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Review

Pathological work-up of sentinel lymph nodes in breast cancer. Review of current data to be considered for the formulation of guidelines

European Working Group for Breast Screening Pathology:[1] G. Cserni[a,*], I. Amendoeira[b], N. Apostolikas[c], J.P. Bellocq[d], S. Bianchi[e], G. Bussolati[f], W. Boecker[g], B. Borisch[h], C.E. Connolly[i], T. Decker[j], P. Dervan[k], M. Drijkoningen[l], I.O. Ellis[m], C.W. Elston[m], V. Eusebi[n], D. Faverly[o], P. Heikkila[p], R. Holland[q], H. Kerner[r], J. Kulka[s], J. Jacquemier[t], M. Lacerda[u], J. Martinez-Penuela[v], C. De Miguel[w], J.L. Peterse[x], F. Rank[y], P. Regitnig[z], A. Reiner[aa], A. Sapino[f], B. Sigal-Zafrani[bb], A.M. Tanous[cc], S. Thorstenson[dd], E. Zozaya[v], C.A. Wells[ee]

[a]*Department of Pathology, Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary*
[b]*Department of Pathology, Instituto de Patologia & Imunologia Molecular da Universidade do Porto, Porto, Portugal*
[c]*Department of Pathology, Saint Savvas Hospital, Athens, Greece*
[d]*Service d'Anatomie Pathologique, Hopital de Hautepierre, Strasbourg, France*
[e]*Department of Human Pathology and Oncology, University of Florence, Florence, Italy*
[f]*Istituto di Anatomia e Istologia Patologica, Turin, Italy*
[g]*Gerhard-Domagk Institut fur Pathologie, Universitat von Munster, Munster, Germany*
[h]*Centre Médicale Universitaire, Geneva, Switzerland*
[i]*Department of Pathology, Clinical Sciences Institute, University College Hospital, Galway, Ireland*
[j]*Department of Pathology, The Breast Unit, HELIOS Medical Centre, Berlin, Germany*
[k]*Pathology Department, Mater Hospital, Dublin, Ireland*
[l]*Pathologische Ontleedkunde, University Hospital, Leuven, Belgium*
[m]*Department of Histopathology, City Hospital, Nottingham, UK*
[n]*Sezione Anatomia Patologica M. Malpighi, Universita di Bologna, Ospedale Bellaria, Bologna, Italy*
[o]*CMP Laboratory, Brussells, Belgium*
[p]*Haartman Institute, University of Helsinki, Helsinki, Finland*
[q]*National Expert & Training Centre for Breast Cancer Screening, Academisch Ziekenhuis Nijmegen, Nijmegen, The Netherlands*
[r]*Department of Pathology, Rambam Hospital, Haifa, Israel*
[s]*2nd Institute of Pathology, Semmelweis University, Budapest, Hungary*
[t]*Institut Paoli Calmettes, Marseille, France*
[u]*Laboratorio De Histopatologica, Centro Regional De Oncologia De Coimbra, Coimbra, Portugal*
[v]*Department of Pathology, Hospital de Navarra, Pamplona, Spain*
[w]*Department of Pathology, Hospital Virgen del Camino, Pamplona, Spain*
[x]*Department of Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[y]*Center of Laboratory Medicine and Pathology, Department of Pathology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*
[z]*Institut fur Pathologie der Karl-Franzens Universitat Graz, Graz, Austria*
[aa]*Institute of Pathology, Donauspital, Wien, Austria*
[bb]*Institut Curie, Section Medicale et Hospitaliere, Paris, France*
[cc]*Division d'Anatomie Pathologique, Laboratoire National de Santé, Luxembourg*
[dd]*Kalmar County Hospital, Kalmar, Sweden*
[ee]*Department of Histopathology, St. Bartholomew's Hospital Medical School, London, UK*

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* Corresponding author. Tel.: +36-76-516700; fax: +36-76-481219.
E-mail address: cserni@freemail.hu (G. Cserni).

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Abstract

Controversies and inconsistencies regarding the pathological work-up of sentinel lymph nodes (SNs) led the European Working Group for Breast Screening Pathology (EWGBSP) to review published data and current evidence that can promote the formulation of European guidelines for the pathological work-up of SNs. After an evaluation of the accuracy of SN biopsy as a staging procedure, the yields of different sectioning methods and the immunohistochemical detection of metastatic cells are reviewed. Currently published data do not allow the significance of micrometastases or isolated tumour cells to be established, but it is suggested that approximately 18% of the cases may be associated with further nodal (non-SN) metastases, i.e. approximately 2% of all patients initially staged by SN biopsy. The methods for the intraoperative and molecular assessment of SNs are also surveyed.

Keywords: Sentinel lymph nodes; Breast cancer; Micrometastasis; Isolated tumour cell; Occult metastasis; Survival; Non-sentinel node metastasis; Frozen section; Intraoperative cytology; Molecular analysis

1. Background

The European Working Group for Breast Screening Pathology (EWGBSP) was founded in 1993 and now operates as part of the Europe against Cancer programme as one of the facets of the European Breast Cancer Network. It consists of 30 breast pathologists from all member states of the European Union (EU). One of the major briefs of the group is the production of European Guidelines which are compatible with and influence various guideline publications in the member states. The European Guidelines are frequently updated, and new tests and new methods of working are considered for each update. The controversies and inconsistencies regarding the pathological work-up of sentinel lymph nodes (SNs) led the EWGBSP to elect a subgroup with the aims of a review of the literature, the acquisition of personal experience and the collection of data and evidence for the future formulation of European Guidelines for the pathological work-up of SNs.

2. The accuracy of SN biopsy

In order to be able to assess the role of special histopathological techniques in the work-up of SNs, it is important to know how reliable the SNs are compared with the gold standard method of staging, axillary dissection and conventional histology involving the haematoxylin and eosin (HE) staining of tissue sections. Therefore, although this work focuses on the histopathology of SNs and the consequences of the pathology report, it includes a brief estimate of the risk of missing metastases that arises from the technique of SN biopsy (SNB) itself.

