EUROPEAN JOURNAL OF CANCER 47 (2011) 887–894

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Distinction of isolated tumour cells and micrometastasis in lymph nodes of breast cancer patients according to the new Tumour Node Metastasis (TNM) definitions

Gábor Cserni [a,*], *Isabel Amendoeira* [b], *Simonetta Bianchi* [c], *Ewa Chmielik* [d], *James DeGaetano* [e], *Daniel Faverly* [f], *Paulo Figueiredo* [g], *Maria P. Foschini* [h], *Dorthe Grabau* [i], *Jocelyne Jacquemier* [j], *Handan Kaya* [k], *Janina Kulka* [l], *Manuela Lacerda* [g], *Inta Liepniece-Karele* [m], *Jose Martinez Penuela* [n], *Cecily Quinn* [o], *Peter Regitnig* [p], *Angelika Reiner-Concin* [q], *Anna Sapino* [r], *Paul J. van Diest* [s], *Zsuzsanna Varga* [t], *Vania Vezzosi* [c], *Jelle Wesseling* [u], *Vasiliki Zolota* [v], *Enrique Zozaya* [n], *Clive A. Wells* [w]

[a] *Department of Pathology, Bács-Kiskun County Teaching Hospital, Nyiri ut 38, H-6000 Kecskemét, Hungary*
[b] *Instituto de Patologia and Imunologia Molecular da Universidade do Porto e Serviço de Anatomia Patologica, Hospital S Joaõ, 4200 Porto, Portugal*
[c] *Division of Pathological Anatomy, Department of Medical and Surgical Critical Care, University of Florence, 50134 Florence, Italy*
[d] *Department of Pathology, Cancer Center and Institute of Oncology, 44-101 Gliwice, Poland*
[e] *Department of Pathology, Mater Dei Hospital, Tal-Qroqq Msida, Malta*
[f] *CMP Laboratory, Bruxelles, Belgium*
[g] *Laboratorio De Histopatologica, Centro Regional De Oncologia De Coimbra, Coimbra, Portugal*
[h] *Section of Anatomical Pathology, Department of Oncology and Hematology, University of Bologna, Bellaria Hospital, 40139 Bologna, Italy*
[i] *Department of Pathology, University of Lund, 221 85 Lund, Sweden*
[j] *Institut Paoli Calmettes, Marseille, France*
[k] *Department of Pathology, Marmara University, School of Medicine, İstanbul, Turkey*
[l] *2nd Department of Pathology, Semmelweis University, H-1091 Budapest, Hungary*
[m] *State Pathology Center, Riga Eastern Clinical University Hospital, Riga, Latvia*
[n] *Department of Pathology, Hospital de Navarra, Pamplona, Spain*
[o] *Department of Pathology, St. Vincent's University Hospital, Dublin, Ireland*
[p] *Institute of Pathology, Medical University of Graz, Graz, Austria*
[q] *Institute of Pathology, Donauspital, A-1220 Wien, Austria*
[r] *Department of Biological Science and Human Oncology, University of Turin, 10126 Turin, Italy*
[s] *Department of Pathology, University Medical Center Utrecht, 3508 GA Utrecht, The Netherlands*
[t] *Institute of Surgical Pathology, University Hospital Zurich, CH-8091 Zurich, Switzerland*
[u] *Department of Pathology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, 1066 CX Amsterdam, The Netherlands*
[v] *Department of Pathology, Medical School, University of Patras, 26504, Rion, Patras, Greece*
[w] *Department of Pathology, University College Hospital, London, WC1E 6JJ, United Kingdom*

[*] *Corresponding author:* Tel.: +36 76 516768; fax: +36 76 481219.
E-mail address: cserni@freemail.hu (G. Cserni).

doi:10.1016/j.ejca.2010.11.011

ARTICLE INFO

Article history:
Received 26 August 2010
Received in revised form 26 October 2010
Accepted 11 November 2010
Available online 16 December 2010

Keywords:
Breast cancer
Isolated tumour cells
Isolated tumour cell cluster
Micrometastasis
Sentinel lymph node
TNM

ABSTRACT

Isolated tumour cells and micrometastases represent two different staging categories and are often dealt with differently when identified in sentinel lymph nodes of breast cancer patients. The reproducibility of these categories was found to be suboptimal in several studies. The new edition of the TNM (Tumour Node Metastasis) is expected to improve the reproducibility of these categories. Fifty cases of possible low-volume nodal involvement were represented by one to four digital images and were analysed by members of the European Working Group for Breast Screening Pathology (EWGBSP). The kappa value for interobserver agreement of the pN (TNM) staging categories and of the isolated tumour cells category were 0.55 and 0.56 reflecting moderate reproducibility, and the kappa of the micrometastatic category (0.62) reflected substantial reproducibility. This is an improvement over the results gained on the basis of the previous edition of the TNM. Maximal adherence to the category definitions supplemented by explanatory texts in the staging manual should result in more homogeneous nodal staging of breast cancer.

1. Introduction

Lymph node status has for a long time been considered as the most important prognosticator of breast cancer free of distant metastases. Although lymph node status has lost some of its power in determining the prognosis of breast carcinoma, it is still an important prognostic feature of the disease and impacts on its treatment.[1]

Sentinel lymph node (SLN) biopsy has revolutionarily changed the approach to axillary nodal staging. The selection of one or a few lymph nodes has allowed pathologists to scrutinise these lymph nodes more carefully, and the common use of serial sections and/or immunohistochemistry has resulted in improved accuracy of staging, especially by finding low volume metastases.[2] The increased use of SLN biopsy has changed the stage related figures of breast cancer by virtually increasing the proportion of stage II, node-positive cases.[3] To avoid stage migration, the staging systems have introduced a new staging category labelled 'isolated tumour cells' (ITC)[4,5] also called 'submicrometastasis' by some authors,[6] which should not be considered a metastasis for staging and therapeutic purposes.

