1C BREAST SURGERY 1

O40 TO ASSESS THE ABILITY OF PRE-OPERATIVE NLR SCORES TO PREDICT RESPONSE TO NEO-ADJUVANT CHEMOTHERAPY IN HER2 RECEPTOR POSITIVE BREAST CANCERS

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Introduction: A recent study has suggested that a patients immune status can affect response to neo-adjuvant Trastuzumab chemotherapy in Her2 receptor positive breast cancers. This is thought to be due to Trastuzumab incorporating the immune system as part of its mechanism of action. Multiple studies have shown that a patients neutrophil-to-lymphocyte ratio (NLR) can be a good predictor of a patients immune status. Our aim is to identify if pre-operative NLR can predict response to neo-adjuvant chemotherapy in Her2 receptor positive breast cancers.

Method: Patients were identified using a prospectively maintained database of patients who received neo-adjuvant Trastuzumab therapy from 2005-2015. The pre-operative NLR was recorded for each patient, with a score >3 considered high risk. The post-operative pathology reports were used to assess pathological complete response rates (pCR) to neo-adjuvant chemotherapy.

Result: In total 69 patients were included in the study, with an average of 54 years. From these, 39 (56.5%) patients had a NLR <3, while 30 (43.5%) patients had a NLR >3. A pCR was achieved in 25 (37.3%) of all treated patients. In patients with a pCR, 16 had a NLR <3 and 9 had a NLR of >3 (p=0.61). In patients not achieving a pCR, 13 had a NLR <3 while 18 had NLR >3 (p=0.13).

Conclusion: A low risk NLR score was not associated with significantly increased pCR rates in Her2 receptor positive patients treated with Trastuzumab. This study suggests that NLR would not be a suitable marker for predicting response to neo-adjuvant chemotherapy.

Take-home message:
Neutrophil-to-lymphocyte ratio has not proven to be a suitable marker for predicting response to neo-adjuvant chemotherapy.

O41 CLINICAL RISK FACTORS FOR POOR AESTHETIC OUTCOME AFTER BREAST-CONSERVING THERAPY (BCT) AS MEASURED BY THREE-DIMENSIONAL SURFACE IMAGING (3D-SI)

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Introduction: Patient satisfaction and quality of life after BCT (surgery and radiotherapy) are correlated with aesthetic outcome. Identifying risk factors for poor outcome allows surgeons to plan their surgery and manage patient expectations. Symmetry of volume and shape are important components of appearance and can be measured using 3D-SI. The aim of this study was to identify the risk factors for poor volume symmetry (VS) and shape symmetry (SS) after BCT.

Method: Ethical approval was obtained. Women who had unilateral BCT 1-6 years ago were recruited. Participants underwent 3D-SI and VS (smaller breast/larger breastx100), and SS (the root mean squared distance between one breast reflected onto the other) were calculated. Univariate linear regression analysis was used to identify clinicopathological variables associated with VS and SS. Variables with p<0.1 were entered into a multivariate model in a forward stepwise manner with a 5% significance.

Result: 200 women participated. Mean age was 60 years (SD11.1). Mean time from surgery was 35.5 months (SD17.8). Median VS was 87% (IQR78-93) and SS was 5.87mm (IQR4.23-7.95). Independent factors for poor VS were increasing specimen weight and level of operating surgeon (trainee supervisor scrubbed). Independent factors for poor SS were increasing specimen weight, BMI of patient and pathological tumour size.

Conclusion: This is the first study to identify risk factors for poor volume and shape symmetry of the breasts after BCT using 3D-SI. This will inform efforts to pre-operatively simulate a 3D image of the appearance of a patient after surgery to provide patient information, aid preparation and decision-making.

Take-home message:
Independent factors for poor volume symmetry were increasing specimen weight and level of operating surgeon (trainee supervisor scrubbed) and independent factors for poor surface symmetry were increasing specimen weight, BMI of patient and pathological tumour size. This will inform efforts to simulate a 3D image of a patient after surgery providing patient information, and aiding preparation and decision-making

O42 THE CONSEQUENCES OF A SINGLE NUCLEOTIDE POLYMORPHISM IN PRE-MIR-146A AND ITS EFFECT ON MATURE CIRCULATING MIR-146A LEVELS

