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Variations in sentinel node isolated tumour cells/micrometastasis and non-sentinel node involvement rates according to different interpretations of the TNM definitions

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ABSTRACT

Breast cancers with nodal isolated tumour cells (ITC) and micrometastases are categorised as node-negative and node-positive, respectively, in the tumour node metastasis (TNM) classification. Two recently published interpretations of the TNM definitions were applied to cases of low-volume sentinel lymph node (SLN) involvement and their corresponding non-SLNs for reclassification as micrometastasis or ITC. Of the 517 cases reviewed, 82 had ITC and 435 had micrometastasis on the basis of one classification, and the number of ITC increased to 207 with 310 micrometastases on the basis of the other. Approximately 24% of the cases were discordantly categorised. The rates of non-SLN metastases associated with SLN ITCs were 8.5% and 13.5%, respectively. Although the second interpretation of low-volume nodal stage categories has better reproducibility, it may underestimate the rate of non-SLN involvement. The TNM definitions of low-volume nodal metastases need to be better formulated and supplemented with visual information in the form of multiple sample images.

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1. Introduction

The prognostic impact of small-volume nodal metastases in breast cancer is widely debated with several studies and reviews suggesting at least a minor disadvantage in survival, and others questioning this.[1,2] With the introduction and acceptance of sentinel lymph node (SLN) biopsy (SLNB) and the resulting increased histopathological scrutiny of the SLNs, the identification rate of low-volume metastases has significantly increased.[3] This has resulted in a stage migration, as many of the former node-negative cases containing occult metastases are now placed into the node-positive micrometastatic group.[4] Because of the statistical artefacts that such a stage migration may cause and the debated prognostic significance of low-volume metastases, the pathological tumour node metastasis (pTNM) classification of malignant tumours and the American Joint Committee on Cancer (AJCC) staging definitions have split the micrometastasis category into two, one consisting of the micrometastasis category per se (pN1mi; micrometastases not larger than 2 mm, but larger than 0.2 mm) and the isolated tumour cell (ITC) category (pN0(i+) for lesions not larger than 0.2 mm).[5,6]

Despite the lack of evidence, the distinction between ITC and micrometastasis seems important, as it influences the treatment decisions. Micrometastases are considered true metastases, and are generally treated as such: i.e. completion axillary dissection is often recommended for such SLN involvement, and systemic treatment decisions also consider patients with SLN micrometastasis as node-positive. On the other hand, ITCs are generally considered node-negative for both staging and treatment decisions [2,7,8].

It has been suggested that the distinction between micrometastasis and ITC lacks reproducibility.[9,10] This is partly due to the different wording of the two main staging resources: the International Union Against Cancer (UICC) definitions suggest some qualitative features such as the assessment of metastatic activity and extravasation in addition to size for the distinction between pN1mi and pN0(i+)[5,11], whereas the AJCC definitions[6] depend only on size.[9] Another cause of the suboptimal reproducibility is the absence of relevant details from the definitions, giving rise to different interpretations.[9,12,13]

Two different interpretations of the current definitions of ITC and micrometastasis[5,6] were recently reported with the identical aim of improving the consistency of nodal staging of breast carcinomas. The European Working Group for Breast Screening Pathology (EWGBSP) suggested that despite an improvement in reproducibility, the distinction between ITC and micrometastasis was still suboptimal,[9] whereas a recent study resulted in a more consistent classification.[12] However, the latter study allows nodal involvement with a much higher overall volume of tumour cells to be classified as ITC. Our group sought to analyse the valid-