Although the prognostic value of low volume metastases has been disputed[7] and is still not clear at present, different policies are generally used for cases diagnosed with ITC and those diagnosed with micrometastasis.[8] In general no further axillary surgery is indicated for ITC,[6,8] and SLN micrometastases should be followed by completion axillary lymph node dissection,[8,9] although this latter approach has been challenged several times.[10] This dichotomy in surgical (locoregional) treatment policies would mandate a reproducible separation of the two staging categories of ITC and micrometastasis.

Previous studies have shown that the understanding of ITC and micrometastasis is not unanimous[11] and the distinction between these two categories was less than optimal on the basis of the definitions given in the relevant texts.[4,5,12] About one quarter to one half of the cases of low volume nodal involvement were ambiguously classified.[13–15] Although much better reproducibility could be reached after an image-guided training,[16] it was also suggested that despite better reproducibility achieved after such a training (kappa value of 0.92),[16] the risk of non-SLN involvement was better estimated with the less reproducible classification of the European Working Group for Breast Screening Pathology (EWGBSP) (kappa value of 0.49)[13] being more restrictive for the lesions that could be classified as ITC.[17–19] Indeed, the rates of non-SLN metastases associated with SLN micrometastases versus ITC were significantly different only when the EWGBSP interpretation was used (18.2% versus 8.5%), whereas these proportions did not significantly differ with the more reproducible interpretation of the staging categories described by Turner and colleagues.[16] (18.4% versus 13.5%).[18]

Because of the problems of reproducibility, the new (7th) editions of the Tumour Node Metastasis (TNM) classification of malignant tumours[20] and of the Cancer staging manual[21] have introduced a few new criteria which should make the diagnosis of ITC more restrictive, and without much emphasis have added the word 'cluster' to the name of the staging category to make it 'isolated tumour cell clusters'. No lymph node involvement with more than 200 cells on a single cut surface should be labelled ITC according to these modifications. The altered definitions should result in better reproducibility.

The present study was carried out to assess consistency of diagnosing ITC or micrometastasis in SLNs of breast cancer and compare this with results gained on the basis of the previous definitions.

2. Materials and methods

Members of the EWGBSP were asked to classify 50 cases of possible low-volume lymph node involvement stained with haematoxylin and eosin (HE) or cytokeratin immunohistochemistry (IHC) represented by one to four 1 megapixel digital images as ITC, micrometastasis or anything else (three categories allowed). The cases could be downloaded or looked at on-line at the following URL: https://www.kmk.hu/kmkweb/index.php?option=com_content&view=article&id=642&Itemid=15. The cases were identical to those of a previous study initiated 7 years ago,[13] but have been mixed up, and all participants were blinded to previous case labels.

In addition to categorisation as above, participants were asked to state

- whether the pictured nodal involvement represented a single or multiple lesion,
- the number of lesions present, if multiple;
- the pN category they would assign to the lymph node: (pN0(i+) if ITC, pN1mi if micrometastasis, pN1a if macrometastasis, pN0 if not cancerous nodal involvement);
- and whether they were confident in assigning categorisation for each case.

Comments could also be given as a free text addendum to the cases.

Interobserver agreement was assessed by kappa statistics.[22] The interpretation of the kappa values followed the arbitrary categories described by Landis and Koch: <0.00: poor, 0.00–0.20: slight, 0.21–0.40: fair, 0.41–0.60: moderate, 0.61–0.80: substantial and 0.81–1.00: very good reproducibility.[23] The kappa values were calculated with all cases included (calculation A), and with cases having at least 10 opinions against the presence of ITC or micrometastasis (cases not fitting into these categories, e.g. macrometastasis or capsular naevi) excluded (calculation B). The kappa values were compared with those of the previous study based on the 6th edition of the TNM.[13] This latter had two circulation of the cases: the first when every participant classified the lesions according to his/her interpretation of the TNM definitions,[4,5] and a second which was done after clarifying some interpretation issues.[13] The problematic areas of the categorisations that remained after the publication of the 7th edition of the TNM staging books[20,21] were highlighted after the analysis of the results. No ethical approval was necessary for the study, as no patients and no patients' data were involved.

3. Results

Twenty-four responses were received from the EWGBSP members listed as authors (two responses were bi-authored). Eleven of the participants took also part in the previous study based on the 6th edition of the TNM classification of malignant tumours published 6 years ago.[13]

Seven cases had unanimous pN classification (Table 1, examples in Fig. 1). The majority opinions on the pN category of the individual cases are shown in Table 1. According to this, there were 18 micrometastases, 29 isolated tumour cells/clusters, 1 macrometastasis and 2 lesions of non-metastatic origin. All cases presently labelled as pN1mi were also classified as pN1mi in the previous reproducibility study,[13] but 1 pN0 (capsular naevus) case and 12 pN0(i+) cases from the present interpretations were also labelled micrometastases earlier. Therefore, the definitions in the latest edition of the TNM have made the category of ITC less restrictive, at least for this European group. The number of cases deviating from the majority classification ranged from 3 to 15 per observer for the micrometastasis (MIC) versus ITC versus 'other' (OTH) classification and from 3 to 16 for the pN classification.

Eleven cases had fully concordant opinion on multiplicity of the lesion or its lack, but 15 cases had less than 60% agreement on whether the lesion was single or multiple (Table 1).

