International Journal of Surgery 35 (2016) 58–63

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Application of a predictive model of axillary lymph node status in patients with sentinel node metastasis from breast cancer. A retrospective cohort study

Salvatore Vieni, Giuseppa Graceffa, Roberta La Mendola, Stefania Latteri, Adriana Cordova, Mario Adelfio Latteri, Calogero Cipolla*

Department of Surgical, Oncological and Oral Sciences, University of Palermo, Palermo, Italy

HIGHLIGHTS

- In about 60% of patients with metatstic SLN, there is no further axillary neoplastic involvement.
- MSKCC nomogram is a valid tool available to select the patients for axillary lymphadenectomy.
- The nomogram has a high reliability and a remarkable utility in clinical practice.

ARTICLE INFO

Article history:
Received 7 June 2016
Received in revised form
8 September 2016
Accepted 11 September 2016
Available online 12 September 2016

Keywords:
Breast neoplasms
Sentinel lymph node biopsy
Lymphatic metastasis
Axilla
Lymph node excision

ABSTRACT

Background and objectives: The Axillary Lymph Node Dissection (ALND) is the standard treatment in patients with invasive breast cancer and sentinel node metastasis, but in 60% of the cases there is no further axillary neoplastic involvement, so this invasive intervention represents an overtreatment. The purpose of the study is to identify patients with low risk of additional nodal metastases, to omit ALND.
Methods: The MSKCC *Additional nodal metastasis nomogram* was applied on a sample of 175 patients with invasive breast cancer who underwent ALND after detection of macrometastasis with the extemporaneous examination of the sentinel lymph node. Patients were classified as "low risk" when the result of the nomogram was $\leq$50%. Sensitivity, specificity, positive and negative predictive values and AUC (Area Under Curve) of the ROC curve of the nomogram were then calculated.
Results: A cut-off by 50% yielded 92.3% sensitivity, 81,4% specificity, 80% positive predictive value and 92.9% negative predictive value. The ROC curve AUC in these patients was 0.885.
Conclusions: The MSKCC nomogram has proven to be an effective tool in estimating the axillary lymph node status and it can potentially be used to better select the patients with sentinel node macrometastasis who can actually benefit from ALND.

1. Introduction

In patients with invasive breast cancer and clinically negative axilla, the sentinel lymph node biopsy (SLNB) is considered to be a safe and reliable tool in the estimation of the neoplastic involvement of axillary lymph nodes and, if it results positive for metastasis, the treatment currently provided in clinical practice is the axillary lymph node dissection (ALND). However, recent evidences show that only in 40% of the cases the sentinel lymph node metastases are associated with a further involvement of the axilla [1] and that the omission of ALND in patients with tumors characterized by favourable histopathological features, no palpable adenopathy and 1 to 2 metastatic sentinel lymph nodes is not associated with a worse prognosis [2,3]. In fact in breast cancer patients with clinically negative lymph nodes, SLNB alone often seems to represent a sufficient treatment together with an effective systemic therapy [4–9]. This leads to the actual need to perform such a demolitive intervention as ALND, with the risk of complications, only basing on neoplastic colonization of the sentinel lymph node (SLN), considering that after surgery patients often undergo adjuvant therapy, which is an effective tool to ensure adequate

* Corresponding author. Department of Surgical, Oncological and Oral Sciences, University of Palermo, Via del Vespro 129, 90127, Palermo, Italy.
E-mail address: calogerocipolla@virgilio.it (C. Cipolla).

http://dx.doi.org/10.1016/j.ijsu.2016.09.015
1743-9191/

locoregional control of disease and to reduce the risk of recurrence [10].

To make surgery more conservative and to customize treatment as much as possible basing on histopathological and biological features of breast cancer [11], many predictive models have been developed in order to identify patients who actually benefit from ALND among those with metastatic SLN. The *Additional nodal metastasis nomogram* elaborated by Memorial Sloan- Kettering Cancer Center (MSKCC) [12] provides a percentage corresponding to the risk of non-SLN metastasis in SLN-positive patients. Considering the maneuverability of the nomogram and the easily accessible information that it requires, the nomogram was applied to a sample of patients with invasive breast cancer and positive SLN to assess its sensitivity, specificity, positive and negative predictive values. In particular, the possibility of using MSKCC nomogram in daily clinical practice has been taken into consideration for those patients at high risk of additional axillary metastasis who undergo ALND at the same surgical time with tumor excision, distinguishing them from those to whom ALND can be reasonably omitted because further axillary involvement is negligible.

