between MX-BCT and BCT-BCT ($p = 0.04$) while there was no significant difference when comparing MX-MX versus MX-BCT patients ($p = 0.79$). Multivariate analyses using surgical group, menopause, lymph node status, grading, pathological response, tumor type, endocrine responsiveness and her2neu status demonstrated no influence of any of these parameters on LRFS. Surgical group (BCT), lymph node status (N0) and grading (G1/2) were predictive for OS while tumor type (ductal), lymph node status (N0) and grading (G1/2) were predictive for DRFS.

Conclusion: There was no significant difference in LRFS, DRFS and OS in patients downsized from mastectomy to breast conservation by neoadjuvant chemotherapy. This was independent of menopause status, endocrine responsiveness, tumor type and pathological response. Thus, BCT is safe after tumor downsizing with neoadjuvant therapy.

MX-BCT: Patient scheduled for mastectomy receiving breast conservation

MX-MX: Patient scheduled for mastectomy receiving mastectomy

BCT-BCT: Patient scheduled for breast conservation receiving breast conservation

LRFS: Local recurrence free survival

DRFS: Distant recurrence free survival

OS: Overall survival

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Intrinsic Susceptibility-Weighted MRI is an effective method of evaluating tumour oxygenation in primary breast cancer and can predict for response to neoadjuvant chemotherapy

S.P. Li[1], A.R. Padhani[2], N.J. Taylor[2], M.W. Ah-See[1], M.J. Beresford[1], D.J. Collins[3], J.A. d'Arcy[3], A. Makris[1]. *[1]Academic Oncology Unit, Mount Vernon Cancer Centre, Middlesex, United Kingdom; [2]Paul Strickland Scanner Centre, Mount Vernon Hospital, Middlesex, United Kingdom; [3]CRUK Clinical MR Research Group, Royal Marsden Hospital, Surrey, United Kingdom*

Background: Intrinsic Susceptibility-Weighted MRI (ISW-MRI), also known as Blood oxygenation level dependent (BOLD) MRI, can provide important functional information about whole tumour oxygenation. Higher values of R_2* (the apparent transverse relaxation rate calculated from ISW-MRI data) imply a more hypoxic tumour environment. This study explores the relationships between pretreatment R_2* and tumour characteristics, and assesses whether changes in R_2* correlate with final clinical and pathological response to neoadjuvant chemotherapy (NAC) in breast cancer (BC).

Materials and Methods: 83 pts with primary BC were selected to undergo dynamic contrast-enhanced MRI (DCE-MRI) and ISW-MRI before and after 2 cycles of NAC. Diffusely infiltrating, necrotic or invasive lobular carcinomas (ILC) were excluded due to paradoxical changes in R_2*. DCE-MRI T_1 & T_2-weighted kinetic parameters (K^{trans}, v_e, k_{ep}, $IAUGC_{60}$, relative blood flow (rBF) & volume (rBV), MTT) and R_2* were obtained for whole tumour regions of interest. Relationships between tumour characteristics (grade, size, ER/PR/HER2 status), MRI kinetic parameters and pretreatment R_2* were assessed using Spearman's rank correlation for continuous variables and the Mann-Whitney U test for discrete variables. Pretreatment and changes in R_2* were correlated with final pathological and clinical response to NAC using paired t-testing.

Results: 31 pts (T2−4, N0−2, M0; median age 44, range 22−62) were available for pretreatment and 27 for response assessment. 37 with ILC, ill-defined or necrotic tumours were excluded, 12 did not undergo their first MRI (mainly due to claustrophobia), 1 had only axillary nodal disease visible, 2 had corrupted MRIs that were not analysable and 4 did not have their repeat MRI. 15 pts received anthracycline based NAC and 12 docetaxel NAC. There were no correlations observed between pretreatment R_2* and tumour characteristics or response. Both rBF & rBV were inversely correlated with R_2* ($r = -0.51$, $p = 0.006$; $r = -0.46$, $p = 0.015$), this correlation disappearing with NAC ($r = -0.39$, $p = 0.112$; $r = -0.37$, $p = 0.081$). There were 16 pathological responders & 11 non-responders, and 23 clinical responders & 4 non-responders. Significant R_2* increases were seen with NAC ($34.8s^{-1}$ vs $-31.1s^{-1}$, $p = 0.006$) with larger increases predicting for final pathological ($36.5s^{-1}$ vs $31.7s^{-1}$, $p = 0.025$) and clinical response ($35.5s^{-1}$ vs $31.7s^{-1}$, $p = 0.017$).

Conclusions: Pretreatment R_2* relates to blood rather than tumour oxygenation as suggested by its relationship with blood volume and flow. With the loss of this relationship after NAC, R_2* may become a more reliable marker of actual tumour hypoxia. Furthermore, responders to treatment displayed more hypoxic cancers after 2 cycles of NAC. ISW-MRI has the potential to predict not only therapy response but to identify those who may benefit most from hypoxia targeting agents.