The kappa values for the relevant classifications are shown in Table 2. The kappa values were also calculated after eliminating the six cases where at least 10 participants felt that the lesion depicted was not of metastatic origin (capsular naevus for case 6 and 36; histiocyte and/or artefactual immunostaining for cases 17 and 44), was a macrometastasis (case 43) or was of insufficient quality for classification (case 20). This latter correction concentrated more on making the distinction between ITC and micrometastasis on a purer set of lesions. All the computations suggested that the reproducibility of the diagnostic categories for minimal nodal involvement improved with the changes introduced in the 7th edition of the TNM (Table 2). While the interobserver consistency distinguishing between the 3 (MIC versus ITC versus OTH) or the four (pN) categories was only fair when EWGBSP members used the TNM (6th edition) definitions (Table 2, column C), it improved to moderate after discussing and clarifying the definitions (Table 2, column D). Despite the minor increase in the overall kappa values in the present study, the reproducibility remained in the moderate range and was substantial only in the micrometastasis (and macrometastasis) categories.

4. Discussion

In the present study we documented that the reproducibility of distinguishing between the two diagnostic/staging categories of low volume lymph node involvement (i.e. micrometastasis versus ITC) slightly improved with the modifications introduced in the definitions of the 7th edition of the TNM. Overall, the reproducibility based on the assessment of 50 cases represented by digital images was found to be moderate, with the categories of micrometastasis and macrometastasis being substantially reproducible and that of ITC being moderately reproducible.

On the basis of the comments given, reproducibility of these categories could be further improved by addressing the issues highlighted in our study and illustrated in Figs. 1 and 2.

The earlier version of the TNM was dichotomous with respect to the 0.2 mm upper limit for ITC: the American Joint Committee on Cancer staging book suggested this measure as the largest size of an individual cluster,[5,16] whereas in the Union Internationale Contre le Cancer (UICC) publication, this was generally interpreted as the size of the whole lesion.[4,13] The introduction of a new limit of around 200 cells on a cut surface as maximum tumour burden acceptable for ITC has reduced the chances of mislabelling a rather large number of discohesive metastatic cells typical for invasive lobular carcinoma as ITC, but has also caused some confusion.

If one looks only at the 'Definitions of TNM' section of the Manual,[21] micrometastasis is defined as being >0.2 mm and/or >200 cells, but none should be >2 mm, and ITC is defined as tumour cells in lymph nodes no greater than 0.2 mm. There is also a note added to the ITC definition mentioning clusters of cells not greater than 0.2 mm or single metastatic cell or clusters with fewer than 200 cells in a single section, leaving free choice to use either of the limits and causing inconsistency in separating ITC from micrometastasis, as

Table 1 – Majority classifications per cases.

