joint pain – no difference in frequency between L and A. Joint stiffness reported by 10 patients was more common with A than L ($p = 0.014$). 56% reporting joint symptoms on L did not have the same problems on A and 55% with problems on A did not report joint symptoms on L. Change over time: By 3 months all bone markers had significantly increased from baseline. Further increases were seen at 6 months in PINP, serum CTx, bone ALP (all $p < 0.00001$) and urinary NTx ($p = 0.04$) but not in PTH. Patients with prior T had significantly greater increases than no prior T group at both 3 and 6 months (all $p < 0.002$). The fall in PTH was less in the prior T group ($p = 0.0004$). Joint problems increased over time irrespective of drug sequence ($p = 0.0009$). Joint symptoms comparing Letrozole and Anastrozole vs Tamoxifen 57% with joint symptoms on T did not have these on A. Conversely 74% with joint symptoms on L and (85%) with joint symptoms of A did not have these on T.

Conclusions: A and L cause similar significant increase in bone turnover which increases at least to 6 months. Prior T has a major effect on how AIs affect bone. Over half of patients with joint symptoms on L or A do not have the same problems on the other drug. Three quarters with joint symptoms on A or L did not have these problems on T.

12 Proffered Paper Oral

Aktivation of the Akt and MAPK pathways in relation to survival for patients with estrogen receptor positive breast cancer subjected to adjuvant tamoxifen

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Background: Resistance to endocrine therapy is a clinical problem also in some patients with an endocrine sensitive breast cancer (BC), expressing significant levels of ER and/or PgR. Cross-talk between the ER and receptor tyrosine kinases (RTK) as the EGFR family and downstream intracellular kinases such as Akt, extra cellular signal related kinase (ERK), c-Jun-terminal kinase (JNK) and p38 has been suggested as one reason for resistance.

The aims of the study was to investigate the expression of phosphorylated MAPK's (pJNK, pERK, pp38) and pAkt in primary BC and to relate expression to survival after adjuvant tamoxifen (tam).

Patients and Methods: A total of 449 patients with operable ER pos. breast cancer, stage I-III diagnosed 1991−96 and treated with tam for 2 or 5 years were included. The median age was 63 years (range 30 to 96). The median follow up time is 9.8 years. Quantification was done by use of a flow cytometry based analyser unit with fluorescent dyed microspheres bound to antibodies.

Results: All four kinases showed a significant reciprocal correlation where pERK/pp38 showed the strongest correlation ($r = 0.6$) ($p < 0.05$). All kinases but pp38 were related to better clinical factors; pAkt with few lymph node metastasis ($p = 0.036$), pERK with smaller tumour size ($p = 0.022$), pJNK with smaller tumour size ($p < 0.01$) and lymph node metastasis ($p = 0.001$). All three were significantly correlated with low S-phase fraction (SPF). Low levels of pAkt was significantly correlated with lover recurrence-free survival (RFS) ($p = 0.007$), a similar tendency not reaching statistical significance was seen for pJNK and pERK. Contrary pat with extreme high levels of at least one kinase (20% of patients) did not benefit from 5 years tam (HR = 1.06; 95% CI = 0.4−2.5, $p = 0.9$) compared to those without extreme levels of any kinase (HR = 0.58; 95% CI = 0.4−0.9, $p = 0.01$).

Discussion: Intracellular signalling of phosphorylated kinases may function differently i.e. to both promote cell survival and apoptosis due to different pathways, iso-forms and co-activators. Both JNK and p38 is reported necessary for tam induced apoptosis (Pearson et. al. 2001, Kyriakis et. al. 2001), while higher levels of p38 has been reported as correlated to less efficacy of neo-adjuvant endocrine therapy (Gutierrez et al. 2005). This rise the hypothesis that modest activated kinases may be a marker of a functional ER thus responding to tam treatment.

Conclusions: Activated kinases are correlated to each other, and all but pp38 to less aggressive BC (smaller tumours, fewer lymph-node metastasis and low SPF). Only lower levels of pAkt were significantly correlated to shorter RFS.

Wednesday, 16 April 2008 16:00–17:25

CLINICAL SCIENCE SYMPOSIUM

Breast cancer surgery: Quo Vadis?

13 Invited

The key role of the surgeon in translational research

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The surgeon is in an ideal position to co-ordinate translational research in breast cancer. The first doctor to see the patient is the surgeon and in patients with a mass the surgeon performs a core biopsy to establish diagnosis. This provides an opportunity to obtain fresh tissue which can then be stored for subsequent research purposes. Most patients with breast cancer come to surgery. The period of time between diagnosis and surgery provides an opportunity to give patients a variety of agents and investigate the effects of these agents on the breast cancer. These pre-operative or window studies have already provided valuable information on the effects of aromatase inhibitors and novel biological agents. It is the ideal setting to investigate new drugs and specifically to establish the biological effects of the drugs and the appropriate dose. Furthermore the surgeon is in a good position to obtain further fresh tissue after drug treatment at surgery. Using micro array techniques to investigate the effects of drugs on cancers, it is possible to identify in much greater detail than was previously possible, the exact mechanisms of the action of a particular drug and the various targets it hits. Current data suggest that analysis of the tumour following a challenge with drugs, gives more useful information than an analysis of the primary tumour prior to any treatment.