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Applying survival based cost-effectiveness analyses to estimate the impact of patent expiry on the cost-effectiveness of letrozole and anastrozole versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer

J. Karnon[1], S. Kaura[2]. *[1]University of Adelaide, Public Health, Adelaide, Australia; [2]Novartis Pharmaceuticals Corp., Oncology, East Hanover, USA*

Background: The latest update of the BIG 1-98 study (76 months) reports a hazard ratio for overall survival (OS) of 0.83 (95% CI 0.71–0.97) for 5yrs letrozole (LET) vs tamoxifen (TAM) (censoring TAM patients who crossed over to LET). At 100 months, ATAC remains to show a significant OS benefit for anastrozole (ANA) compared to TAM. A new framework for the economic analysis of the aromatase inhibitors (AIs) uses observed differences in OS to estimate the incremental cost per life year (LY), and per quality adjusted LY (QALY) gained of 5 years LET versus 5 years TAM, and 5 years ANA vs 5yrs TAM in ER+ postmenopausal women, from a UK NHS perspective, incorporating possible price reductions due to patent expiry for both AIs.

Methods: Survival probabilities over the 1st 7 years post-surgery were extracted from BIG 1-98, and extrapolated to 20 years using data reported by the Early Breast Cancer Trialists' Group for women receiving 5 years TAM. HRs for LET and ANA were applied to TAM event rates for the first 7 and 9 years, respectively. Conservatively, equivalent annual survival probabilities were assumed thereafter. Reduced ANA costs, to account for generic ANA, were applied from year 1, and reduced LET costs, to account for generic LET, from year 2. Two scenarios were considered for the price of generics; scenario 1 assumed a 50% price reduction and scenario 2 a 70% price reduction. Adverse event (AE) cost and five year costs for locoregional recurrence (LR) and metastases (METS) were also applied. A QALY model applied published utility weights for DFS with AEs, LR, and METS. All costs and health benefits were discounted at 3.5% annually.

Results: For LET, the reference case results show that over a 20 year period, the incremental cost per QALY gained (ICQ) is £9,287, with an upper 95% CI of £32,576. Assuming a 50% price reduction from the 2nd year of treatment lowers the ICQ to £4,727. For ANA, the reference case ICQ is £44,294, with an upper 95% CI of TAM dominating ANA [Table 1]. Assuming a 50% price reduction from the 1st year of treatment lowers the ICQ to £16,099. These results suggest that use of LET is a more cost-effective use of healthcare resource, despite the fact that ANA loss of patent will occur one year prior to LET. The clinical benefits associated with LET far outweigh any cost saving resulting from a lower ANA price for 12 months.

Table 1: Incremental cost per QALY gain for Letrozole and Anastrazole

	Letrozole	Anastrazole
Base case	£9,287	£44,294
Scenario 1: Generics priced 50% below current price	£4,727	£16,099
Scenario 2: Generics priced 70% below current price	£2,902	£3,807

Conclusion: Given the extended follow-up periods for both the ATAC and BIG1−98 trials, one would hope to observe some effect on OS. Using estimates of effects with respect to OS, these new economic analyses suggest a preference for LET, with a lower cost per QALY compared to ANA, despite the shorter time to patent expiry for ANA.

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Factors predicting a pathological complete response following neoadjuvant chemotherapy for breast cancer

H. Cho[1], V. Van Belle[2], H. Wildiers[1], R. Paridaens[1], F. Amant[1], E. Van Limbergen[1], P. Moerman[1], A. Smeets[1], I. Vergote[1], P. Neven[1]. *[1]U.Z. Gasthuisberg, Multidisciplinary Breast Centre (MBC), Leuven, Belgium; [2]KU Leuven, Department of Electrical Engineering (ESAT), Leuven, Belgium*

Background: Patients diagnosed with large size or locally advanced breast cancer are frequently treated with neoadjuvant chemotherapy. This work establishes a model, based on demographic and clinicopathological features to predict pathologic complete response (pCR) following neoadjuvant chemotherapy.

Material and Methods: A consecutive group of 335 patients diagnosed with a primary non-metastatic large or locally advanced breast cancer, who had received neoadjuvant systemic therapy between January 2000 and May 2009 at the University Hospitals Leuven was analyzed. After exclusion of 65 patients (58 receiving neoadjuvant hormonal therapy, 4 switching over to neoadjuvant hormonal therapy and 3 refusing operation) 270 patients remained for analysis. pCR was defined as no evidence of invasive tumor in the breast and axillary lymph nodes. Residual in situ lesion without an invasive component is regarded as pCR in this study.