A	B	C[b]	D	E
A1 (2)	pN1mi (23/24; 0.96)	M (22/24; 0.92)	24/24; 1.00	pN1mi (0.94)
A2 (2)	**pN0(i+) (24/24; 1.00)**	M (19/23; 0.83)	23/24; 0.96	pN0(i+) (0.64)
A3 (2)	**pN0(i+) (24/24; 1.00)**	M (18/23; 0.78)	22/24; 0.92	pN0(i+) (0.64)
A4 (2)	pN0(i+) (16/24; 0.67)	S (19/22; 0.86)	16/24; 0.67	pN1mi (0.68)
A5 (2)	pN0(i+) (23/24; 0.96)	S (20/24; 0.83)	21/24; 0.88	pN0(i+) (0.96)
A6 (2)[a]	pN1mi (14/24; 0.58)	S (14/16; 0.88)	14/24; 0.58	pN1mi (0.80)
A7 (2)	pN1mi (13/24; 0.54)	S (18/22; 0.82)	8/24; 0.33	pN1mi (0.52)
A8 (3)	pN0(i+) (12/24; 0.50)	M (17/21; 0.81)	15/24; 0.63	pN1mi (0.84)
A9 (2)	pN1mi (15/24; 0.63)	S (16/24; 0.67)	18/24; 0.75	pN1mi (0.84)
A10 (2)	pN0(i+) (12/24; 0.50)	S (13/22; 0.59)	17/24; 0.71	pN1mi (0.80)
A11 (2)	pN1mi (21/24; 0.88)	S (14/24; 0.58)	20/24; 0.83	**pN1mi (1.00)**
A12 (2)	pN1mi (14/24; 0.58)	S (15/19; 0.79)	10/24; 0.42	pN1mi (0.84)
A13 (1)	**pN1mi (24/24; 1.00)**	S (18/24; 0.75)	23/24; 0.96	pN1mi (0.96)
A14 (2)	pN0(i+) (23/24; 0.96)	M (13/22; 0.59)	21/24; 0.88	pN1mi (0.52)
A15 (2)	pN0(i+) (23/24; 0.96)	**M (24/24; 1.00)**	17/24; 0.71	pN1mi (0.72)
A16 (2)	pN0(i+) (23/24; 0.96)	M (21/24; 0.88)	21/24; 0.88	pN1mi (0.64)
A17 (2)[a]	pN0 (18/24; 0.75)	S (7/8; 0.88)	17/24; 0.71	pN0 (0.56)
A18 (3)	pN0(i+) (23/24; 0.96)	**M (24/24; 1.00)**	20/24; 0.83	pN1mi (0.60)
A19 (3)	pN0(i+) (20/24; 0.83)	**M (22/22; 1.00)**	17/24; 0.71	pN0(i+) (0.56)
A20 (1)[a]	pN0(i+) (16/24; 0.67)	M (12/16; 0.75)	15/24; 0.63	pN0(i+) (0.88)
A21 (1)	pN0(i+) (17/24; 0.71)	**S (17/17; 1.00)**	16/24; 0.67	pN0(i+) (0.68)
A22 (2)	pN0(i+) (20/24; 0.83)	**S (19/19; 1.00)**	18/24; 0.75	pN0(i+) (0.88)
A23 (4)	pN0(i+) (17/24; 0.71)	M (19/23; 0.83)	15/24; 0.63	pN1mi (0.80)
A24 (2)	pN0(i+) (22/24; 0.92)	S (22/23; 0.96)	17/24; 0.71	pN0(i+) (0.76)
A25 (3)	pN1mi (22/24; 0.92)	S (12/23; 0.52)	15/24; 0.63	pN1mi (0.96)
A26 (2)	pN0(i+) (18/24; 0.75)	M (15/24; 0.63)	14/24; 0.58	pN1mi (0.68)
A27 (2)	pN0(i+) (22/24; 0.92)	M (16/23; 0.70)	20/24; 0.83	pN0(i+) (0.84)
A28 (1)	pN0(i+) (22/24; 0.92)	S (21/22; 0.95)	22/24; 0.92	pN0(i+) (0.88)
A29 (2)	pN0(i+) (21/24; 0.88)	**S (21/21; 1.00)**	15/24; 0.63	pN0(i+) (0.72)
A30 (2)	**pN1mi (24/24; 1.00)**	S (16/24; 0.67)	20/24; 0.83	**pN1mi (1.00)**
A31 (1)	**pN1mi (24/24; 1.00)**	S (18/24; 0.75)	22/24; 0.92	**pN1mi (1.00)**
A32 (2)	pN0(i+) (12/24; 0.50)	**S (23/23; 1.00)**	16/24; 0.67	pN0(i+) (0.76)
A33 (2)	pN0(i+) (21/24; 0.88)	**S (22/22; 1.00)**	21/24; 0.88	pN0(i+) (0.88)
A34 (1)	pN0(i+) (23/24; 0.96)	S (13/23; 0.56)	21/24; 0.88	pN0(i+) (0.60)
A35 (1)	pN0(i+) (22/24; 0.92)	M (18/23; 0.78)	18/24; 0.75	pN0(i+) (0.56)
A36 (2)[a]	pN0 (12/24; 0.50)	S (13/14; 0.93)	15/24; 0.63	pN1mi (0.64)
A37 (3)	pN1mi (20/24; 0.83)	S (17/23; 0.74)	20/24; 0.83	pN1mi (0.84)
A38 (4)	pN1mi (23/24; 0.96)	M (12/22; 0.55)	18/24; 0.75	pN1mi (0.96)
A39 (2)	pN1mi (20/24; 0.83)	S (16/24; 0.67)	19/24; 0.79	**pN1mi (1.00)**
A40 (2)	pN1mi (22/24; 0.92)	**S (24/24; 1.00)**	21/24; 0.88	**pN1mi (1.00)**
A41 (2)	pN0(i+) (22/24; 0.92)	M (16/24; 0.67)	17/24; 0.71	pN1mi (0.48)
A42 (3)	pN1mi (19/24; 0.79)	M (12/23; 0.52)	21/24; 0.88	**pN1mi (1.00)**
A43 (2)[a]	pN1a (20/24; 0.83)	S (12/15; 0.80)	21/24; 0.88	pN1a (0.92)
A44 (1)[a]	pN0(i+) (14/24; 0.58)	**S (14/14; 1.00)**	9/24; 0.38	pN0(i+) (0.68)
A45 (4)	**pN1mi (24/24; 1.00)**	M (19/24; 0.79)	19/24; 0.79	pN1mi (0.76)
A46 (2)	**pN1mi (24/24; 1.00)**	S (15/24; 0.63)	24/24; 1.00	**pN1mi (1.00)**
A47 (3)	pN0(i+) (15/24; 0.63)	M (19/24; 0.79)	19/24; 0.79	pN1mi (0.72)
A48 (2)	pN1mi (23/24; 0.96)	S (13/24; 0.54)	24/24; 1.00	**pN1mi (1.00)**
A49 (2)	pN0(i+) (21/24; 0.88)	**S (23/23; 1.00)**	20/24; 0.83	pN0(i+) (0.84)
A50 (2)	pN0(i+) (16/24; 0.67)	S (19/23; 0.83)	17/24; 0.71	pN1mi (0.48)

A: case identifiers (number of digital images per case in parentheses); B: pN classification according to the pTNM 7th edition [20,21UICCAJCC7] based on the majority opinion of the observers (proportion of observers in favour of majority diagnosis); C: opinion on the number of lesions depicted: single (S) versus multiple (M), (proportion of observers in favour of majority opinion); D: proportion of participants confident in their classification; E: classification of the corresponding case after interpretation discussion (2nd round) of the previous, TNM 6th edition based study;[13] pN0, pN0(i+), pN1mi, pN1a: categories of the pTNM classification, for no nodal involvement, isolated tumour cells/clusters, micrometastasis and macrometastasis, respectively.

[a] Cases not included in the kappa analysis of column B in Table 2.

[b] Not all cases were rated by all observers.

described by examples below. Only the 'Summary of changes' section and the explanatory text clarify a few things. For example the summary says that the 0.2 mm size limit is for clusters, and the 200 cell upper limit is for discohesive cells or nearly cohesive clusters. The text further explains that clusters are groups of cohesive or contiguous tumour cells.

