207 Proffered paper oral

70-Gene Signature Prospectively Predicts Prognosis of Patients with Node-negative Breast Cancer: 5 Year Follow-up of the RASTER Study

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Background: The 70-gene signature (MammaPrint®) has been developed to predict the risk of distant metastases in the first 5 years after diagnosis.

Methods: Clinical follow-up was updated for 427 patients with primary breast carcinoma (clinical T1−3N0) who had participated in the microarRAy prognoSTics in breast cancER study and for whom a 70-gene signature had been obtained. Concordance between risk predicted by the 70-gene signature and risk predicted by Adjuvant! Online (AOL) (10-year survival probability <90% was defined as high risk) has been assessed previously. Other endpoints of the RASTER study reported here were distant disease-free survival (DDFS) and distant recurrence free interval (DRFI). Adjuvant systemic treatment decisions were based on the restrictive 2004 Dutch guidelines, the 70-gene signature outcome, and doctors' and patients' preferences.

Findings: The median follow-up was 62 months. In the 70-gene signature low risk group 15% (33/219) of the patients had received adjuvant chemotherapy, versus 81% (169/208) in the 70-gene signature high risk group. In 161 patients the result of the 70-gene signature and AOL were discordant. The 5-years follow-up results defined by the MammaPrint, AOL risk groups and adjuvant systemic therapy use are shown in the table.

70-gene signature	AOL	Endocrine therapy	Chemotherapy	5-year DDFS (%) (95% CI)	5-year DRFI (%) (95% CI)
Low	Low	7/95 (7%)	3/95 (3%)	94.3 (90−99)	95.3 (90–100)
High	Low	29/37 (78%)	21/37 (57%)	94.6 (88–100)	100 (100–100)
Low	High	53/124 (43%)	30/124 (24%)	97.6 (95–100)	98.4 (96–100)
High	High	93/171 (54%)	148/171 (87%)	88.7 (84−94)	89.8 (85−95)

In the group that did not receive any adjuvant systemic treatment (chemotherapy nor endocrine therapy) the 70-gene signature low risk − AOL low risk group (n = 88) had a DDFS of 95.0% (95% CI 90–100) The 70-gene signature low risk − AOL high risk group (n = 70) had a DDFS of 100%.

Interpretation In a prospective community-based observational study, the 5-year DDFS and 5-year DRFI probabilities confirmed the additional prognostic value of the 70-gene signature to clinico-pathologic factors used in AOL risk estimations. If in a comparable cohort diagnosed today the 70-gene signature would be added to standard guidelines used to select patients for adjuvant systemic therapy, a reduction of 29% in the use of adjuvant chemotherapy would be seen. Omission of chemotherapy as judged appropriate by doctors and patients and supported by a low risk 70-gene signature test appeared indeed safe.

Thursday, 22 March 2012 15:30–17:00

CLINICAL SCIENCE SYMPOSIUM

Controversies on Breast Cancer Treatment/Breast Conservation

208 Invited

Imaging in Breast Conservation

Abstract not received.

209 Invited

Radiotherapy in Breast Conservation

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The 2011 systematic overview of radiotherapy effects by the Early Breast Cancer Trialists' Collaborative Group reported retrospective analyses that identify women >60 years with pT1G1ER+pN- invasive carcinomas treated by breast conservation surgery and tamoxifen without radiotherapy as a subgroup with <10% local relapse at 10 years. This raises the question whether the benefits of standard whole breast radiotherapy outweigh the late adverse effects in this subgroup that is well represented in mammographically screened populations. A second controversial issue relates to 2010 guidelines for partial breast radiotherapy (PBRT) developed by professional bodies in North America and Europe that identify subgroups of women regarded as suitable for PBRT in a non-research context mainly on the basis of single arm studies. A third controversy relates to women at high local relapse risk after breast conservation surgery despite current standard therapies, especially young women with high grade (often ER−) tumours, for whom more effective dose escalation is needed. In this group, intensity modulated radiotherapy may be capable of matching dose intensity more effectively to the risk and location of local relapse. One approach involves combining reduced fraction size and reduced dose intensity outside the index quadrant with larger fraction sizes and higher dose intensities inside the index quadrant. Stratification of dose intensity based on predictive biomarkers of tumour response to radiotherapy represents a fourth controversial topic, based on suggestions that ER+ tumours are more likely to be controlled by radiation than ER− tumours. Finally, residual controversies in hypofractionation focus on its suitability for subgroups under-represented in current randomised trials. There is a risk that beneficial treatments are withheld on the basis of spurious concerns about the generalisability of trial results. If a particular hypofractionated schedule is proven safe and effective after breast conservation surgery, why should it need independent testing before it is used for post-mastectomy radiotherapy?

210 Invited

Breast Conservation in Controversial Cases − Surgical Techniques

Abstract not received.

211 Proffered paper oral

Phase III Trial (EORTC 10801) Comparing Breast-conserving Therapy with Radical Mastectomy − Twenty Year Follow-up Results

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Background: The EORTC 10801 trial compared Breast Conserving Therapy (BCT), comprising of lumpectomy and complete axillary clearance followed by whole breast irradiation and a tumor bed boost, with Modified Radical Mastectomy (MRM) in patients with tumors up to 5 cm and both positive and negative axillary nodes. At 13 years follow up MRM demonstrated better local control, but this did not affect Overall Survival (OS) or time to distant metastases (TDM) as compared with BCT. This analysis reports on the 20-year follow-up results.

Materials and Methods: The trial accrued 868 eligible patients between 1980 and 1986, with 448 randomized to BCT and 420 to MRM. Tumors were 2.1−5 cm in 80% of the patients, and 40% of the patients presented with positive lymph nodes. Microscopic margin involvement was observed in 217 of the 448 patients in the BCT arm. Median follow-up was 22.1 years.

Results: Patients' clinicopathological features were similar within the treatment arms. There was no significant difference in the TDM ($P = 0.23$). Rates of distant metastases at 20 years were 42.6% (95% CI = 37.8–47.5%) and 46.9% (95% CI = 42.2–51.6%) in the MRM and BCT arms respectively. Similarly, there was no significant difference in OS ($P = 0.23$), estimated at 20 years as 44.5% (95% CI = 39.3–49.5%) and 39.1% (34.4–43.9%) respectively. After adjusting for clinicopathological features in a Cox proportional hazards model no significant difference in TDM (HR = 1.09; 95% CI = 0.89–1.33) or OS (HR = 1.11; 95% CI = 0.93–1.33) was found. Forty percent of the patients were aged less than 50. There was no indication of a difference by age group (<50 versus $\geqslant$ 50 years) in terms of TDM or OS for the 2 arms.

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),