Because of the well-known learning curve associated with SNB [1–3], only series of $\geqslant 100$ patients with back-up dissection have been included in the review. This first analysis permits an estimation of the risks of missing metastatic lymph nodes in the axilla after a SNB with negative findings.

Table 1 reveals that the false-negative rate of SNB ranges from 0 to 15.2%, whereas the accuracy ranges between 93 and 100%. Multicentre studies [3,12,23,24] may give more accurate estimates, with false-negative rates ranging between 7.2 and 12.9%. Overall, a total of 4550 patients underwent successful SNB and the SNs were found to be predictive of the axillary status in 4403 cases (96.8%). This means that less than 4% of the patients may suffer a false staging, which is always a false-negative staging. This seems valid despite differences in methods between different studies.

It is well known that nodal involvement is more common in larger tumours, and the studies summarised in Table 1 report on heterogeneous populations (most of them including T1 and T2 tumours, but also some T3 and even T4 carcinomas), with mean tumour sizes of 1.7–2.1 cm in series where this parameter is given. Since smaller tumours are less likely to have nodal involvement, the proportion of patients falsely staged after a SNB is probably even lower in the population with T1 tumours than suggested by the figure of 3.2%; however, 4% is an upper estimate for the overall clinically node-negative Stage I and II breast cancer patient group.

3. Yield of detailed histopathological analysis of SNs

The SN theory postulates that SNs are the most likely sites of lymphogenic metastases. Accordingly, a more detailed pathological work-up of SNs is more likely to reveal metastases undetected by conventional histology (occult metastases) than the investigation of other lymph nodes [26–28]. The SNs allow pathologists to identify occult metastases with a higher frequency, but this possibility does not necessarily satisfy an existing need. Many of the occult metastases are micrometastases or involve isolated tumour cells. The TNM classification of malignant tumours currently defines these latter as tumour cells or clusters of tumour cells measuring $\leqslant 0.2$ mm, located in the sinuses of lymph nodes, without evidence of independent growth (invasion, tissue reaction) [29,30]. The same category is referred to by others as submicrometastasis [31]. It is unclear how often these isolated tumour cells reflect metastases capable of further growth and dissemination.

Table 1
Summary of larger non-duplicate series on SNB

A	B	C	D	E	F	G	H	I	J
[4]	*D*	3.0	SS + IHC	100	83 (83)	44	37	2 (5.1)	81 (98)
[5]	*D*	1.8	SS + IHC (6–8 levels)	107	100 (93)	58	42	0	100 (100)
[6]	*D*	1.5	SS + IHC	128	98 (77)	50	43	5 (10.4)	93 (95)
[7]	*D*	ni	SS (5 levels)	145	103 (71)	72	28	3 (9.7)	100 (97)
[1]	*D*	1.8	SS + IHC	174	114 (65)	72	37	5 (11.9)	109 (96)
[8]	*D*	1.5	ST	187	152 (81)	105	42	5 (10.6)	147 (97)
[9][a]	RC	1.2	SS + IHC ($\geqslant$5 levels)	130	122 (94)	59	44	1 (2.2)	103 (99)
[10]	RC	ni	SS + IHC (2–6 levels)	146	118 (81)	ni	ni	8 (ni)	110 (93)
[11]	RC	1.3	SS + IHC	376	371 (99)	191	168	12 (6.7)	359 (97)
[12]	RC	2.6	ST	443	405 (91)	291	101	**13 (11.4)**	392 (97)
[13]	*D* + RC	1.3	SS (6 levels)	100	96 (96)	63	28	5 (15.2)	91 (95)
[14]	*D* + RC	2.1	IHC	104	103 (99)	43	58	2 (3.3)	101 (98)
[15]	*D* + RC	ni	HE + IHC (3 levels)	106	89 (84)	53	34	2 (5.6)	87 (98)
[16]	*D* + RC	1.4	ST	117	95 (81)	64	29	2 (6.5)	93 (98)
[17]	*D* + RC	1.8	SS (15 levels)	119	96 (81)	69	26	1 (3.7)	95 (99)
[18]	*D* + RC	1.7	SS + IHC	136	126 (93)	70	56	3 (5.1)	123 (98)
[19]	*D* + RC	2.9	SS + IHC ($\leqslant$10 levels)	150	145 (97)	93	50	2 (3.8)	148 (99)
[20]	*D* + RC	1.9	SS + IHC (at 2mm)	ni	152 (ni)	84	68	1 (1.5)	151 (99)
[21]	*D* + RC	ni	SS + IHC	186	173 (93)	120	53	1 (1.9)	172 (99)
[3]	*D* + RC	2.2	SS + IHC	535	466 (87)	326	122	**18 (12.9)**	448 (96)
[22]	*D* or *D* + RC	1.4	SS + IHC (at 100–250 μm)	201	184 (92)	78	98	8 (7.5)	176 (96)
[23]	*D* + RC, (*D*, RC)	Median 2	IHC	498	450 (90)	266	164	**20 (10.9)**	430 (96)
[24]	*D* + RC or RC	2.0	various	806	ni (88)	ni	ni	**ni (7.2)**	ni (98)

A: References; B: method of SNB; C: mean number of SNs; D: pathology; E: number of SNBs; F: number of successful SNBs; G: number of patients with true-negative SNs; H: number of patients with positive SNs; I: number of patients with a false-negative SN status (false-negative rate), multicentre studies in bold; J: accuracy.
D, vital dye; RC, radiocolloid; SS, serial or step-sectioning; IHC, immunohistochemistry; HE, haematoxylin and eosin; ST, standard histology; ni, not indicated.
[a] Only 104 patients accepted the axillary dissection. Modified and updated from Ref. [25], with permission [25].

Whether there is a need for a more intensive histological work-up of the SNs, and, if so, what the extent of this work-up should be, requires certain considerations:

- What is the significance of occult metastases in terms of prognosis, and consequently the indication of adjuvant systemic treatment?
- What is the significance of occult metastases in terms of predicting further nodal involvement, and, consequently, the regional control of breast cancer?