Although the participants all had the 7th edition of the TNM[21] at hand by intent, case A32 with a circular cluster

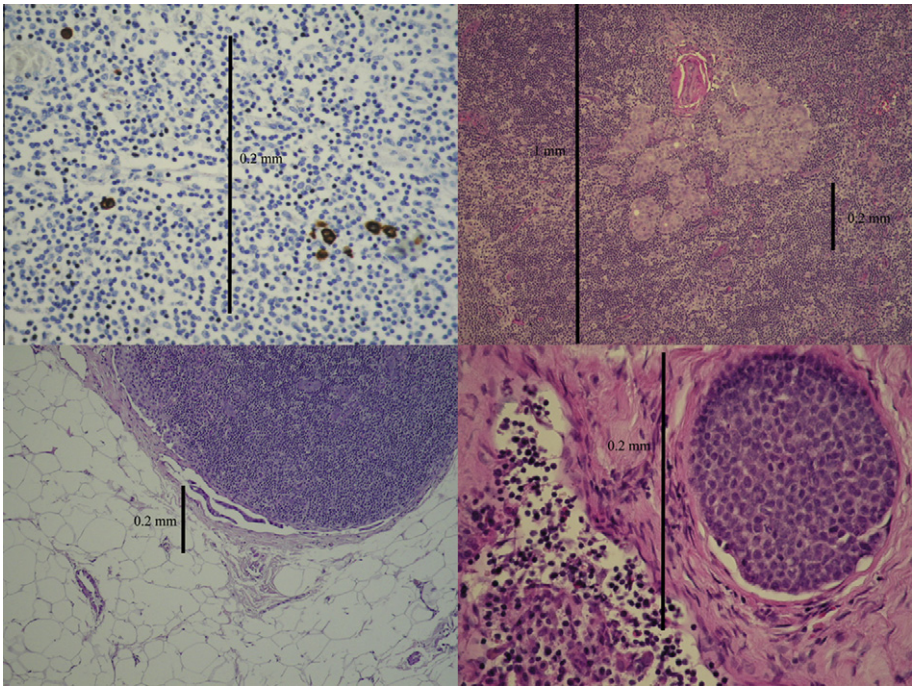

Fig. 1 – Representative examples of unanimous and controversial classifications. Cases A2 (top left, high power, cytokeratin immunohistochemistry) and A13 (top right, medium power, haematoxylin and eosin/HE/) represent lesions unanimously classified as isolated tumour cells (ITC) and micrometastasis, respectively, whereas case A10 (bottom left, medium power, HE) and A32 (bottom right, high power, HE) illustrate cases which just had a majority rating as ITC (further details in text).

Table 2 – Kappa scores for diagnostic and staging categories according to different calculations and their comparison with the Tumour Node Metastasis 6th edition based previous study results.

Kappa scores	A	B	C	D
MIC	0.62	0.64	0.45	0.53
Isolated tumour cells (ITC)	0.57	0.58	0.42	0.48
OTH	0.32	na (0.06)	0.23	0.35
S.E. of kappa for categories	±0.009	±0.009	±0.009	±0.008
Overall (of the above)	**0.55**	**0.56**	**0.39**	**0.49**
S.E. of overall kappa	±0.007	±0.008	±0.007	±0.007
pN0	0.25	na (0.04)	0.22	0.15
pN0(i+)	0.56	0.57	0.35	0.42
pN1mi	0.62	0.64	0.46	0.53
pN1a	0.75	na (0.06)	0.40	0.74
S.E. of kappa for categories	±0.009	±0.009	±0.009	±0.008
Overall (of pN categories)	**0.55**	**0.55**	**0.35**	**0.45**
S.E. of overall kappa	±0.007	±0.008	±0.006	±0.006

A: all cases ($n = 50$), all observers ($n = 24$); B: cases with non-metastatic involvement or suboptimal quality for at least 10 observers removed ($n = 44$), all observers ($n = 24$); C: TNM, 6th edition based previous study circulation 1,[13] all cases included ($n = 50$); D: TNM, 6th edition based previous study circulation 2, [13] all cases included ($n = 50$); MIC: micrometastasis; ITC: isolated tumour cell clusters; OTH: other than MIC or ITC; pN0, pN0(i+), pN1mi, pN1a: categories of the TNM classification, for no nodal involvement, isolated tumour cells and clusters, micrometastasis and macrometastasis, respectively; S.E.: standard error; na: not applicable, value given, as some ratings were still given for these categories – see text.

<0.2 mm, but having >200 cells (Fig. 1) was diagnosed as ITC by only half of the participants. The opposite situation represented by case A11 for example (with a cluster >0.2 mm but having obviously <200 cells, Fig. 2) was diagnosed by the majority as micrometastasis, but ITC was still favoured by 3/24 members. Although the staging book includes the definition of a cluster, lesions with close clusters (each <0.2 mm but with an area involved by multiple such clusters being >0.2 mm in largest dimension) caused reproducibility problems even if the metastatic area in question contained <200 cells. Case A10 is an example which only half of the participants categorised as ITC. Therefore, the suggested hierarchy of the dual limit (size to be used first for cohesive cells forming clusters, and number of cells for non-cohesive but close cells or clusters each smaller than 0.2 mm) needs more stress (or clarification), and should have been included in the

