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Systemic Treatment Decision Making for Patients with Stage I and II, Hormone Receptor Positive, Her2/neu Negative Breast Cancer

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Background: Oncotype DX is a clinically validated risk stratification tool that can predict the risk of recurrence and the benefit of adjuvant chemotherapy in women with hormone receptor positive (HR+), HER2/neu negative early stage breast cancer (EBC). This tool has been available to oncologists in Ontario since April 2010 at significant cost, yet no guidelines exist regarding their use. This retrospective chart review examined the factors that were associated with use of Oncotype DX at a tertiary care cancer centre.

Materials and Methods: One hundred patients (pts) diagnosed with HR+, HER2/neu negative EBC (stage I-II), who underwent Oncotype DX testing between April 1, 2010, and June 30, 2011 were included in the study. A second control group of 100 patients with similar disease characteristics but who did not receive Oncotype DX testing were randomly selected. Data collection included demographics, tumor staging and Adjuvant! Online recurrence risk scores.

Results: Median age in the Oncotype DX group was 58 years (r: 26−77) and 63 years (r: 30−81) in the control group. The Oncotype DX group and control group had 22/15 premenopausal pts, 6/4 perimenopausal pts, and 72/81 postmenopausal pts, respectively. 55, 34, and 4 pts had T1c, T2, and T3 tumors in the Oncotype DX group, respectively, vs 42, 28, and 1 pts in the control group. 10 pts in the Oncotype DX group had tumor cells in at least one lymph node vs none in control group. 80 pts in the Oncotype DX group had greater than grade 1 histology vs 56 in control group. Adjuvant! Online median recurrence risk was higher in the Oncotype DX group [19% (r: 9−48%) with tamoxifen (TAM), 15% (r: 7−38%) with TAM plus an aromatase inhibitor (AI)] than the control group [12% (r: 8−36%) with TAM, 10% (r: 7−29%) with TAM plus an AI]. The mean 10-year recurrence risk in the Oncotype DX group was 20% with TAM and 16% with TAM plus AI, vs 15% and 12% in the control group, respectively. Median Oncotype DX recurrence score was 17 (r: 0−70), with 10-year recurrence risk of 11% (r: 3−34%). Further statistical analysis will be performed.

Conclusions: This single-centre series is aimed at identifying potential clinical and pathological factors which can influence physicians' decision to request Oncotype DX testing for pts with EBC. These results will be used to design a prospective study evaluating these factors and how Oncotype Dx testing may influence treatment decision making.

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A Diagnostic Genetic Test for the Physical Mapping of Germline Rearrangements in the Susceptibility Breast Cancer Genes BRCA1 and BRCA2

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Background: the *BRCA1* and *BRCA2* genes are involved in breast and ovarian cancer susceptibility. About 2% to 4% of breast cancer patients with a positive family history who are negative for *BRCA1* and *BRCA2* point mutations can be expected to carry large genomic alterations (deletion or duplication) in one of the two genes, and especially *BRCA1*. However, large rearrangements are missed by direct sequencing. Molecular Combing is a powerful FISH-based technique for direct visualization of single DNA molecules, allowing the entire genome to be examined at high resolution in a single analysis. We have developed a novel predictive genetic test based on Molecular Combing. For that purpose, we designed specific *BRCA1* and *BRCA2* 'Genomic Morse Codes' (GMC), also covering the non-coding regions and including large genomic portions flanking both genes.

Material and Methods: high-resolution *BRCA1* and *BRCA2* Genomic Morse Codes (GMCs) have been designed. A GMC is a series of 'dots or dashes' (DNA probes with specific sizes and colors) and 'gaps' (uncolored regions located between the DNA probes), designed to physically map and define with a specific 'signature' a particular genomic region. For the *BRCA1* and *BRCA2* GMC design, all repetitive sequences were eliminated from the DNA probes, thus reducing background noise and permitting robust measurement of the color signal lengths within the two GMCs. Both GMCs were statistically validated on samples from 10 healthy controls and then tested on 10 breast cancer patients with a positive family history of breast cancer.

Results: large rearrangements, corresponding to deletions and duplications of one or several exons and with sizes ranging from 3 kb to 40 kb, were detected on both genes, including the characterization of 4 new mutations (for *BRCA1*: Del ex 3, Del ex 24 and Dup ex 5−7; for *BRCA2*: Dup ex 17−20). The nature of the identified large rearrangements was confirmed by high-resolution zoom-in aCGH (11 k) in the same patients, and the exact breakpoints of the new mutations characterized. Importantly, the developed GMC allowed to unambiguously localize several tandem repeat duplications on both genes, and to precisely map large rearrangements in the problematic Alu-rich 5′-region of *BRCA1*.

Conclusions: we propose the developed Molecular Combing genetic test as a valuable tool for the screening of large rearrangements in *BRCA1* and *BRCA2*, to be combined in clinical settings with an essay that allows the detection of point mutations.

