Conclusions: Even after long-term follow-up no significant difference in either TDM or OS between BCT plus radiotherapy and MRM was found, confirming the safety and efficacy of the former as a treatment for breast cancers up to 5 cm.

212 Proffered paper oral

Radio-guided Occult Lesion Localisation (ROLL) Versus Wire-guided Localisation (WGL) in Breast Conserving Surgery for Non-palpable Breast Cancer (ROLL Study): a Randomised Clinical Multicenter Trial

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Background: For the management of non-palpable breast cancer, accurate pre-operative localisation is essential to achieve complete resection with acceptable cosmetic results. Radio-guided occult lesions localisation (ROLL) uses the radiotracer, injected intra-tumourally for sentinel lymph node identification, to guide surgical excision of the primary tumour. In a multicenter randomised controlled trial, we determined if ROLL is superior to the standard of care (i.e. wire guided localisation, WGL) for preoperative tumor localisation.

Methods: Women (>18 yrs.) with histologically proven non-palpable breast cancer and eligible for breast conserving treatment (BCT) with sentinel node procedure were randomised to ROLL or WGL. Patients allocated to ROLL received an intra-tumoural dose of 120 Mbq Technetium^{99} nanocolloid. Guided by a gamma detection probe, the primary tumor was surgically removed together with the sentinel node(s). In the WGL group, patients received a similar intra-tumoural or peri-aureolair dose of technetium in order to allow sentinel node biopsy. Ultrasound or mammography guided insertion of a hooked wire provided surgical guidance for excision of the primary tumour. Primary outcome measures were the proportion of complete tumour excisions (i.e. with negative margins), the proportion of patients requiring re-excision and volumes of tissue removed. Data were analyzed according to intention to treat principle.

Results: Three hundred and fourteen patients with 316 invasive breast cancers were enrolled. Complete tumour removal with negative margins was achieved in 140 (86%) patients in the ROLL group versus 134 (88%) ($p = 0.644$) patients in the WGL group. Re-excision was required in 19 (12%) of patients in the ROLL group versus 15 (10%) ($p = 0.587$) in the WGL group. The volume of the ROLL specimens was significantly larger than that of the WGL specimens (71 vs. 64 cm^3, $p = 0.017$). No differences were seen in the duration and difficulty of the radiological and surgical procedures, the success rate of the sentinel node procedure, and cosmetic outcome.

Conclusion: With this multicentre randomised controlled comparison, the first of its kind in patients with histologically proven breast cancer, we demonstrate that ROLL is not superior to WGL in terms of complete tumor excision and re-excision rates and that ROLL leads to excision of larger tissue volumes.

Thursday, 22 March 2012 15:30–17:00

CLINICAL SCIENCE SYMPOSIUM

The Management of Pre-Invasive Breast Cancer

213 Invited

Magnetic resonance imaging of DCIS and high-risk borderline lesions

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Magnetic resonance imaging (MRI) is the most relevant new imaging technique which emerged in breast cancer care in the last twenty years, opening a new window for diagnosing this disease. The base for MRI lesion detection is the ability to reveal neoangiogenes using dynamic image acquisition before/after intravenous administration of gadolinium-based contrast material. Thus, in the past years, MRI was considered highly sensitive (>90−95%) for invasive cancers but of limited value for detecting DCIS (60−70%). However, this view was determined by the fact that study populations were essentially composed of series of DCIS diagnosed with mammography thanks to the detection of clustered microcalcifications. When this bias was corrected using not only mammography as an entry criterion, MRI showed to be more sensitive than mammography for detecting DCIS (92% versus 56%), in particular when high-grade DCIS were considered (92% versus 48%). Moreover, differently from invasive cancers mainly appearing as 'mass-like' lesions, an important fraction of DCIS are detected on MRI as 'non-masslike' lesions, showing linear, ductal, segmental, regional, or focal distribution, typically non detectable without contrast material administration. Conversely, the dynamic behavior is not relevant fro DCIS, due to a high frequency of continuous increase (type 1) curve which might be falsely interpreted as benign. A peculiar mechanism explaining DCIS enhancement at MRI has been recently investigated: a third compartment for contrast material biodistribution other than the intravascular and interstitial ones, i.e. the intraductal space. This strengthens the higher importance of a high spatial resolution (<1 mm square) in comparison with temporal resolution, for contrast-enhanced state-of-the-art breast MRI. Obviously, sensitivity is depending on the reference standard. When the 5-mm sliced whole breast is used as reference standard and all small foci of DCIS are considered, either MRI or mammography show sensitivity lower than 50%. The role of MRI for preoperative evaluation of DCIS is under discussion. Even though MRI is the most sensitive technique for evaluating tumor extent, under- and overestimation are possible and high-quality research is needed to clearly establish its preoperative role. The transmission of three-dimensional data sets from the radiologist to the surgeon is one of the key steps, also taking in consideration that the woman is studied with MRI in prone position but is operated in supine position. Recent studies have also showed a potential relevant clinical application of MRI in ruling in or out malignancy in the peculiar setting of lesions of uncertain malignant potential (so-callede high-risk or borderline, B3 lesions) found at core needle biopsy under mammographic (stereotactical) or ultrasound guidance. Using the simple criterion of presence or absence of contrast enhancement, MRI shows a negative predictive value of 97% (undetecting only low-grade DCIS), allowing for a reliable exclusion of invasive cancers among high-risk lesions diagnosed at needle biopsy. In such a way, a rational use of MRI for strongly reducing the number of surgical procedures in this setting is proposed.

