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The Usefulness of Routine Immunohistochemical Evaluation of Sentinel Lymph Nodes in Breast Carcinoma Patients

T. Nowikiewicz[1], E. Srutek[1], E. Krajewski[1], R. Laskowski[1], W. Zegarski[2]. [1]*Oncology Centre Bydgoszcz, Department of Clinical Breast Cancer and Reconstructive Surgery, Bydgoszcz, Poland;* [2]*Oncology Centre Bydgoszcz, Surgical Oncology Clinic Collegium Medicum Nicolaus Copernicus University, Bydgoszcz, Poland*

Background: Each diagnostic method to detect occult metastases in sentinel lymph nodes (SLNs) can significantly change the therapeutic methods and long-term results of treatment. In the presented study, attempts to determine the usefulness of immunohistochemistry (IHC) in the pathological assessment of SLNs, have been made.

Material and Methods: A retrospective analysis concerning 728 early stage breast cancer patients with clinically negative lymph nodes, operated between 01.2004 and 05.2011, has been made. In those patients, the sentinel lymph nodes biopsy (SLNB) was performed. It was the surgeon performing SLNB, who decided about intraoperative exam of SLNs by frozen section. Postoperatively a routine hematoxylin-eosin stain (HE) was made. If the HE sections showed no evidence of metastases, cytokeratin (AE1IAE3 and CK7) immunhistochemistry was additionaly used with some patients. The dependence of the number and size of removed lymph nodes on the presence of SLNs metastases was also analyzed. Moreover, the influence of the type of preoperative diagnosis of primary tumor on the presence of SLNs metastases was defined.

Results: The metastases in SLNs were diagnosed in 154 patients (macrometastases in 79.2% of cases, micrometastases − 20.8%). Using IHC techniques enabled detection of metastases in 30 patients (9% macrometastases and 59.4% micrometastases). IHC resulted in an increase in the total number of diagnosed metastases of SLNs, over 24% (by 9.9% for macrometastases, by 146.2% for micrometastases). In the majority of cases (84.9%) the intraoperative assessment of SLNs was performed. According to the analysis, the sensivity of intraoperative evaluation of SLNs was 62% (for macrometastases 76%, for micrometastases 8%) and 100% specifity for the method. There was no statistical correlation between the type of preoperative diagnosis of primary tumor and the presence of metastases or the number and size of removed nodes.

Conclusions: The use of cytokeratin IHC for diagnoses of occult metastases in SLNs patients with early stage breast cancer is a valuable addition to standard histopathological assessment of SLNs. It enables detection of a higher number of metastases, thus modifying the adjuvant treatment.

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Do Screen-detected Breast Cancers Have Free Margins More Often Than Symptomatic Breast Cancers?

L. de Munck[1], S. Siesling[1], J. Bart[2], M.B.E. Menke-Pluijmers[3], R. Otter[1], P.H.B. Willemse[4]. [1]*Comprehensive Cancer Centre the Netherlands, Research, Groningen, The Netherlands;* [2]*University of Groningen University Medical Center Groningen, Department of Pathology, Groningen, The Netherlands;* [3]*Erasmus MC Daniel den Hoed, Department of Surgery, Rotterdam, The Netherlands;* [4]*University Medical Center Groningen, Department of Medical Oncology, Groningen, The Netherlands*

Purpose: To determine whether women with screen-detected breast cancer have involved margins after breast-conserving surgery (BCS) less often compared to women with symptomatic breast cancer.

Methods: Women 50−75 years of age who underwent BCS for invasive breast cancer or ductal carcinoma in situ (DCIS) between July 2008 until December 2009 in the north eastern part of the Netherlands were selected from the population-based Netherlands Cancer Registry. Data were merged with the breast screening programme north and east to identify women with screen-detected breast cancer. The relation to screening history, clinical and pathological factors were evaluated for correlation with margin status.

Results: Of 1,537 women with an invasive breast cancer, 873 (56.8%) were diagnosed through the screening programme. Screen-detected tumours were significantly smaller (87% vs. 69% <2 cm), more often well differentiated (33% vs. 26%), preoperatively confirmed (98% vs. 96%), diagnosed in a non-teaching hospital (60% vs. 56%) and had more often negative lymph nodes (80% vs. 68%). In 170 of the 1,537 (11.1%) women the resection margin was involved.

