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Is full complete dissection axillary necessary for all patients with positive findings on sentinel lymphnode biopsy? Validation of a breast cancer nomogram for predicting the likelihood of non sentinel lymph node

C. Amanti[1], A. Lombardi[1], S. Maggi[1], M. Lo Russo[1], L. Moscaroli[1], R. Maglio[1], M. Pezzatini[1], G. Provenza[1], C. Romano[1], F. Scopinaro[2]. [1]La Sapienza Rome University, Breast Surgery S. Andrea Hospital, Rome, Italy; [2]La Sapienza Rome University, Nuclear Medicine S. Andrea Hospital, Rome, Italy

Background: The sentinel lymph node (SLN) procedure is a reliable technique for assessing axillary lymph node involvement in breast cancer. To identify the individual patient's risk for non-SLN metastases, a nomogram was developed by the Breast Service of Memorial Sloan-Kettering Cancer Center.A nomogram is a tool to depict a complicated calculation created using variable following: pathologic size, tumor type and nuclear grade, lymphvascular invasion, multifocality, estrogen receptor status, method of detection of the SLN metastases (frozen section, serial H&E, routine H&E, IHC) number of positive SLNs and number of negative SLNs. The outcome of the nomogram is the predicted probability of non-SLN metastases. This can be determined by the web site http:// www.mskcc.org / nomograms or through a personal digital compatible application. The aim of this study was to assess to nomogram's preditictive accuracy in a population of breast cancer patients from Italy. in our hospital.

Materials and Methods: We consider 221 consecutive breast cancer patients that underwent an SLN biopsy for a clinical T1/2N0 breast cancer in the our Breast surgery Division. Data concerning these patients were collected in a database. The biopsy revealed metastatic disease in 61 patients (32%). To be included in the study population, patients had to meet the following criteria: patient had to undergo operation for a primary invasive breast cancer, without neoadjuvant therapy; the SLN biopsy had to be successfull and the SLN had to contain any amount of metastasic disease.

Patient and tumor characteristics were collected from the prospective database for each variable of the MSKCC nomogram:
1. tumor type (ductal vs lobular carcinoma), nuclear grade
2. pathologic size
3. presence of lymphvascular invasion
4. multifocality
5. estrogen receptor status
6. method of detection of the SLN metastases (routine histopatology, serial H&E, IHC immunohistochemistry)
7. number of positive SLNs
8. number of negative SLNs

Results: The predicted probability of risk to have additional nodal metastases was calculated for each patient:
1. High Risk (57.3%) range 19−66% LNS/PZ (27/35)
2. Medium Risk (24.5%) range 10−18% LNS/PZ (4/16)
3. Low Risk (16.3%) range 3−9% LNS/PZ (0/10)

In the totality of the patients (61) 16% of the patients have found an inferior value to 10% of additional nodal metastases risk therefore consider you like patients with possibility to avoid a complete axillary dissection.

Conclusions: This method may allow identification of an individual risk extremely low for which the risks associated with complete dissection can overcome the beneficial effects. The nomogram provides a fairly accurate predicted probability for the likelihood of non sentinel limph nodes (SLN) therefore in the practical current it would have to be used to avoid the complete axillary dissection, and its complications, in all the patients with low risk (<10%).

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Axillary recurrencein breast cancer patients after a negative sentinel lymph node biopsy

J. Benson[1], G.C. Wishart[1], P. Forouhi[1], B. Jones[1], S. Pinder[1], E. Provenzano[1]. [1]Addenbrooke's Hospital, Cambridge Breast Unit, Cambridge, United Kingdom

Background: Sentinel lymph node (SLN) biopsy is an accepted standard of care for patients with clinically node negative breast cancer. Validation studies have revealed false negative rates of 5−10%, but few studies have reported rates of axillary recurrence in SLN negative patients without completion axillary lymph node dissection (ALND).