Table 1 – Main outlines of the EWGS and TS classification rules

EWGS	– Capsular (including intravascular) lesions should be considered nodal and any lesion with nodal and simultaneous extranodal involvement should also be considered as nodal, but lesions purely outside the lymph node (e.g. in afferent lymphatic channels or in perinodal fat) should not be recorded as nodal involvement. – Tumour cells (multiple) localised clearly in the parenchyma (and not in the sinuses or vascular spaces) should be considered as micrometastasis (pN1mi) even if they were <0.2 mm and there was no proliferation or stromal reaction associated with them, according to the first description of the distinction between ITC and micrometastasis[11]. – For tumour cells localised in vessels or sinuses, a size not larger than 0.2 mm makes the lesion ITC (pN0(i+) and size >0.2 mm but not larger than 2 mm makes it micrometastasis (pN1mi). – In case of multiple *foci*, only the largest should be considered. – Single tumour cells or clusters arranged in a continuous manner, or separated by only a few cells (e.g. 2–5 cells) distance, should be considered and measured as one *focus* and characterised by its largest dimension. – Cells or clusters arranged in a discontinuous manner (separated by more than a few cells distance) but dispersed homogeneously (evenly) in a definable part of the lymph node should also be considered and measured as *one focus*. – Cells, clusters or *foci* as defined above, arranged in a discontinuous manner and dispersed unevenly, should be considered as one if the distance between the clusters or *foci* is smaller than the smaller cluster or *focus*. – Cells, clusters or *foci* as defined above, arranged in a discontinuous manner and dispersed unevenly, should be considered as distinct and multiple if the distance between the unevenly distributed tumour cells, clusters or *foci* is greater than the smaller cluster or *focus*, and should be characterised by the size of the largest cluster or *focus*. – In case of doubt the lower category (i.e. ITC) should be given.
TS	– The study criteria were based on the concept that ITC and micrometastases were distinguished by the size of the largest tumour cell cluster, regardless of the microanatomic location within or adjacent to the lymph node, and regardless of the number of clusters or single cells. – A cluster is a confluent focus of tumour cells touching other tumour cells. This is determined from the two-dimensional image of the microscopic section. – Clusters or cells separated by a single benign cell or a spatial gap are measured as separate clusters, except when fibroblastic reaction to the tumour cells has caused the separation. – Any lesion composed of non-cohesive cells or clusters not greater than 0.2 mm represents ITC. – Any lesion with largest cohesive cellular lesion greater than 0.2 mm but not greater than 2 mm represents micrometastasis. – Mitotic activity (proliferation) is not considered. – For borderline or indeterminate findings, at the two ends of this spectrum, the lower stage category should be selected.

ITC: Isolated tumour cells; EWGS: European Working Group Study; TS: Turner study.

ity of the two different interpretations by obtaining the rates of non-SLN metastases associated with small-volume SLN involvement categorised according to the two different interpretations.

2. Materials and methods

Members of the EWGBSP were asked to collect SLN cases from their own archives which met the following criteria: (A) SLN involvement falling either in the ITC or in the micrometastasis group on the basis of the original report (no macrometastases were allowed in any of the SLNs); (B) Axillary lymph node dissection with a minimum of 6 non-SLNs removed. Cases which were originally reported as micrometastatic or having ITC in the SLN but were considered to be macrometastatic according to any of the two different understandings of these categories were also excluded.

An electronic spreadsheet (Microsoft Excel file) was used to collect the data: the number of SLNs removed, the number of SLNs involved by micrometastasis on the basis of the original report, the number of SLNs involved by ITC on the basis of the original report, the method of identification of the SLN involvement (haematoxylin and eosin *versus* immunohistochemistry), the number of non-SLNs assessed and the number of non-SLNs involved by metastasis. If the SLN was involved by both micrometastasis and ITC, and similarly, when multiple SLNs had nodal deposits of tumour cells, only the largest lesion was considered.

After the collection of the above data, contributors were asked to reassess each involved SLN from their own institution and reclassify the nodal lesion according to the EWGBSP study rules (further referred to as the EWG study, EWGS)[9] and according to the rules of the more recent study first authored by Turner (further referred to as the Turner study, TS).[12] They were asked to provide the number of SLNs containing micrometastasis and ITC, respectively, based on both interpretations for each case.

Details of the two interpretations were published along with the studies, but are briefly reproduced in Table 1. Some specific situations and their interpretations are also presented in Table 2.

The rates of non-SLN positivity associated with SLN micrometastasis and SLN ITC were calculated for the whole series on the basis of both interpretations. The McNemar test was used for analysing the differences between the distributions of the cases and the Pearson chi-square test for the analysis of any association between the presence of non-SLN metastases and ITCs in the SLNs. All tests were performed with the VassarStats software.[15]

It should be noted that neither the SLNB method nor the histological assessment of the SLNs was homogeneous for this study and this reflects common everyday practice and differences between institutions. However, the method of SLNB biopsy was validated by completion axillary lymph node dissection in all centres. In the cases studied, axillary lymph node dissection (removal of non-SLNs) was performed either

Table 2 – Examples of nodal lesions and their classification as micrometastasis or ITC according to the two interpretations of the definitions of these categories