A large range of involved margins was found between different hospitals (range 2−29%). In a multilevel analysis, taking hospital into account, there was no difference between women with screen-detected cancers compared to women with symptomatic cancers. Nevertheless, margin status was affected by other factors. Larger tumour size, multifocality, positive lymph nodes and the absence of preoperative confirmation were all predictors of involved margins. No difference was found with the number of patients operated per surgeon. Of women with involved margins, 90% underwent a re-excision or amputation. In women with pure DCIS, margins were involved in 60 out of 187 (32.1%) women.

Discussion: Women with breast cancer diagnosed through the screening programme do not have a lower risk of involved margins after BCS than women with symptomatic breast cancer. Factors influencing involved margins were type of hospital, larger tumour size, multifocality, positive lymph nodes and the absence of preoperative confirmation.

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Implant Based Immediate Breast Reconstruction Utilising Strattice™ Mesh and Its Impact On Adjuvant Treatment

E. Evgeniou[1], S. Amonkar[1], C. Hennessy[1], P. Bhaskar[1], H. Cain[1]. [1]*University Hospital of North Tees, Breast, Stockton on Tees, United Kingdom*

Background: The UK national mastectomy and breast reconstruction audit reported improved patient satisfaction with mastectomy and immediate breast reconstruction (IBR). One technique being increasingly used is implant based IBR utilising Strattice™ mesh. However, there are concerns that this technique may delay adjuvant treatment. Given this, we reviewed all cases of IBR using Strattice™.

Methods: Case series of all implant based IBR using Strattice™ performed between March 2009 and March 2011 in our unit.

Results: 21 implant based IBR utilising Strattice™ in 17 patients were studied, 4 were bilateral procedures. 2 patients both BRCA gene carriers had bilateral risk reducing mastectomies and IBR. Mean age at surgery was 52 (range 30−66) years. BMI ranged from 19–35.8 (median 26) kg/m^2. All patients were non-diabetics, 2 of whom were smokers. 10 patients had complications, 9 required a clinical intervention. 4 patients had a 'red flare reaction' associated with a seroma. 5 patients had a wound breakdown with eventual loss of the implant and one patient had an early contracture following radiotherapy. 25% of patients requiring adjuvant radiotherapy had a delay in starting treatment. Half of patients requiring adjuvant chemotherapy had a delay in commencing treatment. 50% of patients requiring chemotherapy also experienced delays between cycles resulting from complications.

Conclusions: 53% (9/17) of patients had complications requiring clinical intervention. We suggest these complications may be addressed at three points; Pre-operatively consideration should be given to the necessity for adjuvant treatment and the type of skin sparing mastectomy procedure. Inter-operatively thorough washing of the mesh, the use of drains and the choice of implant to minimize tension on the skin wound. Post-operatively patience with repeat aspiration of seroma rather than the assumption of mesh infection in patients with a 'red flare' reaction. Utilizing these measures complications could be reduced.

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Effect of One Step Molecular Intraoperative Method in Detection of Micrometastasis in Sentinel Node and Management of Them

J. Sanchez-Mendez[1], M.J. Lopez-Rodriguez[2], C. Escabias Del Pozo[3], J.M. Oliver Goldaracena[3], A. Redondo Sanchez[3], B. Belinchon Olmeda[3], D. Hardisson Hernaez[1]. [1]*H Universitario La Paz − IdiPaz, Breast Unit, Madrid, Spain;* [2]*H Universitario Ramón y Cajal, Breast Unit, Madrid, Spain;* [3]*H Universitario La Paz, Breast Unit, Madrid, Spain*

Background: The implement of molecular intraoperative analysis of sentinel lymph node in breast cancer has changed the scene of the axillar management.

The OSNA (One-Step Nucleic Acid Amplification) method measures the tumoral burden of the node, and theoretically this is different from the classical pathological criteria of node involvement, that guides theclassification and treatment of breast cancer patients.

So it's expected that due OSNA method the number of metastasis and micrometastasis in sentinel nodes has increased, and we don't know if this fact means a better staging or on the other hand it would be an overstaging.

The aim of our study is to analyze the impact of OSNA method in our population, and discuss which could be the best accurate management of these patients.