First, studies dealing with the upstaging of breast carcinomas on the basis of a more detailed histopathological work-up of SNs are summarised (Table 2). These studies permit the conclusion that both serial or step-sectioning and immunohistochemistry (IHC) with cytokeratin (CK) antibodies would increase the rate of detection of metastatic cells and micrometastases. A combination of these two methods unites the opportunities of a more detailed sampling and a more sensitive method of detecting tumour cells, and therefore results in the highest rate (range 9–47%) of 'upstaging'. However, the methods used are very heterogeneous, and the interpretation of the results probably usually includes any type of nodal involvement as metastasis.

The nature of the metastases discovered by a more thorough pathological assessment is usually not documented in the available literature. The homogeneous distribution of tumour cells detected by IHC between the step-sectioned levels has been well documented [43]. As described in another study, most of the metastatic cells found in deeper sections during step-sectioning and immunostaining (occult metastases) belong in the category of isolated tumour cells or micrometastases [44], although a few macrometastases may also be included (up to 75, 67, 50, 33 and 17% if 2, 3, 4, 5 or 6 steps are sectioned at 250 μm from a bivalved SN). However, Weaver and colleagues reported that none of the occult metastases discovered by 100 and 200 μm sectioning of LNs that were negative at the initial HE level was larger than 1 mm [28]. However, that study did not involve a cut through the tissue blocks, and it is not sure that the occult metastases discovered at a depth of 200 μm, for instance, from the original surface do not comprise the edge or tangentional plane of a smaller macrometastasis which could only have been discovered from a deeper section.

4. The prognostic value of occult metastases

Most of our current knowledge on the prognostic relevance of nodal metastases is derived from a standard histological assessment of the lymph nodes. As the identification of occult metastases (defined here as nodal involvement undetected by standard HE histology) is time- and resource-consuming, only a few studies have assessed their prognostic relevance. Table 3 surveys such studies. It seems that larger series with a longer follow-up suggest a survival disadvantage [68], at least in some subgroups of patients, but even recent publications report the contrary, indicating that the question is far from being solved. Statistical analysis may also contribute to the discrepancies in the results. Few studies applied multivariate analysis [67].

If occult metastases are indicative of a poorer prognosis, this may be true for all or only a subset, e.g. the larger ones. At present, although strong evidence is lacking, it seems more reasonable to ignore the presence of isolated tumour cells from the aspect of staging, and therefore the indication of adjuvant systemic therapy, as suggested by the TNM system [29,30], or to include them in the setting of a combined prognostic profile such as the Nottingham Prognostic Index [69,70]. Micrometastases are more likely to denote a prognostic disadvantage, because of their larger size, although no evidence for this is available (Table 3); micrometastases are generally included in the node-positive group according to the TNM system and, if discovered, are probably best regarded as an indication for systemic adjuvant treatment.

Thus, the hunt for isolated tumour cells does not seem justified outside of research protocols. The same might hold true for micrometastases, although there are no clear data on the independent roles of micrometastases and isolated tumour cells; these categories are generally lumped together.

5. The value of detailed histopathology in the prediction of non-SN metastases

The question of whether axillary metastases left *in situ* lead to a survival disadvantage is often debated. The National Surgical Adjuvant Breast and Bowel Project (NSABP)-B4 trial, which formed the basis of the systemic theory of breast carcinoma (stating that breast cancer is a systemic disease from its onset), suggested that there was no benefit from locoregional treatment [71,72], as did the Cancer Research Campaign data [73]. However, a more recent theory of breast carcinoma, the spectrum theory (stating that at least a part of breast carcinomas are local or locoregional) [74] is backed up by studies demonstrating the utility of radiotherapy and its beneficial effects on survival [75–77]. Hence, there is at least some evidence to suggest that locoregional treatment is important. The avoidance of locoregional relapses is also desirable psychologically from the patient's point of view. Accordingly, positive axillary nodes should be removed or treated by radiation therapy.

SNB is accurate enough to predict a negative nodal basin, if the SN itself is negative. It should be established whether minute metastatic foci are relevant in the prediction of a positive status for the remainder of the axillary nodes, and whether a hunt for these foci is justified from this aspect.

A number of studies have assessed the predictive nature of SN metastases as regards further nodal involvement (Table 4). Although the definitions and methods employed in the various studies differ, and a wide range of non-SN involvement is identified in association with micrometastatic or CK-IHC-detected SN involvement (0–43%), these extreme values may reflect small case numbers. The overall experience resulting from the studies listed in Table 4 would favour a risk of non-SN involvement close to 18% (127/705) for micrometastases or isolated tumour cells (considered as a single group) found in the SNs. Isolated tumour cells are included with micrometastases in most studies, and are usually integrated in the group of 'metastases' detected by IHC only. The risk of non-SN involvement seems to be around 12% (29/239) when nodal involvement is detected by IHC only (which most often represents isolated tumour cells) [23,43,47,86,89,90,92]. Data from the Bács-Kiskun County Hospital suggest that isolated tumour cells are seldom associated with non-SN metastases, and small metastases (isolated tumour cells and micrometastases) in SNs, if associated with non-SN involvement, often reflect a failure to detect true SNs obstructed by metastasis (a recognised cause of false-negative SNBs) (data not shown). Intra-operative palpation of the axilla may reveal some of these firm 'non-SNs' and may reduce the percentage of a massive axillary metastatic load associated with minimal involvement of the SN.

The above data and assumptions point to the chances of non-SN metastases remaining in the axilla being low after SNB and a negative intra-operative physical nodal status, even if isolated tumour cells or micrometastases are present in the SNs, either detected or undetected. The risks of a clinically detectable regional relapse may be even smaller [94]. This is also an argument against the cost-effectiveness of hunting for minute nodal involvement.

