Median follow-up was 89 months (5–180). Seven-year local failure rates were 9.3% in the RT group, and 9.6% in the REEX group (ns). Recurrence rates were not influenced by age, margin status, necrosis or nuclear grade. No differences in survival and metastasis-free survival were observed. Seven-year breast preservation rates were 91.4% and 82.8% (p = 0.017).

Conclusions: This retrospective analysis of 208 pts with DCIS treated in a single institution strongly suggest that, in carefully selected pts with close (<2 mm) or focally/minimally involved margins, reexcision could be avoided and satisfactory local control achieved with increasing radiation dose to the tumor bed. Because of the limited data available, this should concern only patients older than 40 years. These results need to be confirmed on independent series.

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Invasive lobular cancer and re-do surgery – extent of the problem!

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Background: Invasive lobular cancer (ILC) is the second commonest form of breast cancer after invasive ductal cancer, accounting for 10−14% of cases.

Standard imaging in the triple assessment pathway of a suspicious breast lesion will consist of mammography and/or ultrasound. However these modalities can underestimate the extent of ILC and lead to inappropriate selection of breast-conserving surgery, and a subsequent requirement for completion mastectomy or re-excision of margins to achieve adequate clearance. There is a growing trend for patients diagnosed with ILC to have a dynamic contrast-enhanced MRI as part of the pre-operative investigative work-up. MRI offers greatly improved staging accuracy but is associated with disadvantages of cost, difficulty in rapid access and false positives which may lead to investigative delay.

We retrospectively analyzed the management of patients diagnosed with ILC to assess the need for this extra imaging modality prior to surgery. A low re-excision rate would question its need.

Materials and Methods: All ILC patients who underwent primary breast surgery over a five-year period, in two district general hospitals (DGH's) in the south-east of England were identified. Patients underwent either wide local excision & axillary dissection (WLE+AxD) or formal mastectomy (MAST) as per multi-disciplinary team decision. If margin involvement was found, subsequent re-excision of margins (REM) or completion mastectomy was performed.

Histological data was analysed to determine type of surgery, tumour size, grade, multicentric, multifocality, ER&PR status, number of lymph nodes involved and margins of excision.

Results: 186 patients with ILC were treated by primary surgery (92 in DGH A and 94 in DGH B). Histology confirmed 149 ILC's, 34 mixed and 3 bilateral ILC's. The average tumour size was 23.9 mm. With regard to tumour grade, 16 cases were histologically grade I, 152 cases were grade II and 18 cases were grade III tumours. Three patients had multicentric disease and 42 had multifocal disease.

112 patients (60%) underwent (WLE+AxD) while 8 patients (4%) had WLE only. 66 patients (35%) had primary mastectomy. In the breast conserving group, 12 patients (10%) required re-excision of margins and 27 patients (23%) required a completion mastectomy. Overall revision surgery rate was noted to be 32.5%.

Conclusion: Our results show a high rate of breast re-do surgery in a bid to achieve disease clearance. MRI is known to improve staging and may substantially reduce the re-excision and completion mastectomy rate. A prospective audit is being carried out to assess the use of MRI in all patients with ILC to aid staging and reduce the burden associated with re-do surgery.

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The role of radiotherapy in the local control of lobular breast cancer

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Background: Results of subgroup analyses of randomized clinical trials have raised questions about the role of radiotherapy after mastectomy for invasive lobular breast cancer.

Patients and Methods: Between January 1995 and December 2002 4947 patients were diagnosed with breast cancer in the South-Eastern part of the Netherlands, of whom 969 had ILC or mixed (with a ductal component) ILC (19.6%). After exclusion of patients with previous invasive (breast) cancer, synchronous bilateral, multicentric, locally advanced or metastatic breast cancer, 805 remained available for analysis. Of these patients, 416 underwent lumpectomy with radiotherapy (L with RT), 217 mastectomy without (M without RT) and 172 mastectomy with radiotherapy (M with RT) to the chest wall and/or regional nodal areas. Complete follow-up was obtained for more than 95% of the patients.

Results: During follow-up 41 patients developed a local recurrence, of which 35 were isolated events at the time of diagnosis. The 5-year actuarial local recurrence rates for the three patient groups are presented in the Table. Despite their more favourable tumour stage, the patients undergoing M without RT had a significantly higher risk of local recurrence than the patients undergoing M with radiotherapy. A multivariate analysis, taking into account differences in tumour size, nodal status, age and adjuvant systemic treatment between the patient groups, showed that the local recurrence risk was almost 3 times lower for the patients undergoing M with RT than for the patients who underwent M without RT (HR: 0.35; 95% CI: 0.13−0.94). The risk of local recurrence in patients undergoing L with RT was not affected by the presence of positive surgical margins, neither in the univariate analysis nor after adjustment for age, tumour stage and adjuvant systemic treatment.

Table. 5- and 8-year actuarial local recurrence rates in patients with invasive lobular breast cancer (Kaplan–Meier method) according to treatment

Follow-up	Treatment					
	L with RT (n = 416)		M with RT (n = 172)		M without RT (n = 217)	
	%	(95% CI)	%	(95% CI)	%	(95% CI)
5-years	3.5	(2.5−4.5)	2.0	(0−4.4)	9.1	(4.9−13.3)
8-years	6.4	(4.7−8.0)	4.0	(0−8.6)	9.8	(5.4−14.2)
P-value (logrank)	L+RT vs. M with RT: P = 0.44		L+RT vs. M without RT: P = 0.03		M without RT vs. M with RT: P = 0.02	

M = mastectomy; L = lumpectomy; RT = radiotherapy.