Materials and Methods: We compare the results from the analysis of sentinel lymph node dissection (SLND) 1 year before and after OSNA method implement in our Hospital (2010 April). In the first period the nodes were analyzed intraoperative (in frozen section) and delayed (in formalin fixed each 200 micrometers sections) with hematoxilin eosin (HE). In the second period the sentinel nodes were fully analyzed by detection of cytokeratin 19 mRNA.

Results: In the previous 12 months to 2010 April, we have recorded 146 SLND in patients with breast cancer, and 156 in the 12 month after that date. Both groups have similar patients characteristics.

There is no significative differences in micrometastasis detection between the intraoperative OSNA method (21/156) and the classical HEintraoperative plus delayed method (18/146) − p = 0.3.

In the same period the macrometastasis fall down a 30% due to a better preoperative evaluation by means of axillary echography ± puncture, that exclude from SLND cytological positive axillary nodes.

Conclusions: The OSNA method provides similar results, about micrometastasis, than manual intraoperative plus delayed HE method.

Conclusions of the recently published ACOSOG Z0011 trial, as well as many papers that are questioning the therapeutic value of complete axillar dissection after sentinel lymph node positive, let's safety avoid it In most of cases of micrometastasis. When the result is a macrometastasis we proceed conform the patient wishes, after discuss the possibilities with her, before surgery, and after to analyze the theoretical benefit in each real circumstances.

Further studies are necessary to analyze the cost-efficacy of OSNA method in expertise pathologist centers.

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Development of New Generation of Breast Implant Using Silsesquioxane Nanocomposites Shell

L. Mousavi[1], A. Seifalian[1], M. Keshtgar[1]. [1]*Royal Free Hospital, Surgery, London, United Kingdom*

Introduction: Silicone implants are being used increasingly worldwide, in breast reconstruction after cancer surgery or breast augmentation procedures. Various complications have been associated to the use of breast implants in which capsular contracture and implant failure are the most common.

To overcome the complications, our group have developed a novel nanocomposite material based on polyhedral oligomeric silsesquioxane-poly (carbonate-urea) urethane (POSS-PCU) for use as tissue implants.

Method: To investigate capsular contracture, we performed in vitro and in vivo experiments as follows:

In vitro: Human monocyte derived macrophages (MDMs) were seeded on the wells of culture plates that were already covered with nanocomposite; equal number of wells covered with silicone used as control. These culture plates were maintained in culture for up to 4 days.

In vivo: we implanted nanocomposite polymers in six healthy sheep for 36 months and a silicone implant served as control. After explantation, we looked for signs of surface degradation on the polymer by performing attenuated total reflectance Fourier transform infrared spectroscopy analysis. Histopathologic and electron microscopic examinations were performed in order to study the interaction between the biomaterial and the host environment in greater detail.

All mechanical property experiments (Shell ultimate elongation, Tensile and Tear test) were conducted with an Instron electromechanical testing system for nanocomposite and silicone with the same protocol in the same environment.

Result: macrophage stimulation on the samples exposed to silicone was more than the nanocomposite, implying more foreign body reaction with silicone. The viability of macrophages cultured on different substrates was not affected.

In vivo tests showed minimal inflammatory reaction of the nanocomposite within the sheep model as compared with the silicone control. The increased fibrinogen adsorption on POSS-PCU, its amphilicity, and large contact-angle hysteresis indicated that our nanocomposite inhibits inflammation by adsorbing and inactivating fibrinogen on its surface. In complete contrast, the control silicone in the same setting demonstrated very significant inflammation and degradation, resulting in capsular formation. Naturally, there was no evidence of degradation of the nanocomposite compared with the silicone control.

Tensile test showed that mechanical strength of our nanocomposite polymer is about 7 times higher than silicone control with half the silicone thickness.

Conclusion: POSS-PCU nanocomposites have enhanced interfacial biocompatibility, better biological stability and stronger mechanical properties as compared with conventional silicone biomaterials, thus making them safer as tissue implants.