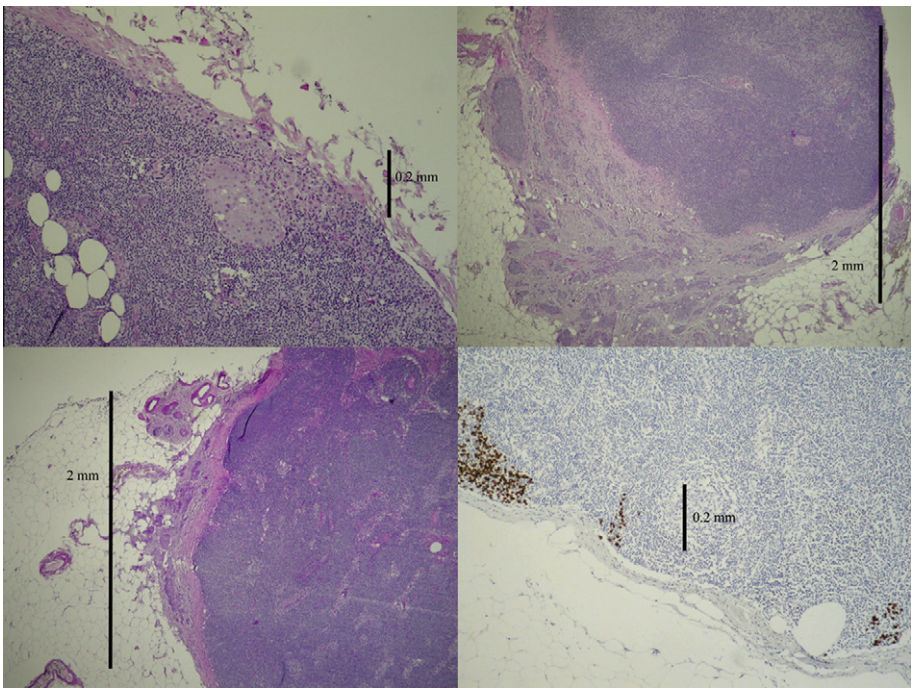

Fig. 2 – Illustration of some problematic issues. Case A11 (top left, medium power, haematoxylin and eosin/HE/) is a lesion >0.2 mm with <200 cells. Case A43 (top right, low power, HE) shows a case diagnosed by the majority as macrometastasis, however the metastasis involves only the nodal capsule and the extracapsular fat tissue, which led some participants to opt for pN0. Case A37 (bottom left, low power, HE) shows a case diagnosed by the majority as micrometastasis, however the metastasis involves only the capsule and the extracapsular fat tissue, which led one participant to opt for pN0 and others to opt for a macrometastasis. Cases A1 (bottom right, medium power, cytokeratin immunohistochemistry) demonstrating a lesion confidently classified by all participants, and labelled as micrometastasis by all but one observer. Discohesive cells (lobular carcinoma metastasis) are present in three separate groups, of which the left one has >200 cells, whereas the other two on the right have <200 cells each. (Further details in text.) Top right panel is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc. from Cancer, Vol. 103, No. 2, 2005, page 360. Copyright [2004] American Cancer Society.

Definitions section as well. There is clearly an overlap between the upper end of ITC and the lower end of micrometastasis, and this is well acknowledged, but a consistent classification requires definitions as clear as possible.

Localisation of the tumour cells was a major issue leading to discrepant interpretations,[13,19] with parenchymal lesions <0.2 mm being upstaged to micrometastasis by many European pathologists,[24] on the basis of previous UICC related publications[4,12] and our earlier work.[13,14] Localisation is not mentioned in the current staging text as a feature distinguishing between ITC and micrometastasis, and is mentioned as a feature widening the scope of nodal lesions. It is stated that lesions exclusively in the perinodal fat should be classified the same way as those in the lymph nodes.[21] Despite this clarification, some pathologists might be reluctant to label extranodal lesions (such as the macrometastasis of case A43 on Fig. 2) or lesions in the capsular lymphatic channels (such as the clusters of case A10 on Fig. 1) as nodal – both cases received ratings as pN0. The presence of extracapsular spread, even if only extracapsular spread is seen, should not prevent the categorisation of the lesion as micrometastasis if the size is not >2 mm (case A37, Fig. 2).[25] One specific occurrence, that of tumour cell emboli in a perinodal lymphatic vessel was not addressed in the present study and is also not specifically mentioned in the explanatory text of the staging book.[21] Some would probably prefer to label such lesions as L1 (lymphatic invasion present) using the category of the UICC staging book[20] as already highlighted earlier,[26] whereas there is also a suggestion to include these among nodal lesions too.[16]

The study highlighted again that determining the number of lesions might sometimes be problematic. This is not very much discussed in the guiding texts, although it may affect the perception and classification of nodal involvement. Case A1 (Fig. 2) was labelled by most participants as multiple lesions, some further specifying in the comments that they thought about a micrometastasis and two ITCs. The staging book has clear statements about the largest of the lesions to be considered for categorisation and that the lesions should not be summed.[21] In contrast, case A10 (Fig. 1) had a few close clusters with <200 cells altogether, but 9/22 participants thought of it as multiple lesions instead of a single ITC category lesion. The fact that a single ITC may consist of several clusters is a source of confusion as highlighted by the results in Table 1. No guidance is given on how to distinguish between single and multiple ITCs, but clearly pathologists' judgment should be relied on, and a larger distance between cells and/or clusters should favour multiplicity. For single lesions composed of several non-cohesive or non-contiguous cells

or clusters, the non-strict upper limit of about 200 cells should apply for the distinction between pN0(i+) and pN1mi, whereas for multiple and separate lesions, each should be assessed separately with the same maximum cell limit, and the number of cells should not be added up.

The pN0 and pN1a categories are not discussed in greater detail here. A few such cases were inserted in the study material with the aim of highlighting possible overdiagnosis and to assess how people dealt with lesions of uncertain metastatic origin. In routine practice, some of these lesions are incorrectly interpreted. The TNM has a basic principle of opting for the lower (less advanced) category when in doubt[21,27] – this was followed by several of the participants in this study too.