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Introduction: MicroRNAs are non-coding RNA molecules that exert post-transcriptional effects on gene expression. MiR-146a plays a key role in inflammation and innate and adaptive immunity, and has been

postulated to function as a tumour suppressor. Single nucleotide polymorphisms refer to variation in DNA sequence at a single base pair. The variant rs2910164 in pre-mir146a is postulated to result in decreased amounts of circulating mature mir146a, increasing the potential for oncogenesis.
Method: Healthy controls from the community along with newly diagnosed breast cancer patients were recruited. DNA and RNA were extracted from whole blood using the MagnaPure Compact automated extraction system. Genotyping for the variant was performed utilising Taqman-based PCR and allelic discrimination. RNA was reverse transcribed and PCR-amplified. The differential expression of mature miR146a across the three genotypes was compared.
Result: 45 healthy controls and 44 breast cancer patients were analysed. Circulating miR-146a levels were found to be significantly down-regulated in patients with cancer and CG or CC genotypes in control patients($p<0.0001$). Circulating miR-146a were similar between the 3 genotypes in the control cohort($p=0.121$). Considering CG and CC genotypes, patients with cancer had significantly lower mir-146a levels than controls with the same genotypes. Reduction in miR-146a expression was seen in the presence of the variant for all molecular subtypes, significantly so for Luminal A($p=0.015$) and Triple negative subtypes($p<0.001$).
Conclusion: The presence of the genotype has a deleterious impact on miR-146a processing impacts inflammatory response and may influence disease progression or metastasis which could represent a potential therapeutic target.
Take-home message:
Circulating mature miR-146a levels were shown to be down-regulated in patients with breast cancer in the presence of CG or CC genotypes,this dysregulation was not identified in patients without an active cancer. We feel the impact of the SNP on mir-146a may influence disease progression or metastasis which could represent a potential therapeutic target.

O43 DEVELOPMENT OF CLINICAL BIOMARKERS HOXC11 AND ADAM22 FOR PREDICTING ENDOCRINE RESISTANCE IN BREAST CANCER PATIENTS

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Introduction: The discovery of the ER and PR biomarkers has led to a vast improvement in the prognosis of breast cancer patients. However, 30% of this cohort will acquire resistance to endocrine treatment and develop tumour recurrence. Currently, there is no reliable way of identifying them. Novel potential biomarkers, HOXC11 and ADAM22 were previously shown to predict endocrine resistance and reduced disease free survival in breast cancer patients. The assays for both must first be developed to a clinical scale protocol and robustly validated, prior to their introduction to the clinic.
Method: 508 primary breast cancer tissue were constructed on to a Tissue Microarray (TMA). Using the TMA, the manual HOXC11 immunohistochemistry (IHC) assay was migrated to an automated system. The automated assay was then run at two independent sites to assess its performance specifications for analytical validation. When the ADAM22 assay was first developed, it was through the use of a polyclonal antibody. Potential monoclonal antibodies were identified, tested and optimized for an IHC assay.

Result: The HOXC11 IHC assay was successfully migrated to automated IHC with an analytical accuracy of 95.4%. This surpassed analytical validation requirements set by the College of American Pathologists and is currently progressed on to the clinical validation stage. A suitable ADAM22 monoclonal antibody has been selected and optimized. This assay is now ready to proceed on to analytical validation.
Conclusion: In the near future, we envision HOXC11 and ADAM22 joining the ER/PR/HER2 biomarker trifecta in improving management strategies for breast cancer patients.
Take-home message:
HOXC11 and ADAM22 are potential new predictive biomarkers for endocrine resistant breast cancer. Assays for both must first undergo stringent validation to prove clinical use.

O44 SRC-1 DRIVES ENDOCRINE TREATMENT-RESISTANT BREAST CANCER PROGRESSION BY SILENCING TUMOUR SUPPRESSOR GENES THROUGH DNA METHYLATION