6. Intra-operative assessment of SNs

The intra-operative assessment of axillary SNs is imperative in most instances, because this may allow a

Table 2
Review of studies assessing the role of serial sectioning and immunohistochemistry in the assessment of SNs

1st author [Ref.]	Number of patients	Number of patients positive by standard HE	Protocols compared[a]	Number (%) of patients upstaged	Comments
Jannink [32]	19	6 (32%)	1HE vs SS and IHC at 0.5 mm	3 (23%)	2 patients upstaged by SS and 1 by IHC
Kelley [33]	28	9 (32%)	1HE vs 4-level HE and 2-level IHC	2 (11%)	1 patient upstaged by SS and 1 by IHC; distance of levels not stated
Kowolik [34]	33	8 (24%)	2HE vs same-level IHC	4 (16%)	2 pN1mi, 2 pN0(i+)
Liu [35]	38	12 (32%)	1 HE vs 3 further HE sections and IHC	5 (19%)	2 patients upstaged by HE and 3 by IHC; distance of levels not stated
Nahrig [36]	40	18 (45%)	1HE vs 4 further HE at 0.15 mm from each other	4 (18%)	1 pN1mi, 3 pN0(i+); evaluates SS too
Czerniecki [37]	41	12 (29%)	1HE vs 4-level IHC	3 (10%)	Evaluates SS too; distance of levels not stated
Mann [38]	51	10 (20%)	1 HE vs same level IHC	10 (24%)	2 of the 3 illustrated cases identified by IHC could have been identified by HE too
Turner [39]	52	10 (19%)	2HE at 0.04 mm vs 2 further levels at 0.16 mm from each other	2 (5%)	
Turner [39]	52	10 (19%)	2HE at 0.04 mm vs 2 IHC at 0.04 mm	8 (19%)	
Turner [39]	52	10 (19%)	2HE at 0.04 mm vs 8 further levels IHC at 0.04 mm from each other	9 (21%)	Evaluates SS too
Noguchi [40]	62	24 (39%)	1 HE vs same-level IHC	1 (3%)	Retrospectively, the metastasis identified by IHC could have been seen on HE
Péley [41]	68	21 (31%)	1 HE vs SS with IHC only at 0.25 mm	12 (26%)	
Yared [42]	96	0	1 HE vs 2-level HE and 1-level IHC at 0.005 mm from each other	17 (18%)	
Fréneaux [43]	103	29 (28%)	1–4 HE vs 1–4 HE+6 IHC levels at 0.15 mm of each slice	35 (47%)	
Cserni [44]	123	55 (45%)	1 HE vs SS at 0.05–0.1 mm, IHC levels at 0.3–0.6 mm from each other	19 (28%)	1 pN1mi and 3 pN0(i+) first identified by IHC
Cserni [44]	123	29 (24%)	1 HE vs SS at 0.25 mm, IHC levels at 0.75 mm from each other	18 (19%)	3 pN1mi and 3 pN0(i+) first identified by IHC
Motomura [20]	152	44 (29%)	1 HE of the largest surface of the SN vs 1HE and IHC at all levels at 2 mm from each other	25 (23%)	
Viale [45]	155	45 (29%)	1HE vs 14 further levels at 0.05 mm from each other; frozen sections	25 (23%)	IHC did not increase the sensitivity of SN assessment
Dowlatshahi [46]	200	34 (17%)	1 HE vs SS with IHC only at 0.25 mm	51 (31%)	24 pN1mi, 27 pN0(i+)
Marin [47]	201	65 (32%)	1 HE vs SS with IHC at 0.5 mm	22 (16%)	
Torrenga [48]	250	69 (28%)	1 HE vs 4 further HE at 0.25 mm from each other	7 (4%)	
Torrenga [48]	250	69 (28%)	1 HE vs same-level IHC	5 (3%)	
Torrenga [48]	250	69 (28%)	1 HE vs 4 further IHC at 0.25 mm from each other	17 (9%)	Evaluates SS too
Weaver [28]	386	104 (27%)	1 HE vs 2 further HE levels at 0.1 mm from each other and 1-level IHC at 0.1 mm	19 (7%)	
Pendas [49]	478	93 (19%)	1HE vs same-level IHC	41 (11%)	
Wong [50]	973	104 (11%)	1 HE vs 2-level IHC	58 (7%)	

HE, haematoxylin and eosin; IHC, immunohistochemistry against epithelial markers, generally cytokeratin with AE1/AE3, MNF-116, CAM 5.2, PanCK antibodies; some studies additionally used epithelial membrane antigen; pN1mi, micrometastasis [29,30]; pN0(i+), isolated tumour cells [29,30]; SS, multilevel assessment by serial sectioning or step sectioning. Modified and updated from Ref. [44].

[a] The standard HE serving as baseline examination comprised halving or macrosectioning SNs at 2–3 mm and examining one HE section from each part, except in two studies, [28,33] where two HE sections were obtained.

one-step procedure for patients with positive findings. Cytological preparations (imprints and scrapings) and frozen sections are the two possibilities for the investigation of grossly negative SNs intra-operatively. The advantages and disadvantages of these techniques are well known [95,96] and are summarised in Table 5. Table 6 provides data on studies of the intra-operative assessment of SNs. The yields of the two methods are very comparable, with accuracy and false-negativity rates ranging from 79 to 98% and from 9 to 52%, respectively, for frozen sections and from 77 to 99% and from 5 to 70%, respectively, for intra-operative cytology. It must be borne

Table 3
Studies on the survival effect (prognostic significance) of micrometastases or occult metastases