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Validation of Three Different Nomograms to Predict the Risk of Non-Sentinel Lymph Node Involvement in Turkish Breast Cancer Patients with Sentinel Lymph Node Metastasis

L. Yeniay[1], A.C. Karaca[2], E. Carti[1], N. Ozdemir[3], U. Yararbas[4], O. Zekioglu[3], R. Yilmaz[1], M. Kapkac[1]. [1]*Ege Universitesi Tip Fakultesi Hastanesi, General Surgery, Bornovoa / Izmir, Turkey;* [2]*Ege Universitesi Tip Fakultesi Hastanesi, General Surgery (Genel Cerrahi ABD), Bornovoa / Izmir, Turkey;* [3]*Ege Universitesi Tip Fakultesi Hastanesi, Pathology, Bornovoa / Izmir, Turkey;* [4]*Ege Universitesi Tip Fakultesi Hastanesi, Nuclear Medicine, Bornovoa / Izmir, Turkey*

Background: The sentinel lymph node biopsy after having proven it's efficacy and reliability by many randomized controlled studies has become an alternative of axillary lymph node dissection (ALND) in convenient patients. ALND still remains as 'the gold standard" for patients with positive SLN. However only 30−50% of the breast cancer patients with positive sentinel lymph nodes (SLN) have non-sentinel lymph node involvement in the axilla. Nomogram accuracies for predicting non-SLN involvement vary between different patient populations. Our aim is to put these nomograms to test on our patient population and determine our individual predictive parameters effecting SLN and non-SLN involvement for our patient population.

Methods: Data collected from 932 early breast cancer patients who underwent SLN biopsy between 2003 and 2011 was retrospectively analyzed. Nomogram values calculated for each patient utilizing Memorial Sloan Kettering Cancer Center (MSKCC), Tenon and MHDF (Turkish) models. Nomograms' accuracies were tested with the calculation of AUC values of ROC curves. Moreover, using our own patient and tumor depended parameters, we established a unique predictivity formula for SLN and non-SLN involvement. Statistics Package for Social Sciences version 16.0 was utilized for statistical analyses. The tests used for statistical analyses were; Chi Square, analysis of variance (ANOVA), receiver-operating characteristic (ROC) curve, Fisher's exact test, Mann-Whitney test and logistic regression. P values under 0.05 were accepted as statistically significant.

Results: All the patients except one were female. Median age was 51.9±11.6 (19−85) years. A total of 2565 SLN were excised. A median number of 2.75 (1−10) SLN was found to have been excised for each patient. Median tumor size was 18±8.9 mm (0.1−50 mm).SLN invasion was present in 271 of the patients. Complementary AD was performed in 244 of these patients and 100 (40.9%) had non-SLN metastasis. The median follow up time was 34 (1−93) months. The calculated AUC values for MSKCC, Tenon and MHDF models were 0.727 (95% CI 0.64−0.8), 0.665 (95% CI 0.59–0.73) and 0.696 (95% CI 0.59–0.79) respectively. In the multivariety regression analyses of the factors effecting the positivity of SLN and non-SLN; tumor size (p = 0), presence of lymphovascular invasion (p = 0) and progesterone receptor positivity (p = 0.012) were found to be correlated with SLN positivity while Cerb-2 positivity (p = 0.004) and size of the metastasis in the lymph node (p = 0.006) were found to correlate with non-SLN involvement in our study group. The AUC value of the predictivity formula established using these parameters was 0.722 (95% CI 0.63–0.81).

Conclusion: The most accurate nomogram for our patient group was the MSKCC nomogram. Our unique predictivity formula using only two predictive variables, proved to be as equally effective and competent as the MSKCC nomogram. However, likewise other nomograms our predictivity formula needs future validation studies.

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A New Predictive Model for Predicting the Non-sentinel Lymph Node Metastases in Breast Cancer Patients with Positive Sentinel Lymph Node Biopsy

A. Lombardi[1], S. Maggi[1], M. Lo Russo[1], C. Bartone[1], L. Bersigotti[1], G. Lazzarin[1], C. Amanti[1]. [1]*Università La Sapienza, Unità di Chirurgia Senologica, Rome, Italy*

Background: Completion Axillary Limph Nodes Dissections (CALND) performed in breast cancer (BC) patients with positive Sentinel Lymph Node (SNL) at definitive histology show additional nodal metastases in only 35% to 50%. Some institutions proposed statistical methods to identify patient's risk for non-SLN metastases. Aim of this paper was developing a new tool with the final goal of avoiding unnecessary CALND.

Materials and Methods: We retrospectively evaluated 593 primary BC patients. 139 positive SLN underwent CALND. The predictive accuracy of five published nomograms (MSKCC, Tenon, Cambridge, Stanford and Gur) was measured by the AU ROC curve. Then we developed a new logistic regression model comparing the performances. Our model was validated by the leave-one-out cross validation method.