SLN lesion examples	Classification according to the EWGS interpretation	Classification according to the TS interpretation	Comment
Single cell in the afferent lymphatic vessel	L1 (not nodal)	pN0(i+)	
Single cell in the capsular lymphatic vessel	pN0(i+)	pN0(i+)	A 3rd interpretation[14] would also classify this as L1
Single cell in a nodal sinus or nodal parenchyma	pN0(i+)	pN0(i+)	
Single cluster ⩽0.2 mm in the afferent lymphatic vessel	L1 (not nodal)	pN0(i+)	
Single cluster ⩽0.2 mm in the capsular lymphatic vessel	pN0(i+)	pN0(i+)	A 3rd interpretation[14] would also classify this as L1
Single cluster ⩽0.2 mm in the subcapsular sinus	pN0(i+)	pN0(i+)	
Single cluster ⩽0.2 mm in the nodal parenchyma	pN1mi	pN0(i+)	
Multiple cells or clusters evenly dispersed, involving an area of the SLN >0.2 mm (in largest dimension), but with largest cohesive cellular cluster size ⩽0.2 mm (no desmoplasia present)	pN1mi or pN1 depending on the size of the involved area	pN0(i+)	
Multiple cells or clusters evenly dispersed, involving an area of the SLN >0.2 mm (in largest dimension), but with largest cohesive cellular cluster size ⩽0.2 mm (with desmoplasia present)	pN1mi or pN1 depending on the size of the involved area	pN1mi or pN1 depending on the size of the involved area	
Single cluster ⩽0.2 mm present in the corresponding areas of two consecutive sections at >0.2 mm interval	pN1mi	pN0(i+)	

ITC: isolated tumour cell; EWGS: European Working Group Study;[9] L1: lymphatic invasion in the TNM system; pN0(i+): symbol for ITC involvement of lymph nodes in the TNM system; pN1: symbol for (macro)metastasis in 1–3 lymph nodes in the TNM system; pN1mi: symbol for lymph node micrometastasis in the TNM system; SLN: sentinel lymph node; TNM: tumour node metastasis; TS: Turner study.[12]

Table 3 – Methods used for the evaluation of the SLNs in the different study sites

Institution identified by senior author (number of cases; number with non-SLN involvement)	Number of HE levels per grossly or intraoperatively negative SLN (distance between levels)	IHC for cases with negative SLN findings on HE staining	Non-SLNs evaluation
Bianchi (180; 24)	Multilevel till extinction of the tissue block(s) (0.1 mm)	At multiple levels (clone AE1/AE3)	Slicing of larger LNs, 3–4 consecutive HE sections per small LN or per slice; IHC only in ILC
van Diest (129; 26)	Slicing of SLNs, 5 levels through each tissue block (0.250 mm)	At all levels (clone CAM5.2 or AE1/AE3)	Slicing of larger LNs, 1 HE section per small LN or per slice; no IHC
Cserni (89; 14)	Multilevel till extinction of the tissue block(s) (between 0.05 and 0.1 mm or 0.250 mm, depending on the period)	At multiple level using different pancytokeratin clones (MNF116, AE1/AE3)	Slicing of larger LNs, 1–3 consecutive HE sections per small LN or per slice; no IHC
Regitnig (54; 9)	Multilevel till extinction of the tissue block(s) (0.125 mm)	At multiple levels (clone MNF116)	Slicing of larger LNs, 2 consecutive HE sections per small LN or per slice; no IHC
Foschini (26; 3)	Three levels per 2 mm-thick slices (0.2 mm)	1 level per slice/block (clone MNF116)	1 HE per lymph node; no IHC
Sapino (14; 4)	Multilevel till extinction of the tissue block(s) (between 0.05 and 0.1 mm depending on the period)	At multiple levels (clone KL1 and AE1/AE3)	Slicing of larger LNs, 2–3 consecutive HE sections per small LN or per slice; no IHC
Callagy (10; 2)	Macroscopic slicing at 2 mm and 3 levels with further levels on equivocal findings (0.1mm)	Only for HE-negative lobular carcinomas	Macroscopic slicing at 2 mm and single level per slice; no IHC
Wells (8; 1)	Macroscopic slicing at 2 mm and 3 levels with further levels on equivocal findings (0.1 mm)	Only for HE-negative lobular carcinomas	Macroscopic slicing at 2mm and single level per slice; no IHC
Kulka (7; 2)	Multilevel till extinction of the tissue block (0.250 mm)	One level (clone MNF116)	Slicing of larger LNs, 1–3 consecutive HE sections per small LN or per slice; no IHC