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Introduction: The most effective strategy for targeting estrogen receptor positive breast cancer is to block estrogen action using endocrine therapy. Unfortunately, resistance to endocrine therapy remains an important clinical problem, with 40% of patients developing refractory disease. SRC-1, a key regulator of estrogen signalling, is overexpressed in 35% of breast cancer patients and is associated with development of endocrine resistant metastasis in models of resistance and in patients. Our aim was to determine the mechanism by which SRC-1 mediates the endocrine treatment-resistant phenotype and identify actionable targets.
Method: The study employed a genome-wide RNA/DNA sequencing of tamoxifen-resistant tumour cells, linking gene expression data with patient survival and utilising 3D tumour explants for therapeutic intervention studies. Sequencing revealed significant gene changes driven by tamoxifen-induced SRC-1 expression. We identified a hub of five differentiation-linked, tumour suppressor genes, silenced by SRC-1 through DNA methylation. We have shown these are important genes in halting tumour proliferation,

migration and mammosphere formation. Clinically, high expression of these genes predicts better relapse-free survival in ER positive (n=695;p=0.0019) and tamoxifen-treated patients (n=335;p=0.032). Finally, utilising 3-D tumour explant, targeted inhibition against DNMT can return the expression of this protective differentiation hub. Here we report a novel mechanism of resistance, in which SRC-1-regulated differentiation genes are silenced. Suppression of this hub allows cells to re-programme, becoming poorly differentiated and aggressive endocrine resistant tumour cells. This study proposes that therapeutic strategies of combined targeted epigenetic therapy with estrogen deprivation could be successful strategy to prevent acquired resistance to endocrine therapy.

Take-home message:

SRC-1 drives disease progression by repressing tumour suppressor genes through DNA methylation. This process is reversible through DNA methyltransferase inhibitor (Aza-deoxycitidine) drug treatment.

O45 THE NEUTROPHIL-TO-LYMPHOCYTE RATIO IS PREDICTIVE OF MORTALITY IN HER2-RECEPTOR POSITIVE BREAST CANCER

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Introduction: Breast cancer represents a heterogenous condition in which the interaction between host immune response and primary oncogenic events can impact disease progression. The neutrophil-to-lymphocyte ratio (NLR) has emerged as a clinically-relevant measure of immune function. Our aim was to analyse NLR values of patients with HER2 over-expressing breast cancer to determine if they were predictive of outcome.

Method: Analysis of a database of 203 HER2 receptor over-expressing patients (123 Luminal B and 80 HER2), treated at a tertiary referral centre, was carried out. All blood tests were recorded within two weeks of initial surgery and obtained from the referral centre's own database.

Result: Of the cohort, 19 (9.4%) were palliative, 18 (8.9%) suffered a recurrence and 23 (10.8%) died at 5 years follow up. No statistically significant difference in average NLR between the HER2 and Luminal B subgroups (p=.339) was observed, nor was there a correlation between NLR and age at diagnosis (p=.230). Selected NLR values (3.5 4, 4.5, 5) were used for further analysis. NLR ≥4 was associated with a shorter survival time in months (mean difference=12.879, p=0.018, 95% CI 2.336, 23.423)(T-Test). A NLR ≥4 was associated with death (p=0.018), but not with recurrence (p=.724)(Chi-square).

Conclusion: These results validate the NLR as a reliable predictor of poor outcome in Her2 positive breast cancer patients. Larger, prospective testing of the ability of NLR to predict response to surgery, radiotherapy and chemotherapy is necessary to validate our findings, including exploring NLR changes during treatment.

Take-home message:

The neutrophil-to-lymphocyte ratio has been demonstrated to be predictive of poor outcome in HER2-positive breast cancer. Further analysis of this simple measure of immune function should be undertaken to identify any further prognostic value it may have with regard to other subsets of breast cancer.

O46 ADIPOSE DERIVED STEM CELLS IN BREAST CANCER PATIENTS AND THEIR POTENTIAL ROLE IN BREAST RECONSTRUCTION

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Introduction: Adipose derived stem cells (ADSCs) offer exciting potential as a novel tool in breast reconstruction as they have the potential to form viable mature adipose tissue.Whilst ADSCs are more accessible then BMSCs, safety concerns still remain with ADSCs particularly those which have been harvested from patients with a history of breast cancer. Aim: To characterise and compare adipogenic potential of ADSCs from breast cancer patients and normal healthy controls.

Method: ADSCs were isolated and expanded from the stromal vascular portion from breast cancer patients as well as normal healthy controls. Cell morphology and immunophenotype were assessed using flow cytometry.Adipogenic differentiation was performed using specific adipogenic medium confirmed with oil red O staining.BMSCs were used as a control.

