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SHORT COMMUNICATION

Development of a novel scoring system to potentially avoid completion axillary lymph node clearance after breast cancer excision and positive sentinel lymph node biopsy

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The advent of sentinel lymph node biopsy (SLNB), in conjunction with tissue-sparing surgery and the improvement of radiotherapy protocols have revolutionized the field of breast cancer surgery, reducing the cases where a mastectomy with axillary clearance would have been the indicated approach [1,2]. The latter has resulted in markedly improved cosmesis, better functional status and quality of life without impairing the final oncological outcome [3]. Therefore, in the absence of pre-operatively identified axillary nodal infiltration, SLNB is now standard practice to assess the need for axillary clearance in cases with operable breast cancer; upon presence of cancerous infiltration of the retrieved sentinel lymph nodes, usually the patients are undergoing further surgery to achieve axillary clearance and adjuvant treatment is considered.

However, on many occasions where SLNB is positive and further surgery for axillary clearance is carried out, the axillary nodes which are removed at the axillary clearance procedure turn out not to be infiltrated. As a result, it would be of great importance to consider if a SLNB could be per se "curative" in these cases, since all the infiltrated lymph nodes are removed during the first procedure. Therefore, the development of scoring systems aiming to predict if a SLNB could be "curative" could result in change of clinical protocols, for instance with introduction of prophylactic/minimally therapeutic adjuvant therapy instead of a repeat surgical procedure to remove the remaining axillary lymph nodes.

Under this notion, we performed a retrospective analysis of all patients that underwent either wide local excision (WLE) or mastectomy with SLNB for invasive ductal adenocarcinoma and we attempted to identify which factors related to tumor characteristics and systemic inflammatory response could be used in a combined system to predict the likelihood of further axillary lymphadenopathy after a positive SLNB. The concept of using in the same scoring system tumor-related parameters in conjunction with biomarkers of systemic inflammatory response lies on the evidence suggesting that cancer growth and progression depends on both more aggressive tumor-related features as well as an impaired immune response, enabling escape from immunosurveillance [4,5]. In order to standardize our patients' characteristics, we included only patients with expression of hormonal receptors (any strength) and absence of HER-2/Neu expression. Also, we excluded patients where a further in situ cancerous component was incidentally found in the examined mastectomy or WLE specimen and we also did not include patients with histological type other than invasive ductal carcinoma, patients with neoadjuvant therapy and patients with previous breast cancer surgery.

We used four parameters to construct our scoring system: the histological grade of the primary cancerous lesion (I-III), the maximal tumor diameter (mm), the sentinel lymph node ratio (number of infiltrated axillary sentinel lymph nodes divided by the absolute number of harvested axillary sentinel lymph nodes-SLNR) and neutrophil-to-lymphocyte ratio (NLR), a widely used marker of systemic inflammatory response and has been shown to be an independent factor

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of survival and response to neoadjuvant therapy in breast cancer [6,7]. While histological grade, tumor size and NLR are proven to be prognostic factors in breast cancer, SLNR has not been validated yet. However, we believe that it represents a logical approach to assess the likelihood of further axillary lymphadenopathy. For example, if 100% of the retrieved sentinel lymph nodes are infiltrated irrespective of their absolute number, then the common practice would be a completion axillary clearance. However, if for instance 25% of the retrieved sentinel nodes are infiltrated and the rest 75% are tumor-free, it would be more reasonable to assume that the likelihood of significant further axillary lymhadenopathy is lower.

The point system allocation was designed as follows: one up to three points were allocated according to the histological grade; in the absence of reference norms for the other three variables (NLR, SLNR, maximal tumor diameter), we calculated the quartile distribution of their values in our sample and a single point was allocated for each ascending quartile, as demonstrated in Table 1. The main principle is that the higher the grade, the greater the maximal tumor diameter and the higher NLR and the SLNR are, the more likely is that further axillary lymph nodes could be positive. Therefore, the minimum score could be 4 and the maximum 15, with this maximum score corresponding to a greater likelihood of further infiltrated axillary lymph nodes, mandating a subsequent axillary clearance.

In our final analysis we included 59 female patients who had positive SLNB in mastectomy or WLE and sequential axillary node clearance (ANC) in a second operation. Of note, a total of 44/59 (74.6%) patients had no further infiltrated axillary lymph nodes after the examination of the ANC specimen. The baseline differences in terms of demographics, tumor characteristics, operative findings and NLR values between the "curative SLNB" and the "non-curative SLNB" groups are summarized in Table 2. The only statistically significant differences between the groups occurred for mean tumor size, mean number of positive sentinel lymph nodes and the value of our proposed scoring system (Table 2). After analyzing our results by splitting the patient sample in the "curative SLNB" vs "non-curative SLNB", we identified that all patients with an overall score ≤ 7 (N=11) had no further axillary lymphadenopathy after the histopathological examination of the axillary clearance specimen (Table 3). The above mentioned findings are graphically demonstrated in Figure 1.