1st author [Ref.]	Method of detection	Number of patients/Details	Occult metastasis or micrometastasis	Prognostic significance
Pickren [51]	Single level vs SS	159/101N+; 51N0 cut by SS; 11 (22%) upstaged	Occult	No (minimum 5-year follow-up)
Huvos [52]	NI	227/63N+ at level I of the axilla of which 18 with micrometastases (<2 mm)	Micrometastasis	No (minimum 8-year follow-up)
Fisher (1) [53]	Single level vs SS	78/78N0 by single level HE; 19 (24%) upstaged	Occult	No (mean follow-up: 61 months)
Fisher (2) [54]	Single level	565/278N+ of which 21 with micrometastases (<2 mm)	Micrometastasis	No (mean follow-up: 49 months)
Rosen [55]	NI	147/147N+ of which 41 with micrometastasis to 1 LN	Micrometastasis	Yes (minimum 10-year follow-up)
Wilkinson [56]	HE vs SS	525/525 N0 of which 84 (16%) upstaged	Occult	No (minimum follow-up: 5 years)
Trojani [57]	HE vs IHC of same sections	150/150N0 by HE; 21 (14%) upstaged; 38% of lobular cancers upstaged	Occult	Yes (mean follow-up: 10 years)
Sedmak [58]	HE vs new HE+IHC	45/45N0 by HE; 9 (20%) upstaged	Occult	Yes (minimum follow-up 10 years)
IBCSG [59]	Single level vs SS	921/921N0 by single level HE; 83 (9%) upstaged	Occult	Yes (median follow-up: 5 year)
Galea [60]	HE vs recut IHC	98/98N0 by HE; 9 (9%) upstaged	Occult (all but one micrometastasis)	No (follow-up out to 14 years)
de Mascarel [61]	HE vs IHC of same sections	218/129N0 non-lobular and 89N0 lobular by HE; 50 (23%) upstaged; 41% of lobular cancers upstaged	Occult	Yes—for DFS and ductal cancers (median follow-up: 15.6 and 9.3 years for ductal and lobular cancers, respectively)
Hainsworth [62]	1 HE vs 1 IHC	343/343N0 by single level HE; 41 (12%) upstaged	Occult (10 macrometastases)	Yes—only for disease-free survival, but not for overall survival (follow-up: median 79 months)
Nasser [63]	HE vs SS+IHC	159/159N0 by original HE; 28 (17%) upstaged by SS, 50 (31%) upstaged by SS+IHC	Occult	No for all. Yes for occult metastases >0.2 mm (mean follow-up: 11 years)
McGuckin [64]	HE vs SS (4 levels)+IHC	208/208N0 by original HE; 53 (25%) upstaged by SS+IHC	Occult	Yes—only for DFS, but not for OS on multivariate analysis (median follow-up: 92 months)
Cote [65]	HE vs 6 levels HE and 1 level IHC	736/736N0 by HE; 52 (7%) upstaged by multiple level HE, 148 (20%) [39% for lobular cancers] upstaged by IHC	Occult	Yes—in postmenopausal women (median follow-up: 12 years)
Colpaert [66]	HE vs 2 further levels IHC	104/104N0 by HE; 24 (23%) upstaged by IHC, 17 (16%) ITC, 7 (7%) pN1mi	Occult	No (median follow-up for patients with and without relapse: 25 months and 91.5 months, respectively)
Millis [67]	HE vs IHC	477/477N0 by HE; 60 (13%) upstaged	Occult	No (median follow-up: 18.9 years)

DFS, disease-free survival; OS, overall survival; SS, multiple level assessment by serial sectioning or step-sectioning; IHC, immunohistochemistry; ITC, isolated tumour cells; N1mi, micrometastasis (≤2 mm, unless otherwise stated); IBCSG: International Breast Cancer Study Group.

in mind that these values may be seriously biased by the depth of the final histology, i.e. the best performances are usually reported when the final histological evaluation considers only the same surface as that involved in the intra-operative assessment [108].

It seems that the best advice is to consider the local resources and to choose the method that best fits the needs and possibilities in a given institution.

7. Molecular analysis of SNs

The molecular assessment of SNs from breast cancer patients is usually performed by means of the reverse transcription-polymerase chain reaction (RT-PCR). This is even more sensitive than IHC, but suffers from a lack of specific markers [117–123], the subsequent problem of interpreting partially positive reactions assayed by multiple markers, the lack of morphological controls and the occurrence of false-negative tests. The relevance of RT-PCR-positive, but HE and IHC-negative SNs is even more debatable than the relevance of occult metastases or micrometastases disclosed by serial sectioning or IHC, because of the very small size of these metastases and/or the question relating to false-positive tests. Table 7 shows studies on the molecular assessment of SNs in breast cancer, the most promising of which seems to be a multiple marker flow cytometric assay that can be used on paraffin-embedded tissue blocks [78]. Because of the high variability of the results and the high rate of upstaging of patients on the basis of RT-PCR tests, molecular analysis of SNs should remain an experimental assessment.