Result: ADSCs were successfully grown from 18 patients(n=18) ,15 from cancer patients,12 breast and 3 abdominal as well as 3 normal controls. ADSCs underwent Immunophenotyping for characteristic stem cell markers positive for CD105,CD45, CD73 and negative for CD31,CD45,CD34.A functional assay in both ADSCs and BMSCs confirmed adipogenic differentiation. There was a greater amount of adipocyte formation (median= 1.046nm, p=0.01) in the ADSCs.

Conclusion: ADSCs can be harvested from various sites and donors and display characteristics similar to BMSCs. A greater amount of adipocyte formation was found in the ADSCs.Given that ADSCs are more readily accessible in the white adipose tissue they would appear to be suitable source of tissue for regenerative purposes'. However further work is required to fully assess the safety and differentiation capacity of ADCSs in breast cancer patients particularly those who have received cytotoxic therapy.

Take-home message:

Adipose derived stem cells offer exciting potential in breast reconstruction , however further work is required to fully elucidate safety concerns.

O47 THE POTENTIAL ROLE OF THREE DIMENSIONAL SURFACE IMAGING (3D-SI) AS AN OBJECTIVE MEASURE OF AESTHETIC OUTCOME AFTER BREAST CONSERVING THERAPY (BCT)

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Introduction: Patient satisfaction with aesthetic outcome is important after BCT (surgery and radiotherapy) because of the correlation with psychosocial recovery. However, to improve surgical outcomes, an objective measure is required. Assessment of images by a panel is costly, time-consuming and could potentially be replaced by3D-SI. This may provide a standardised, quick and cost effective tool for clinical studies. This study investigated the association between breast volume symmetry (VS) and shape symmetry (SS) (measured by 3D-SI) with patient satisfaction (BREAST-Q-BCT questionnaire) and panel assessment.

Method: Ethical approval was obtained. Women who had unilateral BCT 1-6 years ago were recruited. Participants underwent 3D-SI and completed the BREAST-Q. VS (smaller breast/larger breast x100), and SS (the root mean squared distance between one breast reflected onto the other), were analysed. Panel assessment used the Harvard 4-point score.

Result: 200 women participated. Mean age was 60 years (SD11.1). Mean time from surgery was 35.5 months (SD17.8). Median score for BREAST-Q Satisfaction with Breasts was 68 (IQR55-80). Median VS was 87% (IQR78-93) and SS was 5.87mm (IQR4.23-7.95) A Kruskal-Wallis ANOVA revealed a significant association between panel score and both VS and SS ($P<0.001$). The association was greater with SS with four significant pairwise comparisons compared to two with VS. There was a weak correlation of both VS and SS with BREAST-Q scores (correlation coefficients 0.187 ($P=0.008$) and -0.229 ($P<0.001$) respectively).

Conclusion The weak correlations with PROMs confirm the need for objective assessment. 3D-SI measurements are strongly associated with panel assessment, hence we should strive to develop a 3D-SI tool to replace panel assessment.

Take-home message:

3D-SI measurements are strongly associated with panel assessment, hence we should strive to develop a 3D-SI tool to replace panel assessment.

O48 REDUCED NODAL BURDEN BASED ON TUMOUR SUBTYPE CAN HELP TAILOR AXILLARY TREATMENT IN BREAST CANCER PATIENTS WHO HAVE UNDERGONE NEOADJUVANT CHEMOTHERAPY

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Introduction: Few studies have focussed on the effects of tumour biology on nodal burden in breast cancer patients with nodal metastases who undergo neoadjuvant chemotherapy (NAC). The aim of this study was to examine the impact of different biological tumour characteristics on this group to elucidate patient groups that could be amenable to more conservative treatment.

Method: A retrospective review of prospectively maintained databases identified breast cancer patients with positive axillary fine needle aspiration cytology between 2000- 2015. Patients who underwent NAC and subsequent axillary lymph node dissection (ALND) were recorded and tumour characteristics analysed. Rates of complete pathological response(pCR) after NAC by biologic subtype were compared.

Result: 338 patients with breast cancer and nodal metastases underwent NAC and subsequent ALND. With regard to tumour biology, 183 patients (54.1%) were Luminal A (LA), 72 patients (21.3%) were Luminal B (LB), 45 patients (13.3%) were Her2 positive (Her2) and 38 patients (11.2%) were triple negative (TNBC). Complete pathological response rates in the breast and axilla were 19% and 30%. Axillary CPR rates were significantly higher in the Her2 group compared to the LA group (66% vs. 13%; $p<0.001$). Nodal burden (Median positive nodes excised) was significantly lower in the Her2 group compared to the LA group (0 vs 3; $p <0.001$).