2. Materials and methods

2.1. Inclusion criteria of the study

Data on patients who underwent SLNB between January 2009 and June 2015 were collected. All patients received a preoperative diagnosis of breast cancer confirmed by clinical and instrumental examinations (mammography and ultrasound) and core biopsy. 200 women with SLN macrometastasis, found with the intra-operative examination, were selected and subjected to ALND at the same operative time of tumor resection. 25 patients were eliminated from the sample because 20 of them were characterized by histological types of invasive breast cancer that are not included in the nomogram (mucinous, tubular, papillary, mixed types) and the other 5 for incompleteness of the pathological report. The nomogram was then applied to a total of 175 patients, who meet the following criteria: invasive ductal or lobular breast cancer preoperatively diagnosed by mammography, ultrasound and core biopsy; clinically negative axillary lymph nodes (N0); detection of macrometastases (neoplastic aggregates >2 mm) at intraoperative examination of SLN performed by frozen section; execution of complete ALND by the surgeon.

2.2. Patient characteristics

Patient characteristics are different (Table 1). They are all female and aged between 32 and 86 years for a median age of 55.12 years. 164 of them (93.7%) were subjected to quadrantectomy, the remaining 11 (6.3%) to mastectomy, both accompanied by SLNB and subsequent ALND. The histological features of the different cancers were obtained from a preoperative core biopsy performed on breast lesions. In all cases, core biopsy provided information that was fully confirmed by histopathological examination performed on a surgical specimen, establishing itself as a reliable tool for preoperative characterization of breast cancers [13,14]. 157 tumors (89.7%) were ductal type, while only 18 (10.3%) were classified as lobular. As regards the histological grade, 12 breast cancers were G1 (6.9%), 121 G2 (69.1%) and 42 (24%) were G3.

Core biopsy also provided the gene expression pattern of each tumor: 158 patients (90.3%) had ER-positive tumors and 17 (9.7%) of them ER-negative; 148 cancers (84.6%) were PR-positive, 27 (15.4%) lost PR expression; in 87 cases (49.7%) tumors showed HER2/neu overexpression, 88 cancers (50.3%) didn't show it.

The last information supplied by core biopsy, then confirmed by the analysis of the surgical specimen, is the presence of lymphovascular invasion, that is the detection of neoplastic cells within lymphatic and/or blood vessels. 107 tumors of the sample (61.1%) had lymphovascular invasion, 68 (38.9%) did not.

The dimensions of the tumors, obtained from pre-operative ultrasound, varies between 0.2 and 7 cm, for a median of 2 cm. Finally, in 27 patients (15.4%) preoperative imaging showed a multifocal breast cancer.

Table 1
Patient characteristics.

Characteristic	Number of patients and percent
Age	
≤50	66 (37,7%)
>50	109 (62,3%)
Operation	
Quadrantectomy	164 (93,7%)
Mastectomy	11 (6,3%)
Number of positive SLNs	
1	123 (70,3%)
2	43 (24,6%)
3	7 (4,0%)
>3	1 (0,6%)
Number of negative SLNs	
0	86 (49,1%)
1	56 (32,0%)
2	26 (14,9%)
>2	8 (4,6%)
Cancer histotype	
Ductal	157 (89,7%)
Lobular	18 (10,3%)
Histological grade	
G1	12 (6,9%)
G2	121 (69,1%)
G3	42 (24,0%)
ER-status	
Positive	158 (90,3%)
Negative	17 (9,7%)
PR-status	
Positive	148 (84,6%)
Negative	27 (15,4%)
HER2/neu overexpression	
Yes	87 (49,7%)
No	88 (50,3%)
Lymphovascular invasion	
Yes	107 (61,1%)
No	68 (38,9%)
Multifocality	
Yes	27 (15,4%)
No	148 (84,6%)
Tumor size	
T1 (≤2 cm)	88 (50,3%)
T2 (>2 cm e ≤ 5 cm)	81 (46,3%)
T3 (>5 cm)	6 (3,4%)

2.3. Diagnostic and therapeutic procedures and SLN identification

Patients in the sample received a preoperative diagnosis of breast cancer using imaging techniques (mammography and ultrasound) and core biopsy which was performed by Lorad® digital stereotatic table or ultrasound guidance.