Table 4
Studies on SN based prediction of non-SN involvement

1st author [Ref.]	Number of patients with SN+ (non-SN+)	Number of patients with small metastases (non-SN+;%)	Findings	Pathology; Comments
Leers [78]	38 (18)	15 N1mi and ITC (5; 33%)	Micrometastases to SNs are associated with 30% risk of non-SN involvement	3HE+3IHC+MP-FCM; N1mi and ITC considered as one category
Chua [79]	51 (24)	7 N1mi<1 mm (3; 43%)	Both small tumours (T1) or micrometastases <1 mm carry a substantial risk of non-SN involvement	6HE+2IHC; N1mi and ITC considered as one category, micrometastasis definition: <1 mm
Sachdev [80]	55 (21)	18 N1mi (<1 mm) or ITC (3; 17%)	T2 tumours with lymphatic invasion and SN macrometastasis (⩾1 mm) are associated with greater risk of non-SN involvement	HE+IHC; N1mi and ITC considered as one category
Reynolds [81]	60 (28)	27 N1mi or ITC (6; 22%)	T1 and pN1mi(sn) have low risk of non-SN involvement	4HE+IHC; N1mi and ITC considered as one category
Fréneaux [43]	64 (16)	35 only IHC positive (1; 3%)	IHC detected occult metastases are rarely associated with non-SN involvement	1–4HE+(1–4)×6 IHC; N1mi and ITC considered as one category
Cserni [82]	69 (31)	17 N1mi or ITC (5; 29%)	Patients with either SN metastases <1.4 mm or tumours <1.8 cm are <10% non-SN+; patients with T1 tumours<1.8 cm, capsular or subcapsular location of tumour cells in the SN (ITC) and only 1 SN involved have low probability of non-SN involvement	HE step-sectioning+IHC; N1mi and ITC considered as one category
Liang [83]	78 (34)	15 N1mi (0; 0%)	Patients with micrometastatic SN do not obviously require axillary dissection	HE; Only 11 patients had axillary dissection
Marin [47]	87 (40)	29 N1mi or ITC (8; 28%); 18 only IHC positive (4; 22%)	Patients with micrometastatic SN have a risk of non-SN involvement, that might be minimal for ductal type, T1 tumours without vascular invasion	1–7 HE+IHC (whole thickness at 0.5-mm steps); N1mi and ITC considered as one category
Rahusen [84]	93 (46)	30 N1mi (<1 mm^2) (8; 27%)*	Patients with T1a tumours or SN micrometastases <1 mm^2 still have a risk of non-SN involvement	5HE+IHC; N1mi and ITC considered as one category; micrometastasis definition: <1 mm^2
Abdessalam [85]	100 (40)	35 N1a or ITC (7; 20%); 5 only IHC positive (1; 20%)	SN involvement, macrometastatic SNs, vascular invasion, extracapsular nodal involvement all increase the likelihood of non-SN involvement	6FS+SS (HE)+IHC; N1mi and ITC considered as one category divided by method of detection
Kamath [86]	101 (60)	46 N1mi or ITC (7; 15%) and 26 only IHC positive (2; 8%)	SN micrometastases detected by IHC only are associated with a low risk of non-SN involvement	SS (HE)+IHC; N1mi and ITC considered as one category, divided by method of detection
Mignotte [87]	120 (56)	68 N1mi or ITC (15; 22%); 44 only IHC positive (7; 16%)	No subset with very low risk of non-SN + could be identified	SS at 1–2 mm (HE)+6 IHC; N1mi and ITC considered as one category, divided by method of detection
Chu [88][a]	158 (53)	69 N1mi or ITC (5; 6%); 33 only IHC positive (0; 0%)	T1a and T1-2 pN1mi(sn) tumours have low risk of non-SN involvement	4–6HE+2IHC; N1mi and ITC considered as one category
Bergkvist [23]	164 (ni)	18 only IHC positive (3; 17%)		n.i.
Turner [89][a]	194 (88)	89 N1mi or ITC (9; 10%); {20; 22%}[b]; 39 only IHC positive (5; 13%); {10; 26%}[b]	Micrometastatic T1-2 tumours without vascular ivasion, hilar extracapsular nodal spread have low risk of non-SN involvement	4-6HE+2IHC;
Teng [90]	204 (67)	39 only IHC positive (3/26; 12%)	Even patients with SNs positive with CK IHC only require axillary dissection	HE+IHC; probably only ITC identified; only 26 patients had axillary dissection
Weiser [91]	206 (66)	93 N1mi or ITC (17; 18%)	Micrometastatic T1a-b tumours without vascular ivasion, have low risk of non-SN involvement	FS+SS+IHC; N1mi and ITC considered as one category
Wong [92]	389 (144)	28 only IHC positive (3; 11%)	Non-SN involvement was 28% for T1 tumours; a small subset of patients with only CK IHC positive SNs have obvious non-SN metastases	HE/2 mm+IHC performed on only 49% of the cases; The influence of SN metastasis size could not be assessed reliably; probably mainly ITC identified.
Viale [93]	ni	109 N1mi (24; 22%)	12/33 (36%) non-SN involvement with SN micrometastases >1 mm; 12/77 (16%) non-SN involvement with SN micrometastases ⩽1 mm	HE step sectioning+IHC; N1mi and ITC considered as one category

HE, haematoxylin and eosin; IHC, immunohistochemistry; ITC, isolated tumour cells [29,30]; MP-FCM, multiparameter flow cytometry; N1mi, micrometastasis [29,30]; pN1mi(sn), micrometastatic to the SN; FS, frozen section.

[a] Overlapping series from the same institution.

[b] Results with IHC of non-SNs, too.

Table 5
Advantages and disadvantages of intra-operative frozen section and imprint cytology assessment of SNs

Advantages	Disadvantages
Frozen sections	
Tissue diagnosis (nodal architecture)	Freezing artifacts
Usually specific, less deferred diagnoses	Requires more time
Enables differentiation of macrometastases and micrometastases	Some tissue is lost
Histologists are more familiar with the method	More expensive
Can be complemented by rapid IHC	Sampling errors may occur
Imprint cytology	
Simple	Fewer cells assessed
Cheap	More indeterminate and deferred diagnoses
Rapid	Cannot differentiate between micrometastases and macrometastases
May give excellent cytological details	Sampling errors may occur
Requires cytology training	
Can be complemented by rapid IHC	

8. Discussion and conclusions

T1-T2 breast carcinomas patients undergoing SNB may be falsely staged in somewhat less than 4% of the cases, or less for a population with smaller tumours. Multilevel HE assessment by serial or step-sectioning and CK immunostaining may detect otherwise hidden tumour cells in SNs in 9–31% of the cases, depending on the depth of assessment and the size of the tumours. Many of these occult metastases are micrometastases or