Materials and Methods: A retrospective analysis was undertaken to examine axillary recurrence amongst a group of 314 clinically node negative patients undergoing SLN biopsy for symptomatic and screen-detected breast cancer between January 2004 and December 2006 (median tumour diameter 15 mm). The median age of patients was 64 yrs with a range of 23−88 years. Dual localization methods were used and

all patients were classified as sentinel lymph node negative on H&E step sections but included some patients with deposits of isolated tumours cells on either H&E or immunohistochemistry ($\leqslant$0.2 mm). The median tumour diameter for the invasive component was 15 mm (range 2−40 mm). To allow at least 12 months follow up, patients treated after December 2006 were excluded, together with those patients who had died without evidence of recurrence (4) and patients with DCIS only on final histology (18). This left 292 patients available for analysis, the majority of whom had received some form of adjuvant systemic therapy (262/292). Neoadjuvant patients with a negative sentinel lymph node pre-treatment were included as these did not proceed to axillary dissection after chemotherapy.

Results: At a median follow up of 28 months (range 13−48) there has been only one case of axillary recurrence (1/292). This occurred after 4 months and was the first site of treatment failure. Interestingly, the patient had only a single sentinel node harvested and this most likely represented a false negative result (mean number of sentinel nodes 2.9). Eight patients have developed distant disease without evidence of any loco-regional relapse, of whom 6 have since died. Distant relapse occurred after a median interval of 21 months following surgery (with a range of 11−37 months). One patient developed isolated chest wall recurrence after mastectomy and another supraclavicular nodal disease without distant metastases.

Conclusion: This low rate of axillary recurrence (0.34%) accords with other reports in the literature and compares favourably with ALND. Finite rates of false negativity associated with the SLN biopsy technique do not appear to translate into higher rates of axillary relapse. However, any residual disease within the axillary nodes will be low volume and longer follow up is required to substantiate these early observations.

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Validation of a nomogram to predict the risk of non-sentinel lymph node metastasis in breast cancer patients with a positive sentinel node biopsy

R. van la Parra[1], M.F. Ernst[1], S. Mol[2], P.C. Barneveld[3], J.M. Broekman[2], K. Bosscha[1]. [1]Jeroen Bosch Hospital, Surgery, 's-Hertogenbosch, The Netherlands; [2]Jeroen Bosch Hospital, Pathology, 's-Hertogenbosch, The Netherlands; [3]Jeroen Bosch Hospital, Nuclear Medicine, 's-Hertogenbosch, The Netherlands

Background: Completion axillary lymph node dissection (ALND) remains, according to the Dutch guidelines, the standard of care for patients with a positive sentinel lymph node. However, approximately 40−60% of patients with positive SLNs will have no additional metastases. To identify the individual patient's risk for non-SLN metastases, the Memorial Sloan-Kettering Cancer Center (MSKCC) developed a nomogram currently available as an online tool. The purpose of this study was to validate the nomogram in a Dutch population of breast cancer patients.

Methods: The medical records of 183 breast cancer patients who underwent sentinel lymph node biopsy examination and ALND were selected from a prospectively collected database and were reviewed for multiple clinicopathologic variables.

A receiver operating characteristic curve was drawn and the area under the curve was calculated to assess the discriminative power of the nomogram. Also, data of the index and test populations were compared.

Results: The area under the ROC curve was 0.704 (range 0.625−0.738), as compared to 0.76 in the MSKCC study. When the tool was applied solely to macrometastases, the area under the ROC was 0.648 (range 0.552−0.745).

Conclusions: The MSKCC-nomogram seems to be a useful tool to predict the individual patients risk for positive axillary non-sentinel lymph nodes in a Dutch population of breast cancer patients. Further analysis, however, has to be performed to identify subgroups, in which the nomogram is even more predictive. Predicting the risk of additional nodal metastases will allow the surgeon and patient to make an individualized decision regarding the need for completion axillary lymph node dissection.

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Predictive factors for non-sentinel lymph node metastasis in breast cancer patients with a positive sentinel node

R.F.D. van la Parra[1], M.F. Ernst[1], P.C. Barneveld[2], J.M. Broekman[3], K. Bosscha[1]. [1]Jeroen Bosch Hospital, Surgery, 's-Hertogenbosch, The Netherlands; [2]Jeroen Bosch Hospital, Nuclear Medicine, 's-Hertogenbosch, The Netherlands; [3]Jeroen Bosch Hospital, Pathology, 's-Hertogenbosch, The Netherlands

Background: Axillary lymph node dissection remains the standard of care for breast cancer patients with a positive sentinel node. However, in a significant proportion of patients the sentinel node is the only involved

lymph node. The purpose of this study was to indentify factors predictive of non-sentinel lymph node involvement after a positive sentinel lymph node.