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Tumor to Breast Volume Ratio as Measured On MRI: a Possible Predictor of Breast Conservation Surgery Versus Mastectomy

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Purpose: The surgical approach to breast cancer has changed dramatically in the past 20 years. Nowadays the surgical objective is to remove the tumor with negative margins and good cosmetic results. MRI of the breast has become an important imaging tool before surgery, proving to diagnose additional tumors, and to assess the tumor extent. Tumor to breast volume ratio is an important predictor of breast conservation, but was never accurately measured. MRI enables this ratio to be measured. Our purpose was to measure this ratio and to analyze if it can help in the planning of breast cancer surgery.

Materials and Methods: We conducted a retrospective hospital based study of 76 consecutive patients diagnosed with breast cancer that underwent pre-surgery breast MRI between January 2008 and September 2010 at our hospital. The volume measurements were made using a semi-automated method. The breast volume was calculated in the AW workstation. The tumor volume was calculated with CAD (Computer-Aided Diagnosis) software and the AW workstation. The tumor volume was calculated including 10 mm margins. Afterwards the ratio between the volumes was calculated.

Results: 76 patients were included in our study. 64 patients had breast conserving surgery and 12 patients underwent mastectomy. Average tumor volume in the mastectomy group was much larger than in the lumpectomy group ($p < 0.0001$). Average tumor to breast volume ratio in the mastectomy group was 0.30 (30%). In the lumpectomy group, average tumor to breast volume ratio was 0.06 (6%) ($p < 0.0001$).

Conclusion: Tumor to breast volume ratio as measured on MRI is an accurate measuring tool that can help the surgeon in the decision weather to perform breast conserving surgery or mastectomy. This tool should be introduced in the surgical planning of patients diagnosed with breast cancer.

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An Early Experience with SNOLL in the Management of Impalpable Breast Cancer

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Background: The detection of impalpable breast cancer lesions is on the rise due to mass population screening. Radio-guided occult lesion localisation (ROLL) has recently been used in the management of early lesions while sentinel lymph node biopsy (SLNB) has been used to detect occult lymph node metastases. In order to optimise localisation many international centres have proposed a technique involving the combined use of ROLL and SLNB, also known as SNOLL.

Materials and Methods: All patients with impalpable invasive cancer and clinically negative axillae were analysed. The impalpable breast lesions were localised with an intra-lesion injection of 0.1 mls of 99Tc nanocolloid (1 MBq) 1 to 4 hours before surgery. SLNB was identified using 0.2 mls of 99Tc nanocolloid (20 MBq) injected subdermally in the periareolar region within the index quadrant, the day before surgery. All lymph nodes and target tissue that were focally radioactive were denoted using signals from a gamma probe.

Results: SNOLL was utilised on 79 patients (median age, 63; range 57−68) between 2007 and 2009. 76 procedures were for invasive breast cancers. The median primary tumour size was 12 mm (range, 10 -17 mm). Over two thirds of the lesions were in the upper half of the breast. Of these 54.4% were located in the inner quadrant while 15.5% in the outer quadrant. The mean number of SLNBs retrieved was 1.86. In addition to SLNBs, 12 patients (15.2%) had non sentinel lymph node biopsies performed. Of note, none were positive. The number of SLN positive patients was 7 (8.9%) with a mean retrieval of 2.

Conclusion: SNOLL successfully localised all lesions. The combined use of radio-isotopes for lesion and sentinel lymph node removal in early breast cancer is feasible and reliable. Such a technique could rapidly become a standard practice within the NHS.

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Intra-operative Detection of Sentinel Lymph Node Metastasis in Breast Cancer by One Step Nucleic Acid Amplification (OSNA)

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Background: Despite recommendations from international and national breast cancer guidelines there is no standardised histopathological procedure for intra-operative and post-operative analysis of the sentinel lymph node (SLN). In this OSNA study/routine use overview we used the molecular diagnostic OSNA assay for intra-operative SLN analysis in breast cancer patients. OSNA is based on CK19 mRNA amplification and has shown to be as accurate as intensive post-operative histology.

Methods: Eighty SLNs from 47 breast cancer patients were included in the study. A 1 mm middle slice was reserved for intra-operative frozen section staining. The rest of the SLN was homogenised and analysed with the automated OSNA system.

For routine use in 28 patients (45 SLNs) the whole node was dedicated for OSNA without conserving any tissue for histology.

Results were displayed as (++) equivalent to a macrometastasis, (+) for a micrometastasis, (−) for negative, and led to direct axillary dissection if positive.

Results: In the study phase, 20 patients gave a positive OSNA result (22 SLNs with ++, 12 SLNs with +), resulting in a positivity rate of 42.6%. In 27 patients OSNA was negative, with one patient having a very small micrometastasis in the 1 mm middle slice. 6 patients were OSNA positive/histology negative, thereby avoiding a second surgical intervention as axillary dissection was performed intra-operatively. In 14 patients 1 SLN was analysed, in 19 patients 2 SLNs, in 11 patients 3 SLNs, in 3 patients 4 SLNs with the mean analysis time of 29.5, 37, 40, and 51 minutes, respectively.

In OSNA whole node use, 10 patients had a positive OSNA result (8 SLNs with ++, 3 SLNs with +) with a positivity rate 35.7%. 18 patients showed a negative OSNA result.