Table 6
Studies on the intra-operative assessment of SNs

A	B	C	D	E	F	TP	TN	FP	FN	ACC (%)	SENS (%)	SPEC (%)	PPV (%)	NPV (%)	FNR (%)	FRR (%)
FS	[97]	28	1 (2)	HE	IHC	6	17	0	5	82	55	100	100	77	45	23
FS	[98]	47[a]	NI	HE	HE	10	36	0	1	98	91	100	100	97	9	3
FS	[99]	54	2	HE	Mult. HE + IHC	21	31	0	2	96	91	100	100	94	9	6
		74[a]	2	HE	Mult. HE + IHC	27	43	0	4	95	87	100	100	91	13	9
FS	[100]	62	⩾1	HE	HE + IHC same level	19	34	0	9	85	68	100	100	79	32	21
FS	[13]	96	3 (both sides)	HE	HE	24	68	0	4	96	86	100	100	94	14	6
FS	[101]	107	3 consec	HE	3 HE	32	57	0	18	83	64	100	100	76	36	24
FS	[102]	157	NI	HE	Mult. HE + IHC	41	116	0	18	90	69	100	100	87	31	13
FS	[103]	165[a]	NI	HE	Mult. HE at 2–3 mm	19	141	2	3	97	86	99	90	98	14	2
FS	[104]	203	2	HE	Mult. HE at 2 mm + IHC	53	132	1	17	91	76	99	98	89	24	11
IC + FS	[100]	38	⩾1	MG + IHC/HE	HE + IHC same level	3	25	0	10	92	77	100	100	89	23	11
IC + FS	[105]	278	1	DQ	HE same level	53	206	0	19	93	74	100	100	92	26	8
		278	1	DQ	Mult. HE + IHC	53	167	0	58	79	48	100	100	74	52	26
IC	[106]	25	1	RAL	NI	4	19	0	2	92	66	100	100	90	33	10
IC	[100]	38	1	MG + IHC	HE + IHC same level	6	25	0	7	82	46	100	100	78	54	22
IC	[99]	45	⩾2	DQ	Mult. HE + IHC	14	23	0	8	82	64	100	100	74	36	26
		59[a]	⩾2	DQ	Mult. HE + IHC	16	33	0	10	83	62	100	100	77	38	23
IC	[107]	55	=2	HE	HE same level	14	40	0	1	98	93	100	100	98	7	2
IC	[108]	60	=2	HE	Mult. HE + IHC	19	28	0	13	78	59	100	100	68	41	32
IC	[109]	65	⩾2 (1/slice)	P or DQ	Mult. HE + IHC	17	33	1[c]	14	77	55	97	94	70	45	30
IC	[110]	101	⩾2 (1/slice)	P	HE + IHC same level	30	67	1[c]	3	96	91	99	97	96	9	4
IC	[111]	109	2–6	Giemsa	Mult. HE + IHC	32	63	0	14	87	70	100	100	82	30	18
IC	[112]	124[a]	1	HE	HE same level	22	101	0	1	99	96	100	100	99	5	1
IC	[113]	148	=2	Giemsa and P	3-level HE + IHC	40	86	2	20	85	67	98	95	81	33	19
IC	[114]	150	1	HE	3-level HE, IHC in some	20	113	0	17	89	54	100	100	87	46	13
IC	[115]	161[b]	2	IHC	Mult. HE + IHC	30	126	0	5	97	86	100	100	96	14	4
IC	[116]	381[b]	2	DQ	Mult. HE + IHC	15	254	1	35	88	30	100	94	88	70	12
IC	[103]	479[a]	>1	HE	Mult. HE at 2–3 mm	65	409	1	4	99	94	100	98	99	6	1

A, Method; B: reference; C: number of patients; D: number of levels studied intraoperatively; E: stains used intraoperatively; F: final histopathology details: SN, sentinel lymph node; TP, true positive cases; TN, true negative cases; FP, false-positive cases; FN, false-negative cases; ACC, accuracy; SENS, sensitivity; SPEC, specificity; PPV, positive predictive value; NPV, negative predictive value; FNR, false-negative rate (FN/all node positives); FRR, false reassurance rate (FN/(FN + TN)); FS, frozen section; IC, imprint cytology; consec, consecutive; HE, haematoxylin + eosin; DQ, Diff-Quik; MG, May-Giemsa; P, Papanicolaou; RAL, rapid cytological stain RAL 555; IHC, immunohistochemistry for the demonstration of epithelial markers; Mult., multiple; NI, not indicated.

[a] On an SN (and not patient) basis.

[b] On a grossly negative SN (and not patient) basis.

[c] Cases reported as positive on intra-operative assessment and negative by final histology, that the authors did not interpret as a false-positive result, are presented here as false-positive findings, because the standard comparison in this table is the result of histology. Modified and updated from Ref. [95].

Table 7
Molecular analysis of SNs in breast cancer

1st author [Ref.]	Patients (nodes)	Methods	Histology (positive controls)	Results (on a patient basis unless otherwise specified)	Comments[a]
Péley [41]	14 (ni)	Half SN used for CK-20 RT-PCR	SS at 250 μm and IHC (AE1/AE3 CK)	2 positive by HE 3 positive by HE or IHC 10 positive by RT-PCR	21% accuracy, 33% sensitivity, 18% specificity (only 1 histologically positive case testing positive by RT-PCR).
Bostick [118]	22 (22)	2×6 12-μm-thick FS used for multiple marker (CEA, CK19, CK20, GA733.2 and MUC-1) RT-PCR	HE + IHC (CK)	10 SNs (45%) positive by histology 3 SNs (14%) positive for all 5 markers by RT-PCR	59% accuracy, 40% sensitivity, 75% specificity for 4 markers; 59% accuracy, 20% sensitivity, 92% specificity for all 5 markers (only CK20 tested negative in nodes from non-tumour-bearing patients, the other markers show no diagnostic value in this context; 1 SN positive by histology showed no positivity by RT-PCR).
Bostick [119]	41 (57)	2×6 12-μm-thick FS used for multiple marker (C-Met, β1→4-GalNAc and P97) RT-PCR	HE + IHC (CK)	10 SNs (18%) positive by HE 17 SNs (30%) positive by HE or IHC 39 (68%) and 23 (40%) SNs positive for at least 2 markers by RT-PCR	51% accuracy, 82% sensitivity, 38% specificity for any 2 markers; 51% accuracy, 35% sensitivity, 58% specificity for all 3 markers. (1 SN positive by histology showed no positivity by RT-PCR).
Branagan [120]	50 (148)	Half SN used for MG RT-PCR	HE at 500 μm	19 (38%) positive by HE 19 (38%) positive by RT-PCR (8 individual patient difference between histology and RT-PCR results)	84% accuracy, 79% sensitivity, 87% specificity (5 SN positive by histology showed no positivity by RT-PCR).
Kataoka [121]	66 (146)	Half SN used for CEA and MG RT-PCR	HE	17 (26%) positive by HE 29 (45%) and 22 (34%) positive by CEA and MG RT-PCR, respectively, 18 (28%) positive for both markers	82% accuracy, 100% sensitivity, 75% specificity for CEA; 77% accuracy, 71% sensitivity, 79% specificity for MG, 83% accuracy, 71% sensitivity, 88% specificity for both markers. (5 patients with positive SN by histology showed no positivity by MG RT-PCR).
Washer [122]	77 (121)	2×6 12-μm-thick FS used for MAGE-A3 RT-PCR	HE + IHC (CK)	35 (30%) positive by HE or IHC 41 (53%) positive by RT-PCR	55% accuracy, 46% sensitivity, 62% specificity (26 SNs positive by HE or IHC were negative by RT-PCR).
Manzotti [123]	123 (146)	Interval tissue between SS levels used for multiple marker (CK19, maspin, MG1, CEA and MUC-1) RT-PCR	2×15 SS at 50 μm, the remaining tissue at 100 μm on FS; IHC for doubtful cases	43 SNs (29%) positive by histology 77 SNs (53%) positive for at least one of the markers by RT-PCR	75% accuracy, 96% sensitivity, 66% specificity for any marker; 88% accuracy, 80% sensitivity, 92% specificity for 2 of CK19, maspin and mammaglobin-1 chosen on the basis of multivariate analysis. (2 SNs positive by histology showed no positivity by RT-PCR).
Leers [78]	98 (238)	2 500-μm-thick sections of SNs used for detecting MNF-116 positive cells after incubation with FITC labelled antimouse immunoglobulin by FCM; DNA FCM run in parallel	1 level HE + IHC (MNF-116) from both ends of the section analysed	31 positive by HE 37 positive by HE or IHC 38 positive by FCM	100% accuracy, 100% sensitivity, 100% specificity. (The case positive by FCM, but negative by HE + IHC, had nodal MNF-116 positive population with similar aneuploid DNA index as the primary tumour).