Methods: The medical records of 181 breast cancer patients who underwent sentinel lymph node biopsy examination and ALND were selected from a prospectively collected database and were reviewed for multiple clinicopathologic variables.

Results: Univariate analysis showed a significant association between non-sentinel node involvement and primary tumour size ($p = 0.000$), size of sentinel node metastasis ($p = 0.000$), extracapsular node extension ($p = 0.000$) and the number of negative sentinel nodes ($p = 0.002$). In a multivariate analysis, only extracapsular extension remained significantly associated with a positive non-SN status.

Conclusions: Extracapsular extension is an independent predictor of non sentinel node positivity when a positive sentinel node is found. However, more additional factors need to be identified before in selected cases axillary dissection as a surgical staging procedure can be omitted.

Variable	Univariate	Multivariate	
	P	P	Odds ratio (CI)
Tumour size	0.000*	0.23	1.044
SN metastasis size	0.000*	0.107	1.080
Extracapsular extension	0.000	0.003	0.291
Number of positive SNs	0.096*	0.347	1.347
Number of negative SNs	0.000*	0.076	0.606
Age	0.455		
Tumour type	0.065		
Multifocal	0.796		
Lymphovascular invasion	0.616		
ER positive	0.554		
PR positive	0.568		
Mode of detection	0.133		
Parenchymal invasion	0.081		

Categorical p-values were calculated in univariate analysis with Fisher's exact test.
Continues variables (*) were calculated with Mann-Whitney U-test.

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The value of intraoperative frozen section examination of sentinel lymph nodes in breast cancer

S.L.B. van de Vrande[1], J.H.G. Klinkenbijl[1]. [1]Rijnstate Hospital, Surgery, Arnhem, The Netherlands

Background: Sentinel node biopsy is a standard diagnostic component for the treatment of patients with a primary mammacarcinoma. In an investigation of the prognostic survival of this cohort, a sentinel lymph node biopsy is indicated when a positive sentinel node is discovered. By concomitantly performing intraoperative lymph node biopsy and primary tumor resection, patients with a positive sentinel node are not subjected to the inconvenience and risks of second surgical intervention. The aim of this retrospective study was to determine the sensitivity, accuracy and long-term consequences of the frozen section examination of the sentinel node in breast cancer patients.

Methods: Sentinel lymph node biopsy was performed in 616 patients with an invasive tumor of the breast. Frozen sections of the sentinel node were taken from the optimal cross-sectional surface. In the event of a negative node, frozen sections were taken from the remaining sentinel node and stained using hematoxylin-eosin and immunohistochemistry.

Results: Sentinel node frozen biopsy accurately predicted the state of the axilla in 560 (90.9%) patients. There were 50 false-negative findings in patients with sentinel node metastases. The sensitivity and specificity of the intraoperative frozen section examination were 71.6% and 100%, respectively. Follow-up (mean 36.3 months) of all false-negative cases showed no development of local axillary recurrence. The results demonstrated no significant relation between tumor size and frozen section sensitivity. Frozen section investigation was less sensitive in ascertaining micrometastases (sensitivity 61.1%) than macrometastases (sensitivity 84.0%, $p < 0.001$). The majority of the false-negative results were due to the fact that micrometastases were not localized during intraoperative frozen section examination. However, the presence of micrometastases within the sentinel lymph node is of limited value since a positive sentinel lymph node biopsy was attained in only 30% of micrometastatic patients versus 61% of macrometastatic patients.

Conclusion: Intraoperative frozen section examination of the sentinel node is a useful predictor of axillary lymph node status in breast cancer

patients. Seventy-two percent of the patients with metastatic disease were correctly diagnosed and spared a second surgical procedure.