The absence of suspicious lymphadenopathy, which is a basic requirement in order to perform the sentinel lymph node biopsy, was then checked by means of the clinical and ultrasound examination of the axilla.

The identification of SLN was preoperative and intraoperative. The day before surgery, all patients underwent lymphoscintigraphy by means of a subareolar injection of Nanocoll (^{99}Tc labelled human serum albumin), which is a very accurate procedure to identify of the sentinel lymph node [15,16]. Anterior and anterior-oblique scans

were carried out 15, 30 and 180 min after inoculation, then the skin projection of SLN was indicated by a cobalt pen. During surgery, a gamma probe (Neo2000 Gamma Detection System®) was used in order to correctly identify and remove all the lymph nodes marked by the tracer. In a few cases where the radio-guided surgical probe picked up a weak radiotracer signal, about 10 min before the beginning of surgery, a subareolar injection of 0.5–0.8 ml of vital stain (1% lymphazurin) was performed.in order to further improve the accuracy of the procedure. The excised lymph nodes were then sent to the pathologist, who first performed an intraoperative examination [17], then the definitive one. The result of the histopathological intraoperative examination guided the surgeon in choosing whether or not to complete the surgery with ALND: since macrometastasis were detected in all patients, ALND was performed in all cases. The excised lymph nodes were then examined to asses their real metastatic involvement.

2.4. Nomogram application

MSKCC nomogram was retrospectively applied to the sample, it considered for each breast cancer, obtained from pre-operative imaging, the following characteristics: tumor size, histological type, number of positive and negative SLN, method of detection of metastasis, presence/absence of lymphovascular invasion, multifocality and ER-status. In all cases, frozen section was indicated as a method of detection of metastasis. Thanks to the results provided by the nomogram, the ROC curve was obtained and its Area Under Curve (AUC), which is an important accuracy index, was calculated.

A cut-off of 50% was set: patients were classified as “high risk” of further lymph node metastases if nomogram gave a result >50%, and as “low risk” if the percentage was ≤50%. Then the probability predicted by nomogram was compared with the result of histological examinations of lymph nodes removed during ALND. Consequently, false positive and false negative results were counted and sensitivity, specificity and positive and negative predictive values were calculated.

Finally, correlation between each parameter required by the nomogram and the result provided by the same nomogram was evaluated using Pearson's coefficient, and then statistical significance of each correlation was observed.

3. Results

The probabilities of additional axillary metastasis provided by MSKCC nomogram range between 21% and 90%. The ROC curve obtained from the comparison between the results of the nomogram with the results of histological examinations of removed lymph nodes has an AUC equal to 0.885 (Fig. 1). The division into deciles of estimated probabilities shows the distribution of patients of the sample: in most cases a percentage higher than 40% and less than 70% was obtained (Fig. 2).

Among the 175 patients who underwent ALND, only in 78 cases (44.6%) there were lymph node metastasis additional to those localized in SLN. Before calculating the sensitivity and specificity of the model using a cut off of 50%, the distribution of patients with non-sentinel lymph node metastasis into percentage deciles was evaluated (Fig. 3). The majority of patients with axillary metastasis is distributed from the sixth decile and a peak is observed between 61% and 70%. The 65.7%, the 93.7%, the 86.7% and the 85.7% of the patients who fall in the sixth decile, in the seventh decile, in the eighth decile and in the nineth decile respectively are all characterized by axillary metastases detected at histopathological examination of the resected lymph nodes.