214 Invited

Surgery in relation to DCIS biology

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The key aim of surgery for ductal carcinoma in situ (DCIS) is to prevent ipsilateral invasive recurrence (mortality from breast cancer at 15 years is less than 1%).

The goal of surgery for DCIS is to ensure clear surgical margins of greater than 1 mm and to preserve cosmesis. Margin involvement occurs in 25-30% of DCIS undergoing breast conserving surgery leading to re-excision or mastectomy. DCIS size greater than 3cm multifocality, premenopausal status, oestrogen receptor positivity and comedo type, increases margin involvement at excision. A 12-gene Recurrence Score predicts ipsilateral recurrence, identifying a small group (10% of women) after wide local excision (WLE) with a 19% invasive and 27% overall recurrence who should potentially have mastectomy from the outset.

DCIS may be a function of cancer stem cell (CSC) activity. High grade DCIS produces more CSC and expresses more EGF family ligands. CSC are increased by endocrine treatments. In vitro and in vivo models indicate HER tyrosine kinase and NOTCH inhibitors prevent CSC formation and reduce growth.

Oestrogen receptor (ER) positive DCIS in postmenopausal women responds to preoperative endocrine manipulation with a fall in proliferation and significant pathological changes. Limited data indicate a reduction in DCIS size occurs on primary endocrine therapy which lowers the risk of margin involvement. Further studies of primary medical therapy for up to 6 months before surgery are required in ER positive DCIS.

Combining endocrine therapy and anti-CSC strategies will be potentially more effective in preventing local recurrence. Future randomised trials need to identify which DCIS lesions can avoid surgery (or radiotherapy) by primary endocrine therapy.

215 Invited

Radiotherapy in Relation to Biology

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DCIS is considered a precursor to invasive ductal carcinoma and its treatment is ultimately therapy for prevention of local recurrence (LR),

particularly invasive LR. An overview of all four of the randomised trials that compared adjuvant whole breast radiotherapy (RT) vs no RT after breast-conserving surgery for DCIS showed that RT halved the LR rate [1]. It reduced the absolute 10-year intraductal or invasive LR risk by 15.2% (12.9% vs 28.1%, 2P < 0.00001). RT was effective irrespective of age, detection method, focality, tumour size, architecture, grade, comedonecrosis, margin status or tamoxifen use. However, there was no significant effect on breast cancer mortality or all-cause mortality.

Currently, there are no reliable predictors for invasive LR and published data is limited to identification of surrogate markers for clinical outcome. There is a consistent association between younger age and an increased LR risk. High nuclear grade and presence of comedonecrosis are strongly associated with LR and progression to invasive disease. In addition, large tumour size and involvement of surgical margin are associated with LR but the optimal margin size remains controversial. Molecular markers including oestrogen receptor status, HER2/neu oncogene over-expression and p53 tumour suppressor gene mutation have not been reliably associated with LR risk. Approaches derived from global molecular profiling are being investigated for predictive assessment of recurrence.

A principal aim of DCIS research is to determine robust biomarkers to identify women at high risk from those at lower risk of invasive LR, and enable individualised treatment. A single-arm prospective study reported a 5-year LR rate after breast-conserving surgery, without RT of 6.1% in patients with low or intermediate grade DCIS $\leqslant$25 mm in size and resected with margins $\geqslant$3 mm, and 15.3% in patients with high grade DCIS $\leqslant$10 mm [2] Further research on biomarkers may enable more reliable identification of patients who have low absolute risk of LR and for whom RT may provide little absolute gain. In contrast, patients at higher risk of LR may benefit from more extensive surgery and/or RT. The addition of a tumour bed boost to whole breast RT to further reduce LR rate is being investigated in a clinical trial.

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216 Invited

The Pathology of DCIS: Take it or Leave it

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Incidence rates of ductal carcinoma in situ (DCIS) have increased over the past decades largely due to population-based screening for breast cancer. However, data from 1987 to 1999 indicate that invasive ductal carcinoma incidence rates have remained essentially constant. On pathological examination, a subgroup of neoplastic low grade intraductal lesions is even more low risk than classical cribriform ductal carcinoma in situ grade 1 with a cumulative risk on progressive disease of 0.5−1.0% per year, a risk that is comparable to developing local recurrence after breast conserving therapy. These lesions share the same histogenetic alterations and are diagnosed by a variety of terms covering a spectrum of morphological slightly different lesions ranging from columnar cell change to cribriform ductal carcinoma In situ grade I. Within this spectrum, a variety of diagnostic definitions have been proposed like atypical ductal hyperplasia, flat epithelial atypia, columnar alterations with prominent snouts and secretions (CAPSS), etc., etc. Nevertheless, one of the major challenges remains, I.e. the substantial interobserver variation in diagnosing these low risk, low grade intraductal neoplastic lesions.