The ITC or pN0(i+) category was in the moderate reproducibility range on the basis of its kappa values. However, based on the comments, it was considered that most of the diagnostic issues could have been clarified in real practice (comparison with the primary tumour cells, use of immunostains for some HE stained lesions), and therefore the reproducibility of the category may have been better than calculated. Most of the problematic issues (two types of limit for ITC versus micrometastasis, localisation of the tumour cells, multiple clusters in a single ITC) can probably be overcome simply by adherence to the definitions and reference to the explanatory texts in the staging handbook, which would have benefited significantly from some key illustrations. An algorithmic help is given in the chart in Fig. 3.

The present study demonstrates an improvement in the distinction of the staging categories ITC and micrometastasis on the basis of the 7th edition of the TNM when compared to the previous version. This should allow a more reproducible classification provided that pathologists adhere to the definitions. A more reproducible categorisation is the basis of reliable prognostic evaluation and therapeutic recommendations. Despite being seemingly more restrictive for ITC (by limiting the total nodal tumour burden) the 7th edition is less restrictive when compared to the previous interpretation by our group (36% micrometastasis versus 62%). The prognostic impact of the examined low volume lesions is beyond the scope of this discussion, but it must be mentioned that reproducibility is only one facet of the problem. With a less restrictive interpretation of the ITC category, the rate of non-SLN positivity associated with SLN ITCs might be higher, as demonstrated earlier.[17–19] It must also be kept in mind that the arbitrary histological definitions discussed here are not based on contemporary outcome data with most patients diagnosed with invasive breast cancer receiving some form of adjuvant

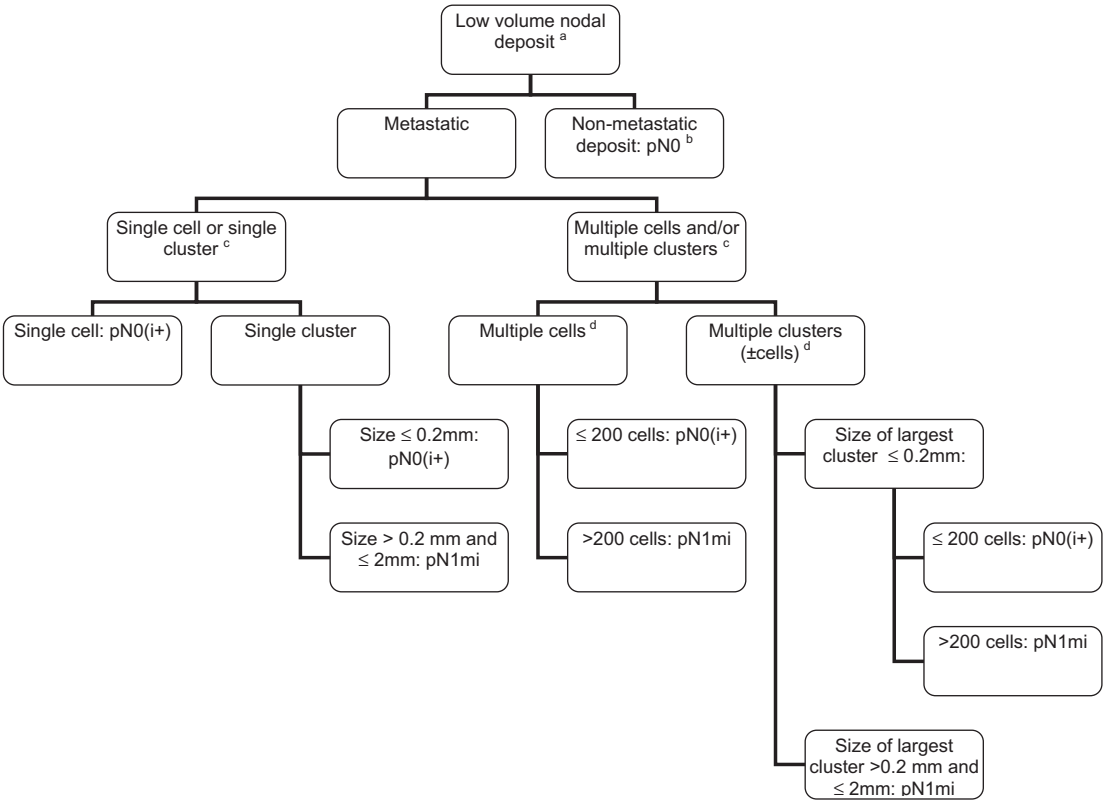

Fig. 3 – Chart for distinguishing between isolated tumour cells/pN0(i+) and micrometastasis/pN1mi according to the 7th edition of the Tumour Node Metastasis classification. [a]Detection method (i.e. haematoxylin and eosin staining versus immunohistochemistry), distance between cells/clusters, their localisation in the sinuses or parenchyma or extension to the extracapsular region does not influence the classification. [b]E.g. naevus cells are generally capsular, but sometimes they are in the trabeculae and rarely extend to the sinuses – immunohistochemistry should be used in doubtful cases. [c]A cluster is a confluent focus of tumour cells touching other tumour cells. However, tumour cells separated by desmoplastic/fibroblastic stroma reaction are interpreted as confluent. [d]The 0.2 mm size limit is for clusters, and the 200 cell upper limit is for discohesive cells or nearly cohesive clusters, and should be evaluated per single section.

therapy. In this context, having a higher rate of non-SLN positivity might not be the only or most important factor in assessing regional or distant recurrence risks. The pathologist's task is to consistently classify the SLN metastases and the 7th edition provides an adequate framework for that purpose.