Once the cut off has been set, cases in which the MSKCC nomogram provided a percentage >50% were considered “positive” and the ones in which predicted probability was ≤50% were considered “negative”. The practical implication of this classification is that the “positive” cases, defined at high risk of lymph node metastasis in addition to those found in the SLN, would be immediately candidated for ALND. On the other hand, in the “negative”

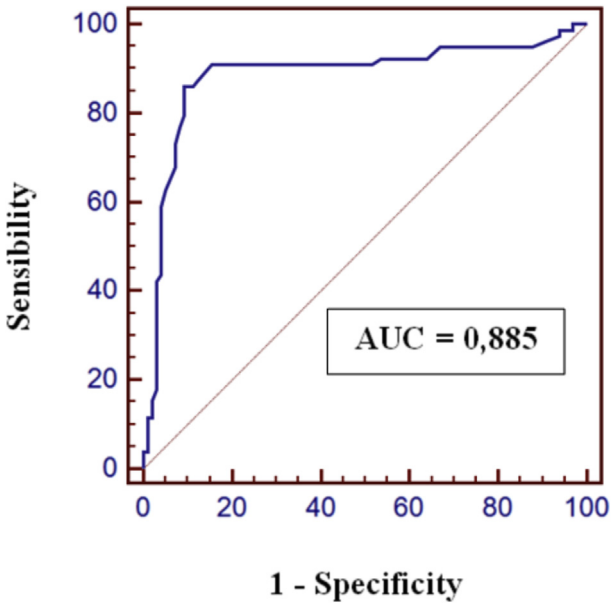

Fig. 1. ROC curve of the nomogram and its AUC.

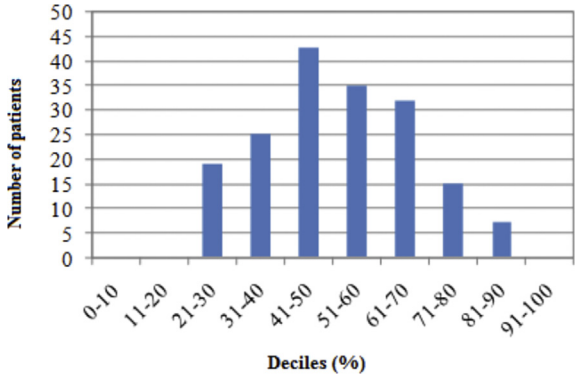

Fig. 2. Patients distribution into deciles of risk estimated by the nomogram.

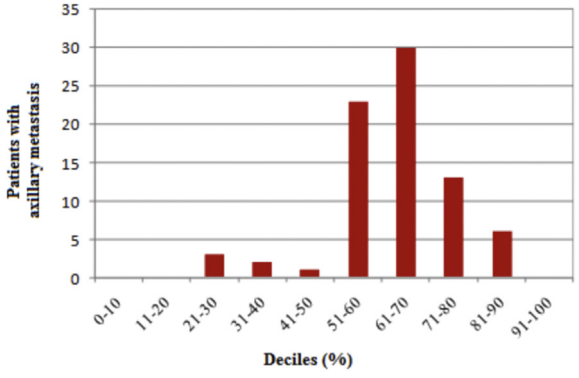

Fig. 3. Additional non-SLN positive patient's distribution into deciles of risk estimated by the nomogram.

cases, interpreted as low risk of additional nodal metastasis, axillary surgery could be omitted following the purpose of the study, because it doesn't produce any advantage.

The percentages obtained in 85 patients were ≤50%, including the 79 cases (92.9%) in which no further axillary metastasis were detected, and the 6 cases (7.1%) characterized by additional metastasis in excised lymph nodes. In the 90 patients in which the nomogram estimated a probability >50%, 72 cases (80%) of lymph node metastases were counted, compared to the 18 patients (20%) without additional axillary metastatic colonization (Table 2).

To sum up, the nomogram achieved the following results: 80% of true positives, which corresponds to the positive predictive value of the model; 20% of false positives; 92.9% of true negatives, which corresponds to the negative predictive value of the model; 7.1% of false negatives. Sensitivity and specificity of the MSKCC nomogram applied to the sample were then calculated: sensitivity was 92.3% and specificity was 81,4%.

As regards the correlation between each of the parameters required by the nomogram and the probability predicted from it (Table 3), tumor characteristics in direct correlation with the result provided by the nomogram are tumor size, the presence of lymphovascular invasion, the number of positive SLNs, multifocality and histological grade; on the other hand, the number of negative SLNs and ER-status are in inverse correlation with the probability provided by the model. The index that best positively correlates with the percentage provided by the nomogram is the lymphovascular invasion, followed by tumor size, number of positive SLNs, the multifocality and finally histological grade. All of these parameters have a statistically significant correlation (P-value <0.05), except for the histological grade. Among the parameters characterized by inverse correlation, only the number of SLNs is negatively correlated in a statistically significant way to the result provided by the nomogram.