Conclusions: Patients with invasive lobular breast cancer whose surgical treatment is followed by radiotherapy have a very low risk of local recurrence. This low risk of local is considered to be a reflection of high sensitivity of lobular carcinoma to radiation. Radiotherapy techniques may also have become more accurate and effective in eradicating microscopic disease.

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Long-term cosmetic changes after breast conserving therapy for patients with stage I and II breast cancer treated in the EORTC "boost versus no boost" trial

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Background: A 16 Gy boost dose results in a better local control but also negatively affects early cosmetic outcome after breast conserving therapy for early breast cancer (Vrieling e.a., Int. J. Radiation Oncology Biol. Phys. 1999; Bartelink e.a., J. of Clinical Oncology 2007). The purpose of this study is to investigate the change in cosmesis 3-, 6- and 9 years after treatment.

Material and Methods: We collected pictures of the breasts from patients participating in the "Boost versus no Boost" trial treated in Tilburg and Utrecht. In this trial pictures were made before radiotherapy and every three years during follow-up. Digitalized pictures were analyzed using specific software (BCCT.core) that enables quantification of seven features (pBRA = change in nipple position, pLBC = change in level of lower breast contour, pUNR = change in nipple level, pBCE = change in distance from nipple to inframammary fold, pBCD = change in length of breast contour, pBAD = change in area of the breast, pBOD = change in non overlapping area between left and right breast), all associated with fibrosis (Cardoso e.a., Artif Intell Med 2007). Changes in the size of the treated breast were quantified and both breasts were compared. We performed a multivariate analysis on the results of these measurements.

Results: We retrieved 1403 sets of photographs from 347 patients with a minimum follow-up of 6 years: 169 randomized to the no boost-arm, 178 to the boost-arm. A continuous increase in time for all seven features was noted. The cosmetic outcome worsened more in the boost- than in the no boost-arm. The difference of the evolution between the two arms was statistically significant for pBRA, pLBC, pUNR, pBCD, and pBOD. In the multivariate analysis, using features representing the most relevant changes of size and shape of the breast (pBRA, pLBC, pBOD), applying a boost, postoperative complications and a maximum dose of >55 Gy in the border plane for whole breast irradiation were significantly associated with a worse cosmetic outcome.

Conclusions: We noted a significant worsening with time after treatment for 5 of the 7 features used for measuring changes in cosmetic results after breast conserving therapy for early breast cancer. In the multivariate analysis boost treatment, postoperative complications and a maximum dose of >55 Gy for whole breast irradiation were significantly associated with worsening of the cosmetic outcome during follow-up up to 9 years.

Thursday, 17 April 2008 12:30–14:30

POSTER SESSION

Locally advanced and recurrent disease

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Clinical activity of the novel epothilone B analog, ixabepilone, in triple negative breast cancer (BC) patients

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Background: Despite advances in BC treatment, many women experience progressive disease secondary to primary or acquired resistance, which may occur from the earliest stage of disease. Ixabepilone, a semi-synthetic analog of epothilone B, is the first member of a new class of antineoplastic agents, developed to have less susceptibility to tumor resistance mechanisms. Patients (pts) with ER/PR/HER2-negative (triple-negative, TNeg) BC has an aggressive clinical course with significant risk of systemic relapse and subsequent poor prognosis, TNeg BC patients have fewer treatment options than those with receptor-positive tumors. We report activity of ixabepilone in several settings of BC in the triple negative sub-set patient population.

Material and Methods: Ixabepilone has been administered as monotherapy, 40 mg/m^2 iv over 3h on day 1 q 3 wks, as well as at the same dose in combination with capecitabine, 2000 mg/m^2 po on days 1−14.

Data on triple negative sub-set are presented from 5 phase II studies including neoadjuvant and metastatic BC (MBC) setting and from a phase III trial of pts with anthracycline/taxane-resistant MBC.

Objectives: response rate (ORR), progression free survival (PFS) and main adverse events (AEs) were reviewed.

Results: See the tables.

In all studies from neoadjuvant to heavily pretreated metastatic disease, the safety profile was comparable between TNeg and Non-TNeg pts., neuropathy was mostly sensory, cumulative and reversible (incidence of G3 ranged from 3% in the neoadjuvant population to 21% in anthracycline/taxane-pretreated disease).

Conclusion: Ixabepilone has consistently demonstrated antitumor activity in patients with TNeg BC, both as monotherapy and in combination with capecitabine, from neoadjuvant to multiple resistant MBC.

Phase II	Status	N	ORR %	pCR %
Neo-adj (080) n = 161	TNeg	42	64%	26%
	No- TNeg	119	60%	15%
Taxane resistant MBC (009) n = 49	TNeg	18	6%	
	No- TNeg	31	16%	
Taxane pretreated MBC (010) n = 65	TNeg	11	55%	
	No- TNeg	65	39%	
TAC resistant MBC (081) n = 126	TNeg	42	12%	
	No- TNeg	84	11%	

* evaluated by Independent Radiological Committee.
TAC, Taxane–anthracycline–capecitabine.