Results: 64 patients (23.7%) experienced a pCR. Univariate logistic regression revealed estrogen receptor (ER) negativity, progesterone receptor (PR) negativity, Human Epidermal Growth Factor receptor 2 (HER2) positivity, high histologic tumor grade, high clinical lymph node stage and non-lobular type as significant predictors for pCR ($p < 0.05$). Age at diagnosis beyond 60 and tumor size had a marginally positive effect; $p = 0.070$ for age and $p = 0.106$ for tumor size. A multivariate analysis taking these variables into consideration showed that ER (odds ratio=0.218, 95% CI 0.111–0.429, $p < 0.001$), HER2 (odds ratio=3.766, 95% CI 1.967–7.209, $p < 0.001$) and the clinical lymph node stage (odds ratio=1.481, 95% CI 1.035–2.119, $p = 0.032$) were the only independent predictors for pCR (see Table).

Conclusions: Our study including 270 consecutive patients diagnosed with large size of locally advanced breast cancer showed that ER, HER2 and the clinical lymph node stage are predictive of pCR.

Table: Multivariate model

Parameters	Estimate	SE	Wald χ^2	Odds ratio	95% CI	p-value
Intercept	−1.5236	0.3742	16.5820			<0.0001
ER	−1.5237	0.3451	19.4950	0.218	0.111–0.429	<0.0001
HER2	1.3260	0.3313	16.0187	3.766	1.967–7.209	<0.0001
Clinical LN stage	0.3928	0.1828	4.6193	1.481	1.035–2.119	0.0316

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Outcome in patients with hormonal receptor positive inflammatory breast cancer substantially improved with adjuvant hormonal therapy

C. Grasic Kuhar[1], M. Unk[2], B. Zakotnik[1]. [1]*Institute of Oncology Ljubljana, Department of Medical Oncology, Ljubljana, Slovenia;* [2]*University Clinic Golnik, Department of Respiratory Disease, Golnik, Slovenia*

Background: Inflammatory breast cancer (IBC) is characterized by extensive lymphovascular invasion, nodal involvement and poor clinical outcome. The aim of our study was to evaluate the role of adjuvant hormonal therapy on outcome of hormone receptor positive (HR+) IBC.

Material and Methods: We retrospectively evaluated the outcome of two series of IBC patients treated at the Institute of Oncology Ljubljana, Slovenia, in years 1983−87 (series A) and 2001−05 (series B). Patients without distant metastatic disease were included (59 patients in each of series).

Results: Patients were aged 28−74 (median 54) and 34−83 (median 56) years in series A and B, resp. Axillary lymph nodes were involved in 54/58 and 38/50 pts undergoing induction chemotherapy, mastectomy and axillary dissection (series A and B, resp.). Hormonal receptors were positive in 27/50 (9 unknown) and 31/58 (1 unknown) of pts (series A and B, resp.). HER2 status was determined only in series B (22/52 HER2+, 7 unknown). All pts in series A were treated with CMF chemotherapy, whereas pts in series B were treated with anthracyclines alone (56%), combination of anthracyclines and taxanes (36%) or CMF chemotherapy (7%). In series A 7/27 HR+ pts received adjuvant hormonal therapy (tamoxifen, mean duration 18 months). In series B 28/31 HR+ pts received adjuvant hormonal therapy (mean duration 39 months; 7 received tamoxifen, 12 aromatase inhibitors, 9 switched from tamoxifen to aromatase inhibitors). Adjuvant trastuzumab was applied in 7/22 HER2+ pts. Adjuvant radiation therapy received 73 and 81% of pts (series A and B, resp.). Median relapse-free (RFS) and overall (OS) survival was 16.9 vs. 34.2 months ($p = 0.01$) and 33.8 vs. 56.6 months ($p = 0.06$); series A vs. B, resp. Improved RFS in series B is probably due to more potent chemotherapy (anthracyclines and taxanes vs. CMF), trastuzumab and hormonal therapy. In patients with HR+ IBC RFS was 75.4 vs. 16.5 months (series B vs. A, resp.), probably due to adjuvant hormonal therapy. In series B median RFS in HR+ IBC according to type of hormonal therapy was: 25 vs. 34.9 months vs. not reached (tamoxifen vs. aromatase inhibitors vs. switch; $p = 0.015$) and only 15 months in HR− IBC.

Conclusions: Patients with HR+ IBC seems to benefit substantially from adjuvant hormonal therapy. Of them switching strategy (from tamoxifen to aromatase inhibitors) seems to be the most effective. Prospective randomised trials addressing this issue are warranted.