Despite the retrospective nature and the small sample of our study, we attempted to demonstrate that the combination of basic tumor-specific characteristics (tumor size and grade), operative anatomical findings (sentinel lymph node ratio) and gross biomarkers of systemic inflammatory response (NLR) can lead into the formation of integrated scoring systems that could be useful to avoid a second surgical procedure to achieve axillary disease clearance, a procedure which can frequently impair the patients' long-term quality of life (e.g. lymphedema, pain, limb functional deficit, poor cosmesis). Our initial results, including only patients with standardized type of breast cancer (only invasive ductal carcinoma, absence of in situ component in specimen, no neoadjuvant treatment, ER/PR positive & HER2 negative status), demonstrated that 11/59 (19.5%) patients who had an overall score ≤ 7 had no further infiltrated axillary lymph nodes and therefore it could be argued that they underwent a further resection procedure in the absence of focal can-

Table 1. Summary of our proposed scoring system to stratify patients as relatively low and high risk for further axillary lymphadenopathy after positive SLNB

Scoring variables	*Point allocation system*			
Grade	I	II	III	N/A
(No. of points)	(1)	(2)	(3)	
	1st quartile	2nd quartile	3rd quartile	4th quartile
Tumor diameter (mm)	≤18	(18-21.5)	(21.5-34)	>34
(No. of points)	(1)	(2)	(3)	(4)
	1st quartile ≤0.33	2nd quartile	3rd quartile	4th quartile
SLNR	(1)	(0.33-0.50)	(0.50-0.67)	>0.67
(No. of points)		(2)	(3)	(4)
	1st quartile	2nd quartile	3rd quartile	4th quartile
NLR	≤1.7	(1.7-2.3)	(2.3-3)	>3
(No. of points)	(1)	(2)	(3)	(4)

SLNR: sentinel lymph node ratio, NLR: neutrophil to lymphocyte ratio, N/A: not applicable

Table 2. Baseline differences between demographics, tumor characteristics, operative findings and NLR values between the "curative SLNB" and the "non-curative SLNB" groups

Parameters	*"Curative" SLNB Status*	*N*	*Mean*	*SD*	*p value*
Age	"Curative"	44	60,88	13,35	0.41
	"Non-curative"	15	57,53	12,58	
Tumor size	"Curative"	44	23,01	9,99	0.052
	"Non-curative"	15	32,93	17,47	
Tumor grade	"Curative"	44	2,27	0,59	0.70
	"Non-curative"	15	2,33	0,49	
Number of SLN retrieved	"Curative"	44	2,52	0,93	0.27
	"Non-curative"	15	2,80	0,77	
Number of positive SLN	"Curative"	44	1,16	0,37	0.03
	"Non-curative"	15	1,80	0,68	
Neutrophil-to-lymphocyte ratio (NLR)	"Curative"	44	2,26	1,14	0.26
	"Non-curative"	15	2,53	0,74	
Sentinel lymph node ratio (SLNR)	"Curative"	44	0,53	0,26	0.092
	"Non-curative"	15	0,66	0,24	
Overall score	"Curative"	44	8,73	1,85	0.03
	"Non-curative"	15	10,20	1,37	

For abbreviations see footnote of Table 1

Table 3. Overall score fluctuation differences between the "curative SLNB" and "non-curative SLNB"

Curative status	*N*	*Minimum*	*Maximum*	*Mean*	*SD*	*p value*
Overall score "Curative" SLNB	44	5	12	8.73	1.85	0.03
Overall score "Non-curative" SLNB	15	8	12	10.20	1.37	

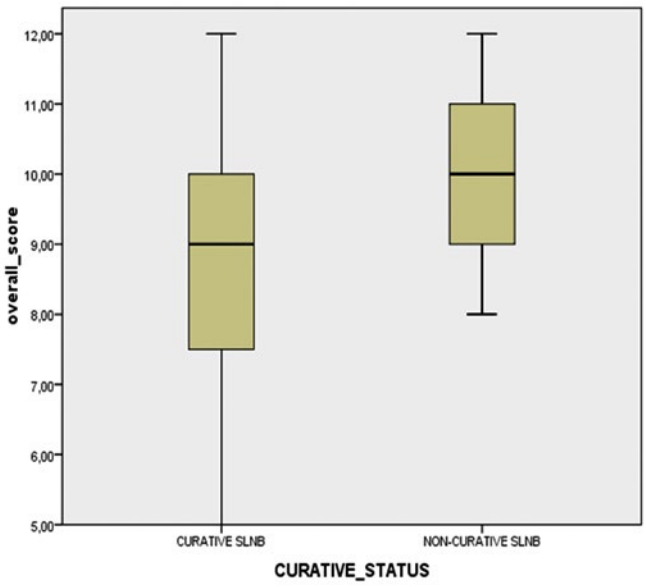

Figure 1. Graphical representation of overall score differences between the "curative SLNB" and "non-curative SLNB" groups: all patients with score ≤ 7 (N=11) had a "curative SLNB", with no further positive axillary lymph nodes detected in the axillary clearance specimen (p=0.03;Table 3 also).

cerous spread in the axilla. However, further management of those patients would be a debate with the answer being unclear using the currently available evidence. Nevertheless, we strongly believe that our proposed integrated scoring system in its current or modified form provides a new direction for future randomized trials that could push the boundaries of tissue-sparing surgery further, without compromising the oncological outcome. Its novelty lies on the joint use of tumor-related features and means to assess the profile of systemic inflammation in the same scoring system, a fact which, to the best of our knowledge, has not been incorporated in any of the previously validated relevant risk stratification systems [8-10]. We aim to validate our preliminary results in a larger group of patients, with greater diversity in terms of the underlying primary breast cancer.

Conflict of interests

The authors declare no confict of interests.

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