Conclusions: OSNA is a standardised technique for intra-operative SLN investigation which could replace both intra-operative and post-operative histology as most or all of the tissue can be analysed during the primary surgery.

Wednesday, 21 March 2012 12:00–13:15

POSTER SESSION

Epidemiology, Prevention, Screening

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Efficacy of Bilateral Risk-reducing Mastectomy on Primary Breast Cancer Risk in Healthy BRCA1 and BRCA2 Mutation Carriers

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Objective: To assess the efficacy of bilateral risk-reducing mastectomy (BRRM) on primary breast cancer (PBC) risk in healthy BRCA1 and BRCA2 mutation carriers.

Methods: In total 552 proven BRCA1/2 mutation carriers under surveillance at the Erasmus MC Family Cancer Clinic (395 BRCA1 and 157 BRCA2) were followed up until June 30, 2011. Participants had no history of breast or ovarian cancer, and had both breasts as well as both ovaries in situ at DNA diagnosis. Eventually 152 BRCA1 and 50 BRCA2 mutation carriers underwent BRRM. Women contributed person-years of observation (PYO) to the surveillance group from the date of DNA diagnosis to the date of PBC, BRRM, ovarian cancer, death, or last FU. Contribution of PYO to the BRRM group started at the date of BRRM until similar endpoints as described for the surveillance group.

Results: During 3051 PYO, 54 PBC cases were observed in the surveillance group (median age at diagnosis 43 years), while no PBC cases occurred during 1283 PYO in the BRRM group (median age at BRRM 35 years), corresponding with incidence rates per 1000 PYO of 18 and 0, respectively. In the BRRM group, one woman presented with distant metastases of BC almost 4 yrs after BRRM (no PBC found at BRRM), and died afterwards. After a mean FU of 11.5 years, 4 women died of BC in the surveillance group. With an overall mean FU of 10.3 years, the mortality rate per 1000 PYO was 1.0 in the surveillance group versus 0.6 in the BRRM group. To estimate the effect of BRRM (versus surveillance) on mortality, a multivariate Cox model with BRRM as a time-dependent covariate was performed and revealed a hazard ratio of 0.58 (95% CI, 0.05–6.90).

Conclusions: BRRM in healthy BRCA1/2 mutation carriers can reduce the probability of PBC occurrence to zero. Longer FU is warranted to confirm survival benefits.

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BRCA1 Carriers and Oral Contraceptives − Risk-benefit Calculation on Breast and Ovarian Cancer

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Background: The weak association between oral contraceptive (OC) use and risk of breast cancer is not regarded as a contraindication for OC use in the general population. This is partly because it is still not certain whether the association is causal. Even if it were, the absolute excess risk of breast cancer would be small, and might be outweighed by its contraceptive effects and positive health outcomes as the substantial protection against ovarian cancer. The implications of the OC-cancer risk associations may differ between the general population and BRCA1 carriers because of the higher risk of the disease during reproductive years in carriers.

Methods: To illustrate potential implications, we calculated the excess number of breast and ovarian cancers that would arise in the 20 years following a 5 year period of use of OC at six 5-year age ranges under the assumption that the associations of breast and ovarian cancer associated with OC use are the same among BRCA1 carriers as estimated for the general population. Incidence rates of breast/ovarian cancer among BRCA1 carriers are based on Antoniou et al. AJHG 2003. When estimating the absolute numbers of breast or ovarian cancer cases we took into account the decreasing population at risk due to the mortality to other causes. The BRCA1-related excess breast cancer mortality was incorporated in the ovarian cancer model, as was the benefit on ovarian cancer mortality in the breast cancer model. We assumed that the risks of the two cancers are independent and that the survival of breast and ovarian cancer is similar for carriers and women in the general population.

Results: Based on these calculations, the estimated extra cases of cancer per 10,000 women during 20 years of follow-up, for use of OC between the ages 20−24, 25−29, 30−34, 35−39, 40−44, 45−49, were 0, 2, 8, 17, 28, and 38 respectively, in the general population and -109, -172, -210, -286, -312, and -288 respectively, in BRCA1 carriers. We conducted several sensitivity analyses.

Conclusions: Assuming that the associations of OC and risk of breast and ovarian cancer are the same for BRCA1 carriers as for women in the general population, the protective effect on ovarian cancer might outweigh the risk increasing effect on breast cancer.

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Risk Factors Associated with Lobular Carcinoma in Situ: Results of the GLACIER Study

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Background: Lobular carcinoma in situ (LCIS) is a form of non-invasive breast cancer that is often clinically undetectable and confers an increased risk of subsequent invasive breast cancer in either breast. Approximately 50−70% of subsequent cancers are invasive lobular carcinomas (ILC), suggesting that LCIS is a precursor lesion in a similar manner to DCIS. However, it is also argued that LCIS may be a marker for the subsequent development of invasive breast carcinoma, as LCIS increases the risk of invasive cancer in both breasts and of all morphological subtypes. Currently, in the UK, LCIS is considered a risk factor for subsequent