Conclusion: HER2 positivity is associated with increased rates of axillary pCR and reduced nodal burden after NAC. Patients with HER2 receptor amplification could be amenable to less aggressive axillary surgery post NAC.

Take-home message:

Her2 positivity is associated with increased rates of axillary pCR and reduced nodal burden after neoadjuvant chemotherapy. Patients with HER2 receptor amplification could be amenable to less aggressive axillary surgery post neoadjuvant chemotherapy.

O49 THE SIGNIFICANCE OF PERFORMING SENTINEL NODE BIOPSY WITH RISK REDUCING MASTECTOMY

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Introduction: Risk reducing mastectomy (RRM) is performed in increasing number of patients due to increasing awareness of family history and recurrence risks. In our unit, sentinel node biopsy(SLNB) is performed routinely at the time of mastectomy. The Aim of this study is to assess the if performing SLNB routinely in RRM justifies the risk profile associated with axillary operations. Patients and methods: All patients who had RRM between April 2006 and April 2016 were retrospectively reviewed. Patient's characteristics, the indication of RRM, history of previous breast cancer diagnosis, SLNB and RRM histolopathology were recorded.
Result: 159 were included in the analysis. 51 patients (32.1%) had bilateral and 108 (67.9%) had unilateral RRM. All patients who had bilateral RRM were BRCA1 23/51 and BRCA 2 16/51 gene mutation carriers or high risk family history 12/51. All unilateral RRM were performed after developing contralateral breast cancer with BRCA1 in 9/108 patients, BRCA2 in 8/108 patients, high risk family history in 18/108 patients. 73/108 were done due to patients wishes with no other risk factors. The histology of the RRM was normal in 107 patients (67.3%), Benign breast changes in 42 (26.4%), LCIS in 6 (3.8%), atypical proliferation in 3 (1.9%) and DCIS in 1 (0.6%). SLNB was done in 137 cases (86.2%) and was negative in all cases.
Conclusion: Sentinel lymph node in the context of risk reducing mastectomy is not justified in this study to be routinely performed with risk reducing mastectomy.
Take-home message:
Sentinel lymph node in the context of risk reducing mastectomy is not indicated.

O50 INVESTIGATING THE ROLE OF SINGLE NUCLEOTIDE POLYMORPHISMS IN NRG1 AND DIRC3 IN PREDISPOSITION TO BREAST CANCER

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Introduction: The NRG1(neuregulin1) gene interacts with EGFR and HER2, is anti-proliferative; and is silenced in breast cancer. The DIRC3(Disrupted in Renal Cancer 3) gene is dysregulated in thyroid and renal cancers. Two intronic variants in NRG1(rs2439302) and DIRC3(rs966423) have been associated with thyroid cancer, but have not been investigated in breast cancer, although breast and thyroid cancers share some genetic loci(e.g.PTEN). The aim of this study was to investigate the role of rs2439302 and rs966423 in breast cancer predisposition.
Method: A case-control study was undertaken, including unselected patients with breast cancer, and unaffected female controls over 60 years with no personal/familial history of breast cancer. DNA was extracted from blood using the Roche automated MagNA Pure Compact system, and genotyped using Taqman-based PCR. Data was analysed using SPSS.
Result: A total of 1520 samples were genotyped at the two loci. Increased disease risk was significantly associated with mono-allelic (OR 1.27 (1.01-1.59), p=0.04) but not bi-allelic (OR= 1.28 (0.95-1.73), p=0.1) rs966423 C allele. Homozygosity for rs2439302 was significantly associated with a reduced risk of cancer (OR=0.72 (0.54-0.96), p=0.02), but heterozygosity was associated with increased odds (OR=1.26 (1.0-1.59), p=0.05).
Conclusion: Heterozygosity, but not homozygosity, for variant rs966423 was significantly associated with breast cancer risk, while rs2439302 had conflicting impact depending on genotype. The clinical significance of these findings requires further evaluation.
Take-home message:
Breast cancer risk was significantly associated with heterozygosity, but not homozygosity, for the intronic variant in DIRC3(rs966423); while the intronic variant in NRG1(rs2439302) had conflicting impact depending on genotype. The clinical significance of these findings requires further evaluation.