Conflict of interest statement

None declared.

Acknowledgements

The help of the Skyline Computers running the Department of Informatics at the Bacs-Kiskun County Teaching Hospital, especially the help of Szabolcs Toth and Bela Fekete is acknowledged for making the cases available for on-line viewing and downloading. The financial support of the EWGBSP by the European Commission is also acknowledged.

REFERENCES

1. Cserni G. Sentinel node biopsy and nodal staging. In: Kahán Zs, Tot T, editors. Breast cancer, a heterogeneous disease entity. The very early stages. Dordrecht: Springer Science + Business Media B.V.; in press.
2. Giuliano AE, Dale PS, Turner RR, et al. Improved axillary staging of breast cancer with sentinel lymphadenectomy. *Ann Surg* 1995;**222**:394–401.
3. Weaver DL. Sentinel lymph nodes and breast carcinoma: which micrometastases are clinically significant? *Am J Surg Pathol* 2003;**27**:842–5.
4. Sobin LH, Wittekind C, editors. *UICC TNM classification of malignant tumours*. 6th Edn. New York: John Wiley and Sons Inc.; 2002.
5. Greene FL, Page DL, Fleming ID, et al., editors. *AJCC cancer staging handbook – TNM classification of malignant tumors*. 6th Edn. New York: Springer Verlag; 2002.
6. Schwartz GF, Giuliano AE, Veronesi U. Consensus conference committee. In: Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast, April 19–22, 2001, Philadelphia, Pennsylvania. Cancer 2002;94:2542–51.
7. Cserni G, Amendoeira I, Apostolikas N, et al. Pathological work-up of sentinel lymph nodes in breast cancer. Review of current data to be considered for the formulation of guidelines. *Eur J Cancer* 2003;**39**:1654–67.
8. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* 2005;**23**:7703–20.
9. Wasif N, Maggard MA, Ko CY, Giuliano AE. Underuse of axillary dissection for the management of sentinel node micrometastases in breast cancer. *Arch Surg* 2010;**145**:161–6.
10. Cserni G, Bori R, Sejben I, et al. Analysis of predictive tools for further axillary involvement in patients with sentinel-lymph-node-positive, small (< or =15 mm) invasive breast cancer [Hungarian]. *Orv Hetil* 2009;**150**:2182–8.
11. Cserni G, Amendoeira I, Apostolikas N, et al. Discrepancies in current practice of pathological evaluation of sentinel lymph nodes in breast cancer. Results of a questionnaire-based survey by the European Working Group for Breast Screening Pathology. *J Clin Pathol* 2004;**57**:695–701.
12. Hermanek P, Hutter RV, Sobin LH, Wittekind C. Classification of isolated tumor cells and micrometastasis. *Cancer* 1999;**86**:2668–73.
13. Cserni G, Bianchi S, Boecker W, et al. Improving the reproducibility of diagnosing micrometastases and isolated tumor cells. *Cancer* 2005;**103**:358–67.
14. Cserni G, Sapino A, Decker T. Discriminating between micrometastases and isolated tumor cells in a regional and institutional setting. *The Breast* 2006;**15**:347–54.
15. De Mascarel I, MacGrogan G, Debled M, Brouste V, Mauriac L. Distinction between isolated tumor cells and micrometastases in breast cancer: is it reliable and useful? *Cancer* 2008;**112**:1672–8.
16. Turner RR, Weaver DL, Cserni G, et al. Nodal stage classification for breast carcinoma: improving interobserver reproducibility through standardized histologic criteria and image-based training. *J Clin Oncol* 2008;**26**:258–63.
17. Cserni G, Bianchi S, Vezzosi V, et al. Variations in sentinel node isolated tumour cells/micrometastasis and non-sentinel node involvement rates according to different interpretations of the TNM definitions. *Eur J Cancer* 2008;**44**:2185–91.
18. Cserni G. Isolated tumour cells versus micrometastases and non-sentinel node involvement in breast cancer. *Lett Eur J Surg Oncol* 2009;**30**:1565–6.
19. Van Deurzen CHM, Cserni G, Bianchi S, et al. Nodal stage classification in invasive lobular breast carcinoma: influence of different interpretations of the pTNM classification. *J Clin Oncol* 2010;**28**:999–1004.
20. Sobin L, Gospodarowicz M, Wittekind Ch, editors. *UICC TNM classification of malignant tumours*. 7th Edn. New York: John Wiley and Sons Inc.; 2009.
21. Edge SB, Byrd DR, Compton CC, et al., editors. *AJCC cancer staging handbook: from the AJCC cancer staging manual*. 7th Edn. New York: Springer; 2009.
22. Fleiss JL. The measurement of interrater agreement. In: Fleiss JL, editor. *Statistical methods for rates and proportions*. 2nd Edn. New York: John Wiley and Sons, Inc.; 1981. p. 212–36.
23. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**:159–74.
24. Lebeau A, Cserni G, Dietel M, et al. Pathological examination of sentinel lymph nodes: work-up – interpretation – clinical implications. *Breast Care* 2007;**2**:102–8.
25. Cserni G. Axillary sentinel lymph node micrometastases with extracapsular extension: a distinct pattern of breast cancer metastasis? *J Clin Pathol* 2008;**61**:115–8.
26. Carter BA, Page DL. Sentinel lymph node histopathology in breast cancer: minimal disease versus artifact. *J Clin Oncol* 2006;**24**:1978–9.
27. Wittekind Ch, Greene FL, Henson DE, Hutter RVP, Sobin LH. *TNM supplement – a commentary on uniform use*. 3rd Edn. New York: Wiley-Liss; 2003.