The other active area of translational research which involves surgeons is neoadjuvant therapy. Work in our own Edinburgh Breast Unit demonstrated that aromatase inhibitors appeared to be of greater potential than tamoxifen and this was subsequently confirmed in a randomised clinical trial. By collecting tissue at diagnosis, during and after treatment, it has also been possible to identify patterns and early changes within tumours which predict for subsequent response. By conducting such studies, it should be possible to better delineate those patients who benefit from endocrine, chemotherapeutic, and biological agents. By investigation of those who are either primarily resistant or subsequently develop resistance to the different treatments, it should also be possible to investigate pathways to circumvent this resistance.

Obtaining high quality tissue specifically collected for research is pivotal to improving our understanding and obtaining better treatments for our patients. The surgeon is in an ideal position to collect such tissue and more surgeons should be involved in translational research.

14 Invited

Oncoplastic surgery: extending breast conservation possibilities

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The number of breast cancer patients treated with breast conservation is expanding. However, when proposing breast conserving therapy, one should be sure to leave a normal appearing breast, as secondary reconstruction of breast deformities is difficult: it requires further operations and often leads to disappointing results. The objectives for conservative breast cancer surgery are thus to develop surgical techniques that allow wide resections with free histologic margins, but do not distort the breast. However, in patients with large, ill-defined or poorly situated tumours, cosmetic results after conservative surgery can be poor and clear resection margins difficult to obtain. Oncoplastic surgery is a novel surgical approach, which integrates plastic surgery techniques at the time of the initial lumpectomy. Initially this approach was developed to allow wide breast excisions and prevent breast deformities. Oncoplastic surgery has furthermore allowed us to extend the indications of breast conserving surgery to tumours that would otherwise be treated by mastectomy.

Methods: All Oncoplastic techniques are based upon plastic surgery techniques that are used to immediately reshape the breast at the time of the initial conservative surgery. They can be unilateral or bilateral, as a contralateral symmetrization is often necessary to obtain breast symmetry. When indicated, this symmetrization is performed during the same initial operation as the lumpectomy. Over the years, we have developed a wide range of techniques, to be able to answer most clinical situations, depending on the breast volume and the tumour location. We present a prospective study of 300 patients who were operated on for breast carcinoma between July 1985 and December 2002. All patients had a wide tumor excision, with a remodelling mammoplasty and immediate

contralateral symmetrization. The procedure was proposed for patients in whom conservative treatment was possible on oncologic grounds but where a standard lumpectomy would have led to a poor cosmetic result. Standard institutional treatment protocols were followed. Depending upon ongoing protocols at the time of treatment, patients were proposed pre-operative chemotherapy to downsize their tumours.

Results: In a series of over 300 patients, mean tumor size was 32 mm (range 10–110). The mean weight of the lumpectomy specimen was 220g, as compared with 30g for a standard lumpectomy, showing the extent of resection one can perform by performing these oncoplastic techniques. Postoperative treatments (chemotherapy, hormonal treatment or radiotherapy) were not modified because of the surgical treatment, and all patients received post-operative radiotherapy. Results showed actuarial 5-year local recurrence rate of 8% (1.8−16.9), overall survival rate of 93.7% (91–100) and metastasis free survival rate of 88.4% (72.5−93.2). Cosmesis was favourable in 82% of cases.

Conclusions: The use of oncoplastic techniques and concomitant symmetrization of the contralateral breast allows extensive resections for conservative treatment of breast carcinoma and results in a favourable oncologic and aesthetic outcome. The indications for oncoplastic surgery are patients for which the ratio between tumor volume and breast volume is such that a standard excision is not technically feasible, whilst conservative treatment is safe by oncologic grounds. This approach is useful in extending the indications for conservative therapy. It is fully compatible with preoperative chemotherapy and postoperative radiotherapy and chemotherapy, and is now part of our multidisciplinary approach for breast cancer treatment.

15 Proffered Paper Oral

Intra-operative sentinel lymph node metastasis detection in breast cancer by "One-step Nucleic Acid Amplification (OSNA)" – results of the French multicentre prospective study

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Background: Sentinel lymph node (SLN) biopsy is widely used as a staging procedure in early breast cancer. Conventionally used procedures for intra-operative assessment are frozen sections or touch imprint cytology, but they show insufficient sensitivity. The OSNA method was developed to accurately detect metastases ($\geqslant$0.2 mm) in an intra-operative setting. The objective of this French multicentre (8 centres) prospective study was to evaluate diagnostic performance of OSNA in comparison to intensive histological examination.