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Concordance of Her 2 neu and hormone receptor status between primary tumors and sentinel lymph node metastases

L. Strien[1], M. Leidenius[2], K. von Smitten[2], P. Heikkilä[1]. [1]University Central Hospital Helsinki, Department of Pathology, Helsinki, Finland; [2]University Central Hospital Helsinki, Department of Surgery, Helsinki, Finland

Background: Earlier a 90−98% concordance has been observed between the primary and metastasis in both HER-2 neu and the hormone receptor status, though partly studied only on behalf of the oestrogen receptor (ER) and normally not all these factors simultaneously on the same nodes. Mostly they have included only distant metastases and macrometastasis, or the analysis was only made using immunohistochemistry (IHC).

For these reasons, our aim was to study the concordance in HER-2 neu amplification, as well as ER and progesterone receptor (PR) status between the primary tumours and SN (sentinel node) metastases, including also micrometastases and ITC.

Methods: The HER-2 neu amplification status and the status of hormone receptors ER and PR was evaluated in 99 sentinel node metastases from 38 primary tumours that were HER-2 neu positive in chromogenic in-situ hybridisation (CISH) and from 61 primary tumours that were CISH−. They consisted of $23 + 23 = 46$ macrometastases, $6 + 28 = 34$ micrometastases and $9 + 10 = 19$ isolated tumour cells (ITC).

Results: No metastatic tissue for the CISH-analysis was found in 4 macro + 18 micro + 12 ITC = 34 cases. In the CISH+ primary tumours, 26 of 29 metastases were CISH+, including 23 macrometastases, 3 micrometastases and 3 ITC. Three were discordant turning negative in the metastasis. In the CISH− primary tumours, 35 of the 36 examined metastases were CISH−, while one micrometastasis showed a low level amplification of HER 2 neu gene.

The ER/PR status was concordant between the primary tumour and the SN-metastasis in 53/77 (68.8%), consisting of 29 macrometastases, 19 micrometastases and 5 ITC. No metastatic tissue for the analysis was found in 22/99 cases, consisting of 3 macro-metastases, 11 micrometastases and 8 ITC were cut. Altogether 24/77 cases were discordant.

Both the HER-2 neu amplification status and the ER and PR status could be assessed in 62/99 metastases. Full concordance in both HER-2 neu amplification status, that is positive or negative, as well as in the ER and PR status between the primary tumour and metastasis was observed in 38/62 (61.3%), that is 15/26 (57.7%) of the CISH+ cases and 23/36 (63.8%) of the CISH− cases. Of the 38 fully concordant cases were 24 macrometastatic, 13 micrometastatic and 1 ITC.

Conclusions: High concordance in HER-2 neu amplification, ER and PR status was observed between the primary tumours and their metastases, even with micrometastases and ITC, when evaluated separately. However, the full concordance between the primary tumour and the metastasis was observed less frequently.

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The distribution of axillary lymph nodes metastases and sentinel node biopsy after neoadjuvant chemotherapy in patients with locally advanced breast cancer

J. Li[1], L. Wang[1], Y. Liu[1], T. Zhao[1]. [1]Shandong Cancer Hospital, Breast Cancer Center, JiNan, China

Background: The use of neoadjuvant chemotherapy (NCT) becomes more ubiquitous in the treatment of locally advanced breast cancer (LABC), and axillary lymph nodes (ALN) downstage could be obtained in 20−30% pts. To perform SLNB substituting axillary lymph node dissection (ALND) in this pts population, the distribution of ALN metastases, SLNB successful rate (SR) and false negative rate (FNR) should be proved to be similar to that in early breast cancer.

Methods: First, we collected data of 370 LABC pts who underwent ALND after 2−3 cycles of NCT from 1996 to 2006. The ALN status at each level was analyzed. Then we performed SLNB followed by ALND in 88 pts after NCT from 2003 to 2007. We used Methylene blue alone in 81 pts and combined with 99mTc-SC in another 7 pts. The SR, FNR and accuracy of SLNB after NCT were evaluated.

Results: The distribution of ALN metastases in LABC after NCT was quite the same as that in early breast cancer, with very low incidence of skip metastases. After NCT, 30.3% pts had negative axilla, and ALN were positive only at L1 in 39.5% pts (Table 1).

The SR, FNR, and accuracy of SLNB with Methylene blue alone were 82.7% (67/81), 18.2% (10/55) and 85.1% (57/67), respectively; the rates with Methylene blue combined with 99mTc-SC were 100% (7/7), 16.7%