In current practice, most women undergo surgery to excise the high end of the risk spectrum, i.e. the unambigious DCIS grade I lesions, regardless of extensiveness and patient's features, such as age and co-morbidity, to exclude that the core biopsy was containing just the tip of the iceberg. For the more ambigious lesions, patient management can vary enormously due to different opinions and interpretations of the multidisciplinary breast team. Most likely, the majority of women with such a lesion would not benefit from surgery due to the low risk of developing extensive DCIS and/or invasive ductal carcinoma. In addition, if lesions do develop from a low grade in situ component, these are almost always well differentiated, small sized, hormone receptor positive, HER2 negative invasive carcinomas with an exceptionally favorable prognosis. In fact, the risk of dying due to the disease might not be significantly higher than in the non affected population. It is therefore unsure whether surgical excision (followed by radiotherapy in case of breast conserving treatment) of such lesions can be considered as adequate treatment or overtreatment. To solve this issue, proper follow-up of patients with such lesions without surgical intervention is required to justify either surgery or a watchful waiting policy.

217 Proffered paper oral

Adjuvant Radiotherapy After Breast-conserving Surgery for Ductal Carcinoma in Situ − Fifteen-year Results of the EORTC Randomized Phase III Trial 10853

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Background: The incidence of ductal carcinoma in situ (DCIS) has increased in the last decades due to mammographic screening and accounts currently for 25% of the new breast cancers. We present the 15-years results of a randomized controlled trial that investigated the role of adjuvant radiotherapy (RT) after a local excision (LE) for DCIS.

Patients and Methods: Between 1986 and 1996, 1010 patients with a complete excision of DCIS <5 cm were randomized to no further local treatment or RT (50 Gy in 25 fractions to the whole breast).

Results: After a median follow up of 15.8 years, radiotherapy continued to reduce the risk of a local recurrence (LR) (HR = 0.52; 95% CI = 0.40–0.68): the LR free rate was 69% in the LE arm, which was increased to 82% in the LE+RT arm. There were comparable reductions in the incidence of a *DCIS* LR (HR = 0.49; 95% CI = 0.33–0.73) and an *invasive* LR (HR = 0.49; 95% CI = 0.33–0.73). The 15-years cumulative incidence for LE alone compared to LE+RT for *DCIS* LR was 14.9% versus 7.5% respectively, and for an *invasive* LR this was 15.5% vs. 9.8% respectively.

When the hazard rate of a LR was analysed within three time windows (0−5, 5−10 and from 10 year onwards), this was estimated as 2.0% (95% CI = 1.4−2.6) during the first 5 years in the group receiving RT and 4.0% (95% CI = 3.2−4.8) in the group treated only with LE, 1.2% (95% CI = 0.8−1.7) and 2.0% (95% CI = 1.4−2.8) respectively in the next five years, and 0.6% (95% CI = 0.4−1.0) and 1.3% (95% CI = 0.8−1.9) respectively from 10 year onwards. The protecting effect of RT on a *DCIS* LR was similar throughout all time frames, the effect of RT on an *invasive* LR was observed mainly in the first 5 years after treatment.

The differences in LR in both arms did not lead to a difference in distant metastasis (HR = 0.99, 95% CI = 0.61–1.61) or death (HR = 1.02; 95% CI = 0.71–1.44).

Women with a *DCIS* LR had a similar survival prognosis after the event as compared to those without a LR. However, after an *invasive* LR their prognosis was significantly worse as compared to the non-recurring patients; this is reflected by a HR of 5.2 (95% CI = 3.1−8.7) for overall mortality and a HR of 17.7 (95% CI = 8.9–35.2) for breast cancer related mortality.

Conclusion: At 15 years, almost 1 in 3 women developed a LR after LE for DCIS. RT reduced this risk by 50%, equally divided over *invasive* or *DCIS* recurrences. The majority of the LRs occurred within five years after treatment; radiotherapy seemed to have a continuous protecting effect with respect to *DCIS* recurrence; but only a temporary protecting effect with respect to *invasive* recurrences in the first 5 years after treatment. Although no survival difference was seen between the two treatment groups, women who experienced an invasive recurrence had a significant worse survival compared to women who had a DCIS recurrence or no recurrence at all.

Thursday, 22 March 2012 15:30–17:00

CLINICAL SCIENCE SYMPOSIUM

Barriers to Effective Care

218 Invited

External Barries to Effective Care in Clinical Research

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Therapeutic drug development in oncology has reached new heights in recent years with the emergence of targeted agents. More than 20 years on from the development of trastuzumab to treat HER2+ breast cancer, clinicians still only have limited registered therapeutics for treatment i.e. trastuzumab and lapatinib. This phenomenon is not specific to breast