β1→4-GalNAc, β1→4-*N*-acetylgalactosaminyltransferase; CEA, carcinoembryonic antigen; CK, cytokeratin; C-Met, hepatocyte growth factor; FCM, flow cytometry or flow cytometric; FS, frozen section; GA733.2, gastrointestinal tumour-associated antigen 733.2; HE, haematoxylin and eosin; IHC, immunohistochemistry; MG, mammaglobin; MNF-116, a wide spectrum cytokeratin antibody; MUC-1, mucin antigen 1; P97, melanotransferin; RT-PCR, reverse transcription-polymerase chain reaction; SS, multilevel assessment by serial or step-sectioning.

[a] Accuracy (= overall concordance), sensitivity, specificity calculated against the most sensitive histopathological assessment (generally HE + IHC) used.

isolated tumour cells [29,30], the prognostic significance of which is unclear: larger ones, arbitrarily classified as micrometastases, may be worse than smaller ones, arbitrarily classified as isolated tumour cells, but attempts have not been made to separate these entities or distinguish between size categories that may be relevant in terms of prognosis. Non-SN involvement associated with occult SN metastases or micrometastases detected by a more detailed work-up has been reported to range between 0 and 43%. Although the proportion is smaller for small tumours (T1a, T1b), only a few studies have made this distinction, and a cumulative estimate of approximately 18% non-SN involvement associated with micrometastases or isolated tumour cells seems adequate.

No metastases are detected by standard HE assessment in 60–70% of patients suitable for SNB; 10–20% of these patients, equivalent to 6–14% of all patients, are upstaged by the detailed pathology. Approximately 18% of the patients upstaged by the enhanced pathology, i.e. 1–2% of all the patients, may have further nodal metastases. Omission of a detailed pathological assessment including IHC for the investigation of SNs seems to add little to the rate of false staging of SNB.

However, it should be considered that the false-negative rates are most often determined via IHC including histology protocols (Table 1), which decrease the rate of false-negative biopsies. The extreme values in the tables in this article suggest that there may be large variations in these estimates between institutions. These conclusions are based on heterogeneous data, and on the whole suggest that an intensive work-up of SNs may not be justified on a population level, but coordinated research into the role of a detailed SN histopathology appears warranted. This should evaluate the role and extent of the histological work-up required for the detection of macrometastases, and should try to differentiate smaller nodal involvement into categories which may or may not influence the prognosis (e.g. micrometastases and isolated tumour cells).

The reviewed literature demonstrates that the use of immunostains for the detection of isolated tumour cells and micrometastases is very common. Most centres experience a limited number of cases where the SN metastasis is first discovered by IHC, and then is retrospectively also found on the HE-stained slides; in some instances, these may involve parts of macrometastases or more commonly micrometastases. Such instances, however, are uncommon, and the costs of IHC may not justify its use as a routine procedure. The data summarised above support the view that the IHC approach is optional in routine patient management. This is in accordance with several published guidelines and collective opinions [31,124,125]. (A cost-effectiveness analysis of IHC in this setting is lacking at present, and is awaited.) The role of step-sectioning is somewhat more controversial, because the step-sectioning of grossly sliced lymph nodes may reveal occult macrometastases not seen on the first section. Some recommendations suggest that step-sectioning or multiple level assessment should be used, although the optimum distance between these steps is controversial; the investigation of multiple levels has been recommended by some groups [31,126], whereas others suggest only that the SNs should be studied at a minimum of three levels (which can also be done by macroslicing the nodes) [125], while others state that the pathological assessment of SNs should aim to achieve an optimum rate of detection of small metastatic deposits within the frames of logistic possibilities [127]. A multilevel assessment (with different definitions) is therefore generally recommended and seems justified on the basis of this review.

The intra-operative assessment of SNs is strongly recommended whenever a one-step selective surgical axillary treatment is planned for SN-positive patients; the choice of the method should be individual (institutional), depending on the available resources (including human resources), as frozen sections and imprint cytology perform similarly. Imprints are probably a better choice, thanks to the lower cost, lesser time-requirements and lack of tissue damage.

At the moment, because of the controversies over the interpretation and the lack of specific markers, the molecular analysis of SNs should be restricted to research purposes.

The above considerations should be taken into account in the formulation of guidelines relating to the histopathological work-up of SNs. It must be accepted that future results may well influence the formulation of these guidelines.

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