Table 3
Correlation and statistic significance for each parametre. LVI = lymphovascular invasion; SLN = sentinel lymph node; ER = estrogene receptor.

Parameter	Correlation coefficient (r)	P-value
Tumor size	0,5601	<0,0001
LVI	0,5954	<0,0001
Number of positive SLNs	0,5393	<0,0001
Number of negative SLNs	−0,4619	<0,0001
Multifocality	0,2362	0,0016
Histological grade	0,1424	0,0616
ER-status	−0,2432	0,7494

4. Discussion

The results obtained from the application of MSKCC nomogram to patients of the sample are extremely significant: it shows great effectiveness in predicting the presence of lymph node metastases in addition to those found at intraoperative examination of the SLN. An optimal staging has a role also in the choice of treatment. In breast cancer as in many other cancers the use of targeted agents is overwhelming [18].

The search for a predictor that best describes the status of axillary lymph nodes has been carried out for a long time in order to predict prognosis and to plan the most appropriate therapeutic strategy is very helpful the examination of the histopathological and biological characteristics of each breast cancer. The extension of surgery could have an impact on the well-being of physicians apart from the stress induced by surgery-related complications [19]. This effect can be added to the impact in the patient's quality of life and clinical management. For this reason, a lot of studies have tried to assess the most significant parameters associated with the presence of axillary lymph node metastases. The most important predictors are the tumor size and the presence of lymphovascular invasion, demonstrated by several univariate analyses. New biomarkers could be useful in the selection of those patients who are more suitable for axillary lymph node dissection. miRNAs are emerging as potential diagnostic and prognostic biomarkers in several malignancies [20]. According to a British study, the observation of those parameters could guide the surgeon in the choice of the right treatment of the axilla, but none of them, individually examined, can be considered a safe and useful marker for the selection of patients to who didn't need ALND [21]. A recent publication has considered as important predictors the diameter of tumor and lymphovascular invasion as together tumor localization and multifocality. The locations at higher risk seem to be the retroareolar and of course the external quadrants [22]. Moreover the histological subtype of breast cancer and in particular the pattern of gene expression are strongly connected with the presence of lymph node metastases: recent evidences have estimated the luminal B type at higher risk, followed by luminal A type. Both seem to be characterized by an increased risk of additional nodal metastases in patients with positive SLN, especially when compared to the “triple negative” cancers, that very rarely spread to the axilla [23], although they are burdened with a worse prognosis.

An important observation is that, except for the tumor site, all the parameters above mentioned as significant predictors of axillary status are all covered by MSKCC nomogram. It offers the advantage of processing all information about tumors and taking into account the characteristics of each breast cancer it gives a reliable estimate in terms of percentages of risk of nodal metastasis. The factors that mostly influence the predictive model are lymphovascular invasion, tumor size, number of metastatic SLNs and, as evidenced by the group that developed the nomogram, the method of detection of metastasis. This shows the importance of the accuracy of preoperative diagnostic techniques and of intraoperative examination of the SLN that provide the information required by the model.

Considering the current trend to make surgery as conservative as possible, without betraying the principle of basic oncological radicality, MSKCC nomogram is a tool characterized by great potential in order to avoid an aggressive and unjustified intervention such as ALND in patients with a positive SLN but at low risk of additional axillary metastasis.

Literature shows that nowadays the choice of the cut off is completely arbitrary and prospective studies are needed to define an appropriate threshold value that divides the patients at high and low risk of additional lymph node metastases. Previous retrospective studies [24,25] have often fixed the cut off at 10%, but such a

Table 2
Patients classification into risk categories using cut off of 50%.

Predicted probability and risk category	Total number of patients	Patients with additional nodal metastasis	Patients without additional nodal metastasis	False positive	False negative
≤50% (Low risk)	85	6	79	18 (20%)	6 (7,1%)
>50% (High risk)	90	72	18		

low value doesn't offer significant advantages. In fact, in most of the case series, including our own, nomogram predicted a probability <10% in very few patients with positive SLN, then its use would have a limited clinical impact. So our purpose was to establish a higher cut off (50%), that in our series proved to be reasonably reliable in assessing the risk of additional lymph node metastases.