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Endometrial cancer after breast cancer and relationship with tamoxifen

C. Brugier[1], V. Fourchotte[1], B. Asselain[2], C. Plancher[2], A. De La Rochfordière[3], P. Cottu[4], P. Petrow[5], S. Alran[1], X. Sastre[6], R.J. Salmon[1]. [1]*Institut Curie, Surgery, Paris, France;* [2]*Institut Curie, Biostatistics, Paris, France;* [3]*Institut Curie, Radiationtherapy, Paris, France;* [4]*Institut Curie, Medical Oncology, Paris, France;* [5]*Institut Curie, Radiology, Paris, France;* [6]*Institut Curie, Pathology, Paris, France*

Background: Breast cancer and endometrial cancer are frequently diagnosed in the same patient. Tamoxifen use in breast cancer patients may increase endometrial cancer incidence. The purpose of the study was to analyze endometrial cancer with breast cancer history characteristics and prognosis, and whether or not the use of tamoxifen influences the prognosis of endometrial cancer.

Materials and Methods: A retrospective study has been conducted in patients with endometrial cancer in a single institution with 3 groups according to breast cancer history: breast cancer history with tamoxifen use; breast cancer history without tamoxifen use, no history of breast cancer. Diagnosis modalities, histologic characteristics, FIGO status, and survivals were studied.

Results: From 1994 to 2004, 401 patients had been referred to Institut Curie for an endometrial cancer and 363 were eligible for the study: 80 (22%) of patients had a previous diagnosis of breast cancer history. Among them, 43 patients had tamoxifen (group 1) and 37 did not (group 2). The median duration of tamoxifen use was 48 months [4–108]. In the group 3 (no history of breast cancer), there were 283 patients.

Systematic pelvic ultrasound diagnosis was more frequent in tamoxifen group (14% vs 5 and 4%) $p = 0.02$. Carcinosarcoma histologic type was more frequent in tamoxifen group (11.7% vs 5.4% and 4.2%) $p = 0.1$. Well differentiated tumors were less frequent in tamoxifen group (42.5% vs 55.5% vs 61.7%) $p = 0.08$. No difference was noted in FIGO status. The 5-year OS was poorer in Tamoxifen group than in the 2 other groups (respectively 61.3% vs 73.25 vs 82%); $p = 0.0006$. Prognostic factors for endometrial cancer associated with OS in the multivariate analyzis were age at diagnosis, FIGO status and tamoxifen use (RR = 3.83 [1.68–4.77]; $p < 0.001$). The 5-year Local Relapse Free Survival was poorer in Tamoxifen group 82.55 vs 93.1% vs 95.9% ($p = 0.02$).

Conclusion: In this study, breast cancer history with tamoxifen use appears as a poor pronostic factor in endometrial cancer suggesting a tamoxifen role in endometrial cancer agressivity.

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ASTRRA study: a randomised phase III study for evaluating the role of the addition of ovarian function suppression (OFS) to tamoxifen in young women (<45 years) with hormone-sensitive breast cancer who remain in premenopause or regain menstruation after chemotherapy − a Korean Breast Cancer Study Group (KBCSG) trial

W.C. Noh[1], M.H. Hur[2], S.H. Ahn[3], Y. Jung[4], S.J. Lee[5], E.S. Lee[6], B.W. Park[7], J. Jong[7], S. Han[8], C.H. Park[9]. [1]*Korea Cancer Center Hospital, Surgery, Seoul, South Korea;* [2]*Kwandong University College of Medicine Cheil General Hospital and Women's Healthcare Center, Surgery, Seoul, South Korea;* [3]*College of Medicine University of Ulsan and Asan Medical Center, Surgery, Seoul, South Korea;* [4]*Ajou University School of Medicine, Surgery, Suwon, South Korea;* [5]*Yeungnam University College of Medicine, Surgery, Daegu, South Korea;* [6]*Korea University College of Medicine, Surgery, Seoul, South Korea;* [7]*Yonsei University College of Medicine, Surgery, Seoul, South Korea;* [8]*Inje University Sanggyepaik Hospital, Surgery, Seoul, South Korea;* [9]*Hallym University College of Medicine and Korean Breast Cancer Society Group (KBCSG), Surgery, Seoul, South Korea*

Background: About 60% of newly diagnosed breast cancer patients are premenopausal in Korea and it is already known that these young women have worse prognosis compared to postmenopausal patients. Tamoxifen resistance may contribute to the poor prognosis in this group, however the clinical role of adding OFS for young women who remain premenopausal or resume menstruation after chemotherapy is still controversial. There are several ongoing trials such as SOFT, TEXT, PERCHE, but in these trials, the menopausal status was assessed only one time after chemotherapy. The ASTRRA study is aimed to answer 2 main questions. One is, if the addition of OFS to an adjuvant chemotherapy plus tamoxifen in young women with ER+ tumour who remain premenopausal will provide benefit and the other is, if the delayed OFS followed the monitoring of the menopausal status until 2 years after an adjuvant chemotherapy will be beneficial in terms of disease-free survival (DFS).