HE: haematoxylin and eosin; IHC: immunohistochemistry, to demonstrate epithelial markers (generally cytokeratins); LN: lymph node; SLN: sentinel lymph node.

within the frames of the validation period of SLNB or was done on a selective basis for patients with SLN involvement. The methods used for the histological evaluation of the SLNs are briefly summarised in Table 3. In general, it can be stated that all units used a multilevel assessment for the SLNs, and the majority (involving 96.5% of the cases) also used immunohistochemistry routinely to improve the detection rate of low-volume metastases if the HE findings were negative. Non-SLNs were submitted to standard histological assessment involving the evaluation of one to few HE stained sections depending on the size of the lymph nodes (Table 3). The two cases of non-SLN ITC associated with SLN micrometastasis (according to both readings) were considered non-SLN-negative.

Contributors evaluated their cases using the circulated guidance used for the EWGS[9] and the training information used in the TS.[12] Reclassification of the cases reflected the individual interpretation of the definitions and cases. Some centres performed a dual reading of the cases, and consensus ratings were entered in the study. Patient identification was not included in the study; only anonymous re-evaluation of the SLNs was carried out without any therapeutic or other consequence, therefore no ethical permission was deemed necessary.

3. Results

There were 517 breast cancer cases entered in this study. These were all originally diagnosed as SLNs affected by either micrometastasis ($n = 421$), ITC ($n = 58$) or a small metastasis, not otherwise specified ($n = 38$), as the most significant SLN lesion; 235 (45%) of these were identified by immunohisto-

Table 4 – Concordance between the ITC and micrometastasis classification of the cases according to the TS and EWGS rules

	TS ITC	TS micrometastasis	Total
EWGS ITC	82	0	82
EWGS micrometastasis	125	310	435
Total	207	310	517

ITC: isolated tumour cell; EWGS: European Working Group Study;[9] TS: Turner study.[12]

Table 5 – Distribution of the non-SLN positive cases between the diagnostic categories of ITC and micrometastasis according to the two interpretations

Institution identified by senior author	EWGS		TS	
	Proportion of non-SLN-positive cases with SLNs involved by micrometastasis	Proportion of non-SLN-positive cases with SLNs involved only by ITC	Proportion of non-SLN-positive cases with SLNs involved by micrometastasis	Proportion of non-SLN-positive cases with SLNs involved only by ITC
Bianchi	21/149	3/31	10/80	14/100
van Diest	25/113	1/16	22/94	4/35
Cserni	14/75	0/14	9/57	5/32
Regitnig	7/42	2/12	6/35	3/19
Foschini	3/23	0/3	3/18	0/8
Sapino	4/11	0/3	3/7	1/7
Callagy	2/10	0/0	2/8	0/2
Wells	0/6	1/2	0/5	1/3
Kulka	2/6	0/1	2/6	0/1
Total	79/435 (18.2%)	7/82 (8.5%)	57/310 (18.4%)	28/207 (13.5%)

ITC: isolated tumour cell; EWGS: European Working Group Study;[9] non-SLN: non-sentinel lymph node; SLN: sentinel lymph node; TS: Turner study.[12]

chemistry (IHC). This original distribution of SLN involvement was only used for case selection, because the definition of ITC and its distinction from micrometastasis in the TNM system dates from 1999[11] and its universal usage in the staging system was introduced in January 2003 after the publication of the 6th edition of the TNM books.[5,6] Before this date, ITCs were generally recorded as micrometastasis.

The median (mean ± standard deviation; range) numbers of SLNs and non-SLNs in this series were 1 (1.7 ± 1; 1–7) and 15 (15.7 ± 6.4; 6–44), respectively. Of the 517 cases, 85 (16.4%) had non-SLN involvement.

As expected, many cases that were classified as micrometastasis on the original report were reclassified as ITC after the reassessment of cases according to definitions used for both studies. This transition was obviously due to the fact that some of the cases were from before 2003.

The distribution of cases between the two staging categories of ITC and micrometastasis according to the two interpretations of these categories is shown in Table 4. The proportion of SLN cases diagnosed with ITC was greater when diagnosed according to the TS interpretation (40% *versus* 16%; McNemar $p < 0.000001$). Of the 235 cases identified by means of IHC, a greater proportion belonged to the micrometastasis category according to the EWGS rules (178 *versus* 85).