Material and Methods: The semi-automated OSNA test is based on a short sample preparation step and subsequent rapid amplification of reverse-transcribed CK19 mRNA. Results are obtained within 30 minutes. A total of 311 SLN from 145 breast cancer patients were analysed. Fresh SLN were cut into four slices. Two alternate slices were analysed by OSNA while the remaining two slices were subjected to Haematoxylin & Eosin and immunohistochemistry (IHC) examination (5 levels with CK19 and AE1/AE3). In case of discordant results, the lysates of homogenized samples were subjected to RT-PCR and Western Blotting in order to verify OSNA results and to detect whether the discordant results were caused by tissue allocation bias (TAB): localisation of tumour deposits in only one slice due to study design.

		Histological examination (H&E and IHC)		Total
	Nodes	Positive (size $\geqslant$0.2 mm)	Negative	
OSNA	Positive	29	10#	39
	Negative (<2.5×10^2 copies/ml)	6* (2)	266	272 (268)
	Total	35 (31)	276	311 (307)

() Results after Discordant case investigation (DCI).
*4 of those 6 cases were due to TAB. 1 sample was positive with H&E but negative by CK19 IHC. DCI is still underway for 1 sample.
#2 of those 10 cases had positive OSNA results very close to the cut-off level. For 4 samples, low CK19 mRNA copy numbers (190 to 480 copies/μl) were found by QRT-PCR and DCI is still in process for 4 samples.

Results: See the table.

After the present DCI correction because of tissue sampling (4 cases), the overall concordance rate was 96.09% (sensitivity = 0.9355, 95% CI: 0.7928–0.9821; specificity = 0.9638, 95% CI: 0.9346–0.9802), which might even be higher in case TAB is detected in the remaining 5 discordant samples.

Conclusion: OSNA is a rapid and useful tool for intra-operative assessment of SLN metastases which expressed CK19 (96.6% of the tumours in this study) and could improve the standardization of this examination.

16 Proffered Paper Oral

Impact of magnetic resonance on breast cancer surgical treatment

D. Martinez-Cecilia[1], M. Alvarez-Benito[2], P. Rioja-Torres[1], A. Arjona-Sánchez[1], C. Muñoz-Villanueva[3], G. Bascuñana-Estudillo[1], S. Rufian-Peña[1]. *[1]Hospital Universitario Reina Sofia, General Surgery, Cordoba, Spain; [2]Hospital Universitario Reina Sofia, Radiology, Cordoba, Spain; [3]Hospital Universitario Reina Sofia, Investigation and Statistics, Cordoba, Spain*

Background: One of the most widely used indications for magnetic resonance imaging (MRI) in breast cancer is to preoperatively evaluate diagnosed tumors for size, extent of disease, multifocality, multicentricity and bilaterality.

The main objective of this study was to evaluate the influence of preoperative MRI on the surgical treatment of breast cancer, by detecting multifocal, multicentric and contralateral lesions not diagnosed with conventional techniques.

A secondary aim was to evaluate the efficacy of MRI in the evaluation of the tumor size.

Patients and Methods: 712 patients underwent surgical intervention in our hospital between January 2005 and January 2007 for breast cancer. The preoperative staging algorithm includes bilateral mammography and ultrasound, with axillary exploration and fine needle aspiration biopsy (FNA). When histological diagnosis of malignancy was done, MRI was performed. If any additional lesions were discovered, a new FNA was performed.

Data were collected prospectively and evaluated retrospectively. Therapeutic intention was registered before and after the result of the MRI. Additional tumor foci newly diagnosed by MRI were checked with the specimen study. Tumor size in the three different image techniques was compared with the pathological size.

Results: 249 patients were included in our study. 20 additional malignant lesions were found in 18 patients (8%), changing the surgical approach in 15 patients (3 required contralateral surgery, 1 required double lumpectomy in the same breast, 11 changed from lumpectomy to mastectomy). These lesions were: 13 infiltrating ductal carcinoma, 4 invasive lobular carcinoma, 1 papillary carcinoma, 1 tubular carcinoma, 1 ductal carcinoma in situ.

But the surgical treatment was also changed due to a larger size of the tumor on the MRI: 16 patients changed from lumpectomy to mastectomy and 1 patient from lumpectomy to quadrantectomy.

Therefore MRI changed the surgical management in 32 patients (13%). After checking the specimens of these patients, the changes resulted to be beneficial in 22 patients (9%), non beneficial in 6 patients (2.4%) and uncertain in 4 patients (1.6%). Spearman's rank correlation coefficient was strongly positive (rs = 0.729) when tumor sizes were compared in MRI and pathology results. The association was strong, but less, when comparing pathology results with mammography (rs = 0.658) and ultrasound results (rs = 0.629).

Conclusions: Preoperative MRI modified the surgical approach in, at least, one out of every nine patients in our series.

MRI was also the best technique for diagnosing the size of the lesion in the preoperative staging of the breast cancer.

Breast MRI has been incorporated into our staging protocol, and should be considered as a necessary technique for breast cancer staging.