If the nomogram had been applied to the 175 patients of the sample as described above, 79 of the 97 women without metastatic involvement of axilla wouldn't have received ALND. Despite of the rare complications of the intervention, to be always taken into consideration, it's a great opportunity to have the possibility to identify among the patients with SLN metastasis, those who actually benefit from axillary surgery. The greatest advantage is that MSKCC predictive model can be used immediately after the communication of the result of intraoperative histopathological examination of SLN and, thanks to the information derived from preoperative ultrasound, mammography and core biopsy, it immediately provides its probability of further nodal metastasis.

On the other hand, in 6 patients with small cancers (T1) in which the probability obtained from nomogram was ≤50%, the histopathological examination of the dissected lymph nodes showed the presence of metastases. However those cancers had histopathological and biological features (low dimension, ER+, PR+, Her2\neu-, etc.) that suggest a favourable prognosis. In all cases the patients were treated with adjuvant radiotherapy and hormonal therapy, which are effective means to check the locoregional and systemic disease respectively.

ALND is currently assumed to be replaceable with other locoregional ways of control of the disease in patients with clinically negative axilla. Many trials demonstrated that patients affected by T1/2N0 breast cancers treated with conservative surgery, postoperative radiotherapy and adjuvant systemic therapy do not benefit from ALND [6,26]. Moreover, lymph nodes irradiation instead of surgery seems to represent an effective alternative, as it was shown in the annual meeting of the American Society of Clinical Oncology (ASCO), in which the results of the trial AMAROS [1] promoted by the European Organization for Research and Treatment of Cancer (EORTC) were examined. This trial randomized a sample of breast cancer patients with T1/2N0 tumors and positive SLN in two groups: the first had undergone ALND and the patients of the second one had had radiotherapy addressed to the three nodal levels of axilla and to medial supraclavicular lymph nodes. After a 5 years follow-up, there are no significant differences in terms of axillary recurrence in both groups but a higher incidence of complications in the group that had undergone ALND was observed. Furthermore, we nowadays know little about the possible difference in outcomes deriving from sentinel node biopsy among female and male breast cancer patients [27].

Despite the encouraging results of the cited randomized trials, guidelines are still unclear and surgeons usually still perform ALND in case of SLN metastasis. MSKCC nomogram may represent a useful tool and the role of ALND in patients with SLN metastasis should be reduced.

5. Conclusions

To sum up we have reason to believe that the application of MSKCC monogram to the sample is a very reliable and usefull predictive model in daily clinical practice. It's a tool that can add important information to the intraoperative examination of the SLN in order to guide the surgeon in choosing the most reasonable treatment of axillary lymph nodes and represents a significant phase in the process towards a conservative treatment approach that suggests the performance of axillary surgery only when justified.

Ethical approval

Ethical approval was not required.

Author contribution

Salvatore Vieni, Giuseppa Graceffa, Calogero Cipolla and Roberta La Mendola: study concept, data analysis, writing and approved final version.

Sefania Latteri and Roberta La Mendola: data collection and drafting.

Mario Adelfio Latteri, Adriana Cordova: approved final version.

Conflict of interest

The authors declare no potential conflicts of interest.

Guarantor

Salvatore Vieni.

Research registration unique identifying number (UIN)

researchregistry1320.

Acknowledgements

No funding organization did support this study.

References

[1] M.E. Straver, P. Meijnen, G. van Tienhoven, C.J. van de Velde, R.E. Mansel, J. Bogaerts, N. Duez, L. Cataliotti, J.H. Klinkenbijl, H.A. Westenberg, H. van der Mijle, M. Snoj, C. Hurkmans, E.J. Rutgers, Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial, Ann. Surg. Oncol. 17 (7) (2010) 1854–1861.

[2] E. Senkus, S. Kyriakides, F. Penault-Llorca, P. Poortmans, A. Thompson, S. Zackrisson, F. Cardoso, ESMO Guidelines Working Group, Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 24 (6) (2013) 7–23.