The metastatic non-SLN rates for the diagnostic categories and institutions are shown in Table 5. If the SLNs contained only ITC, the non-SLNs were affected by the metastatic process in 7/82 cases (8.5%; 95% CI: 4.2% to 16.6%) according to the EWGS classification, and in 28/207 cases (13.5%; 95% CI: 9.5% to 18.9%) according to the TS classification. The 5% difference (95% CI: −4.0% to 11.9%) of these proportions was not significant (z-ratio: −1.172; Pearson $p = 0.24$).

4. Discussion

The distinction between the ITC and micrometastasis categories of the pTNM system is also a distinction between node-negative and node-positive status.[16] As such it may impact upon decisions concerning completion axillary dissection and systemic adjuvant treatment.[2]

The main purposes and probably advantages of introducing the ITC category at the lower end of micrometastasis were 1. to avoid the stage migration arising from more thorough pathological assessment of SLNs; 2. to account for possible artefacts of passive tumour cell transport to the SLNs during preoperative biopsy, localisation procedures, breast massage or the operative trauma itself and 3. to prevent overtreatment of low-volume nodal involvement in the light of the disputed prognostic significance of micrometastatic disease.

Since the definition of ITC is more restrictive according to the EWGBSP interpretation, and some lesions are obviously discordantly categorised (Table 2), it is not surprising that the rate of micrometastasis was higher according to the EWGS classification.

One of the main advantages of the TS interpretation of the staging definitions seems to be its reproducibility. When assessed on the basis of digital images, expert breast pathologists were able to achieve a consistent classification of the nodal lesions (kappa: 0.92).[12] In contrast, the EWGBSP achieved a worse interobserver agreement amongst both expert breast pathologists (kappa: 0.49)[9] and community hospital-based pathologists (kappa: 0.47).[10] A probable explanation for the differences in reproducibility might be that the TS classification is simpler, as it is based only on the simple size criteria, but another factor may be the fact that this interpretation was aided by a series of visual examples. Although reproducibility was not retested, it is likely that the mentioned kappa values characterise the classifications in this study too.

In contrast, one of the disadvantages of the TS interpretation seems to be the virtual downstaging of rather high-volume metastases as ITC. Lobular carcinomas are often associated with a specific pattern of nodal infiltration, namely the presence of multiple discohesive cells in the lymph node

(sinuses and parenchyma). These are generally not associated with desmoplasia and are therefore, with a few exceptions, labelled as ITC according to TS, with a possible comment that the pN categorisation does underestimate the nodal metastatic load. Indeed, the TS categorisation would not reflect the total volume of nodal involvement, which seems an important factor determining the prognostic impact of nodal metastases. The TS system would also allow some macrometastases (according to the EWGS understanding[17]) to be put into the ITC or at best into the micrometastatic category as exemplified by Fig. 1 of the TS publication.[12] Other tumour types which may be similarly virtually downstaged would include tubular carcinomas with tubules not larger than 0.2 mm infiltrating the nodal parenchyma without desmoplasia and micropapillary carcinomas with multiple close but separate inside out clusters without desmoplasia.

The prognostic effects of the differences in classifications cannot be assessed in the short term, but current axillary treatment decisions can be somewhat better monitored. It is estimated that around 15% of the SLNs with micrometastatic disease and about 9–10% of the cases with ITC in the SLNs are associated with non-SLN involvement.[18] Although micrometastases are sometimes disregarded, and some studies suggest that axillary dissection may be omitted if the SLN contains only micrometastatic disease,[19–21] it is common to perform completion axillary dissection with this finding.[2,7,8] On the other hand, many patients with SLNs affected only by ITC did not undergo an axillary dissection after the validation phase, and this may represent some selection bias, due to the lower than possible percentage of cases with ITC.