[3] S. Zakaria, G. Pantvaidya, C.A. Reynolds, C.S. Grant, S. Sterioff, J.H. Donohue, D.R. Farley, T.L. Hoskin, A.C. Degnim, Sentinel node positive breast cancer patients who do not undergo axillary dissection: are they different? Surgery 143 (5) (2008) 641–647.

[4] D.N. Krag, S.J. Anderson, T.B. Julian, A.M. Brown, S.P. Harlow, J.P. Costantino, T. Ashikaga, D.L. Weaver, E.P. Mamounas, L.M. Jalovec, T.G. Frazier, R.D. Noyes, A. Robidoux, H.M. Scarth, N. Wolmark, Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial, Lancet Oncol. 11 (10) (2010) 927–933.

[5] H.S. Park, B.J. Chae, B.J. Song, S.S. Jung, W. Han, S.J. Nam, H.J. Youn, B.K. Ko, D.W. Kim, Korea breast Cancer society. Effect of axillary lymph node dissection after sentinel lymph node biopsy on overall survival in patients with T1 or T2 node-positive breast Cancer: report from the korean breast Cancer society, Ann. Surg. Oncol. 21 (4) (2014) 1231–1236.

[6] A.E. Giuliano, K.K. Hunt, K.V. Ballman, P.D. Beitsch, P.W. Whitworth, P.W. Blumencranz, A.M. Leitch, S. Saha, L.M. McCall, M. Morrow, Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial, JAMA 305 (6) (2011) 569–575.

[7] A.E. Giuliano, L. McCall, P. Beitsch, P.W. Whitworth, P. Blumencranz, A.M. Leitch, S. Saha, K.K. Hunt, M. Morrow, K. Ballman, Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial, Ann. Surg. 252 (3) (2010) 426–432.

[8] S. Milgrom, H. Cody, L. Tan, M. Morrow, C. Pesce, J. Setton, K. Rogers, B. Arnold, A. Eaton, J. Catalano, B. McCormick, S. Powell, A. Ho, Characteristics and outcomes of sentinel node-positive breast cancer patients after total mastectomy without axillary-specific treatment, Ann. Surg. Oncol. 19 (12) (2012) 3762–3770.

[9] A. Cyr, F. Gao, W.E. Gillanders, R.L. Aft, T.J. Eberlein, J.A. Margenthaler, Disease recurrence in sentinel node-positive breast cancer patients forgoing axillary lymph node dissection, Ann. Surg. Oncol. 19 (10) (2012) 3185–3191.