Another possible disadvantage of the classification used in the TS is that it seemed to increase not only the rate of ITC but also the rate of ITC associated non-SLN metastases. Our study demonstrates that the rate of non-SLN metastasis is somewhat higher with the TS approach than with the EWGS approach (13.5% *versus* 8.5%), although this difference did not prove to be statistically significant. Therefore, despite better reproducibility, the interpretation of the ITC and micrometastasis definition according to the TS may (to a minor extent) fail to achieve one of the aims of the segregation of the former micrometastatic category into a node-negative and a node-positive subgroup as it seems to perform somewhat less perfectly in identifying a minimal risk ITC category. In contrast, the EWGS classification rules put more patients into the micrometastatic category, and therefore probably increase the upstaging that the introduction of the ITC category was designed to prevent. However, with a restrictive approach to the ITC diagnostic category, it may be possible to separate cases which are associated with a somewhat lower risk of non-SLN metastasis, and can therefore more optimally be considered node-negative, i.e. pN0(i+).

Our study evaluated two different understandings of the staging categories of ITC and micrometastasis in breast cancer patients. However, there are probably other interpretations (Table 2) [13] and obviously many different practices of SLN examination as highlighted in a questionnaire-based study by the EWGBSP.[22] With different histology protocols, different rates of low-volume metastasis will be discovered in the SLNs, but none of the workable conventional histology protocols will disclose all ITCs, as these are relatively randomly distributed within the SLNs. On the other hand, an almost complete detection of micrometastatic disease can be targeted by several histological protocols.

Considering our results, it is likely that publications such as the French multi-centre study[23] or the report from the European Institute of Oncology[24] suggesting high rates (16% and 15%, respectively) of non-SLN metastasis associated with SLN ITCs used a less restrictive interpretation of the definitions for ITC and/or a less rigorous measurement. Indeed, accurate size was available only in 70% of the cases of the French study[23] and Viale from the European Institute of Oncology does not take into consideration the location of the tumour cells in the lymph node when distinguishing between ITC and micrometastasis.[13] Similar interpretation issues may bias the results of any studies dealing with the possible prognostic effect of low-volume nodal involvement, as well as its impact on the recommendations for locoregional therapy. It should not be forgotten that other factors such as tumour size and lymphovascular invasion also influence the rate of non-SLN positivity.[25–27] It is likely that the results of the American College of Surgeons Oncology Group – Z10 trial and possibly some other American results reflect the TS interpretation, whereas some European results are more likely to reflect the EWGS understanding of the ITC *versus* micrometastasis distinction. Caution is, therefore, mandatory when assessing results published in this field and care should be taken if the results are wildly contradictory; the study populations (cases), the definitions (or their interpretation) or the methods may be different and this may lie behind the discrepancy. Although there are cases of nodal involvement which are obviously categorised the same way by all pathologists, there are also cases that cannot be classified unanimously using the current TNM definitions of staging categories. Indeed, pathological nodal staging (pN categorisation) is the translation of the microscopic visual input into the diagnostic categories defined in the staging manuals.[5,6] Therefore, the publications would be greatly enhanced by visual examples of the written definitions. The lack of such visual examples may be an important factor contributing to the mediocre interobserver agreement achieved in the EWGS and the variability in interpretation that the worded definitions allow. Although two ways of interpreting these definitions were tested in this work, Table 2 alludes to another discordant interpretation by experts, namely the presence of tumour cells in the capsular lymphatics of the lymph node which would not be interpreted as nodal lesions.[14] Another article expressing what 6 European expert pathologists meant by ITC also suggests minor differences in understanding and therefore classification.[13]

In keeping with the conclusions of both studies testing the reproducibility of the ITC and micrometastasis categories in breast cancer SLNs,[9,12] the authors highlight that the present definitions of these staging subgroups are not sufficiently formulated and do not allow a reproducible classification in about 24% of the cases. Despite better reproducibility found in the TS, we demonstrate that classifying nodal involvement according to the definitions used in that study may, to a minor extent, increase the rate of ITC associated non-SLN involvement, and therefore may virtually increase the false-negative (negative SLN associated positive non-SLN)

rate of SLNB. Both the simplicity and the visual examples aided the better interobserver agreement in the pN classification of SLN findings, but this potential drawback must be considered before rewording the definitions. The EWGBSP interpretation of low-volume nodal metastases seems to better discriminate between lesions with a lower and higher risk of non-SLN involvement. Its less than optimal interobserver agreement could probably also be improved by sample images.

Neither of the two interpretations of the arbitrarily set low-volume pN categories may be ideal. About a quarter of the cases may be differently staged by one or the other, and this may prevent reliable staging and prognostic conclusions. As visual examples using sample images may improve the definitions and their interpretation, as shown by the TS, whatever modification the TNM endorses in its next update, such images should not be omitted.

5. Conflict of interest statement

None declared.

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