[10] E.P. Mamounas, G. Tang, Q. Liu, The importance of systemic therapy in

minimizing local recurrence after breast-conserving surgery: the NSABP experience, J. Surg. Oncol. 110 (1) (2014) 45–50.
[11] A. Goldhirsch, E.P. Winer, A.S. Coates, R.D. Gelber, M. Piccart-Gebhart, B. Thürlimann, H.J. Senn, Panel members, Personalizing the treatment of women with early breast cancer: highlights of the st gallen international expert consensus on the primary therapy of early breast Cancer 2013, Ann. Oncol. 24 (9) (2013) 2206–2223.
[12] K.J. Van Zee, D.E. Manasseh, J.L.B. Bevilacqua, S.K. Boolbol, J.V. Fey, L.K. Tan, P.I. Borgen, H.S. Cody III, M.W. Kattan, A nomogram for predicting the likelihood of additional nodal metastases in breast Cancer patients with a positive sentinel node biopsy, Ann. Surg. Oncol. 10 (10) (2003) 1140–1151.
[13] C. Cipolla, S. Fricano, S. Vieni, C. Amato, L. Napoli, G. Graceffa, S. Latteri, M.A. Latteri, Validity of needle core biopsy in the histological characterisation of mammary lesions, Breast 15 (1) (2006) 76–80.
[14] H.M. Verkooijen, Core Biopsy After Radiological Localisation (COBRA) Study Group, Diagnostic accuracy of stereotactic large-core needle biopsy for non-palpable breast disease: results of a multicenter prospective study with 95% surgical confirmation, Inter J. Cancer 99 (6) (2002) 853–859.
[15] F. Armas, M.J. Hernández, V. Vega, I. Gutiérrez, C. Jiménez, M. Pavcovich, B. Báez, P. Pérez-Correa, V. Núñez, Comité de Patología Mamaria del Complejo Hospitalario Materno Insular. Utility and advantages of single tracer subareolar injection in sentinel lymph node biopsy in breast cancer, Cir. Esp. 78 (4) (2005) 260–265.
[16] C. Cipolla, S. Vieni, S. Fricano, D. Cabibi, G. Graceffa, R. Costa, S. Latteri, M.A. Latteri, The accuracy of sentinel lymph node biopsy in the treatment of multicentric invasive breast cancer using a subareolar injection of tracer, World J. Surg. 32 (11) (2008) 2483–2487.
[17] C. Cipolla, D. Cabibi, S. Fricano, S. Vieni, I. Gentile, M.A. Latteri, The value of intraoperative frozen section examination of sentinel lymph nodes in surgical management of breast carcinoma, Langenbeck's Arch. Surg. 395 (6) (2010) 685–691.
[18] G. Di Fede, G. Bronte, S. Rizzo, C. Rolfo Cervetto, G. Cocorullo, G. Gulotta, V. Bazan, A. Russo, Monoclonal antibodies and antibody fragments: state of the art and future perspectives in the treatment of non-haematological tumors, Expert Opin. Biol. Ther. 11 (11) (2011) 1433–1445.
[19] A. Russo, R. De Luca, G. Cicero, A. Civilleri, G. Bronte, J. Dispenza, S. Vieni, R. Guarneri, V.L. Cascio, F.P. Guadagna, E. Foddai, F. Pace, Well-being among Italian medical oncologists: an exploratory study, Oncology 86 (2) (2014) 72–78.
[20] L.R. Corsini, G. Bronte, M. Terrasi, V. Amodeo, D. Fanale, E. Fiorentino, G. Cicero, V. Bazan, A. Russo, The role of microRNAs in cancer: diagnostic and prognostic biomarkers and targets of therapies, Expert Opin. Ther. Targets 16 (Suppl 2) (2012) S103–S109.
[21] E. Aitken, M. Osman, Factors affecting nodal status in invasive breast cancer: a retrospective analysis of 623 patients, Breast J. 16 (3) (2010) 271–278.
[22] E. Yoshihara, A. Smeets, A. Laenen, A. Reynders, J. Soens, C. Van Ongeval, P. Moerman, R. Paridaens, H. Wildiers, P. Neven, M.R. Christiaens, Predictors of axillary lymph node metastases in early breast cancer and their applicability in clinical practice, Breast 22 (3) (2013) 357–361.
[23] W. Zhou, Z. He, J. Xue, M. Wang, X. Zha, L. Ling, L. Chen, S. Wang, X. Liu, Molecular subtype classification is a determinant of non-sentinel lymph node metastasis in breast Cancer patients with positive sentinel lymph nodes, PLoS One 7 (4) (2012) e35881.
[24] Smidt ML, Kuster DM, van der Wilt GJ, Thunnissen FB, Van Zee KJ, Strobbe LJA. Can the memorial sloan-kettering Cancer center nomogram predict the likelihood of nonsentinel lymph node metastases in breast Cancer patients in The Netherlands? Ann. Surg. Oncol. 12(12): 1066–1072.
[25] X. Bi1, Y. Wang, M. Li, P. Chen, Z. Zhou, Y. Liu, T. Zhao, Z. Zhang, C. Wang, X. Sun, P. Qiu, Validation of the Memorial Sloan Kettering Cancer Center nomogram for predicting non-sentinel lymph node metastasis in sentinel lymph node-positive breast-cancer patients, OncoTargets Ther. 8 (2015) 487–493.
[26] G. Martelli, P. Boracchi, I. Ardoino, L. Lozza, S. Bohm, G. Vetrella, R. Agresti, Axillary dissection versus no axillary dissection in older patients with T1N0 breast cancer: 15-year results of a randomized controlled trial, Ann. Surg. 256 (6) (2012) 920–924.
[27] L. Ottini, C. Capalbo, P. Rizzolo, V. Silvestri, G. Bronte, S. Rizzo, A. Russo, HER2-positive male breast cancer: an update, Breast Cancer (Dove Med. Press) 2 (2010) 45–58.