ORIGINAL ARTICLE

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

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Aims: To evaluate aspects of the current practice of sentinel lymph node (SLN) pathology in breast cancer via a questionnaire based survey, to recognise major issues that the European guidelines for mammography screening should address in the next revision.

Methods: A questionnaire was circulated by mail or electronically by the authors in their respective countries. Replies from pathology units dealing with SLN specimens were evaluated further.

Results: Of the 382 respondents, 240 European pathology units were dealing with SLN specimens. Sixty per cent of these units carried out intraoperative assessment, most commonly consisting of frozen sections. Most units slice larger SLNs into pieces and only 12% assess these slices on a single haematoxylin and eosin (HE) stained slide. Seventy one per cent of the units routinely use immunohistochemistry in all cases negative by HE. The terms micrometastasis, submicrometastasis, and isolated tumour cells (ITCs) are used in 93%, 22%, and 71% of units, respectively, but have a rather heterogeneous interpretation. Molecular SLN staging was reported by only 10 units (4%). Most institutions have their own guidelines for SLN processing, but some countries also have well recognised national guidelines.

Conclusions: Pathological examination of SLNs throughout Europe varies considerably and is not standardised. The European guidelines should focus on standardising examination. They should recommend techniques that identify metastases $>$ 2 mm as a minimum standard. Uniform reporting of additional findings may also be important, because micrometastases and ITCs may in the future be shown to have clinical relevance.

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 32 breast pathologists from all member states of the European Union. 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 investigation of sentinel lymph nodes (SLNs) led the EWGBSP to perform a literature review on the pathological assessment of SLNs to assess current evidence that would allow the formulation of the relevant section of the European guidelines.[1] It was also decided to perform an assessment of current practice, to estimate the diversity of SLN investigations and highlight the main issues of controversy in both the methods of evaluation and the interpretation that require clarification and detailed description in the guidelines.

MATERIALS AND METHODS

A questionnaire was designed to assess current practice concerning the pathological investigation of SLNs in breast cancer (full questionnaire submitted as an appendix and available online at http://www.clinpath.com/supplemental). The first part (general data and section A) assessed the breast cancer workload of the responding department, whether SLN specimens were seen by the given department or not, and also the method of SLN biopsy (SLNB). Part B investigated the use and methodology of the intraoperative assessment of SLNs. Part C explored the final histological investigation, including the use of immunohistochemistry (IHC). Part D was about reporting the findings, and was particularly tailored to investigate the categories of micrometastasis, isolated tumour cells (ITCs), and submicrometastasis. Part E assessed the use of molecular methods for investigating SLNs, and part F concerned local and national guidelines.

Members of the EWGBSP were asked to circulate the questionnaire to institutions in their own countries, together with a letter asking for the contribution of the targeted department. Replies to the questionnaire could be sent in by e-mail, fax, or post, or alternatively the form could be completed online. Data collection started in March 2003 and

Abbreviations: CK, cytokeratin; EIO, European Institute of Oncology; EWGBSP, European working group for breast screening pathology; HE, haematoxylin and eosin; IHC, immunohistochemistry; ITC, isolated tumour cell; RT-PCR, reverse transcriptase polymerase chain reaction; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy

Table 1 Breast cancer volume load and the proportion of SLN specimens among the questionnaire respondents

Profile	No SLNs	SLNs	All	Proportion with SLNs in daily practice
Unknown		1	1	
<100 BCs/year	78	35	113	0.31
100–200 BCs/year	42	97	139	0.70
201–500 BCs/year	21	84	105	0.80
>500 BCs/year	1	23	24	0.96
All	142	240	382	0.63

BC, patients with breast cancer; SLN, sentinel lymph node.

ended in June 2003. Data received after this deadline were not included in the analysis.

Not all questionnaires were fully completed, therefore only the total number of replies for a given question was considered when counting the percentage distribution of replies to the given question. Free text replies were interpreted by the main author (GCs) according to their meaning.

RESULTS

Reply rates and conditions of SLNB (section A)

Of 382 institutions replying to the questionnaire, 240 (63%) were dealing with SLNs from patients with breast cancer in their routine practice. In general, larger units dealt with SLNs more frequently than did smaller units (table 1). The method of SLNB was radioguided in 80 units, vital dye guided in 25 units, combined in 108 units, and unspecified in three units; in addition, 24 units reported the use of more than one method.

A backup axillary staging procedure—that is, a surgical staging procedure completing SLNB independently of the SLN status—is not performed in 71 units (30%). A backup staging procedure is done (at least in some of the affiliated surgical departments) in 159 units (66%), and consists of axillary clearance in most (n = 150) and lymph node sampling in the others (n = 9). No data were available from 10 participants.

Intraoperative assessment (section B)

No intraoperative assessment is performed in 95 units (40%), whereas the other units use some type of intraoperative assessment, which is most often frozen section examination (table 2). Intraoperative IHC is used in only a small number of laboratories (n = 14; 10% of laboratories performing intraoperative assessment) and, in general, is done in laboratories performing frozen section analysis (n = 5) or a combination of frozen sectioning and imprint cytological analysis (n = 6).

Final histopathology (section C)

The use of intraoperative assessment as definitive pathological evaluation

The aim of the first question of this section (''Is your final histology evaluation the same as the intraoperative assessment? Yes, if no paraffin wax embedded material is examined'') was to assess the number of units making an exclusive intraoperative investigation by giving definitive diagnoses intraoperatively, as reported by the European Institute of Oncology (EIO), in Milan.[2] It seems that some of the respondents had difficulty in understanding the question. There were 30 replies saying that the final SLN histology was the same as the intraoperative histology. This is clearly the result of misunderstanding the question, because some of those replying with YES to this question were from units that do not perform intraoperative assessment, or that use a one level intraoperative assessment and a multilevel final histological workup. After eliminating these replies, 16 laboratories remained, which is still probably an overestimate. However, at least some units follow the EIO practice, and there may be a maximum of 15 units from among those that replied, apart from the EIO itself (10% of those using intraoperative methods, and 6% of all respondents dealing with SLN specimens).

Table 2 The use of intraoperative assessment of sentinel lymph nodes

	One level	Multiple levels	Unspecified	All
Frozen sections	50	51		101
Imprint cytology	7	7	2	16
Both methods	15	12	1	28
All	72	70	3	145

Slicing and sectioning of the SLNs

With a few exceptions (10; 4%), laboratories use the whole SLN for microscopical analysis. Most laboratories section (macroscopically slice) larger SLNs (151 of 237; 64%), or assess both parts of bisected SLNs (79 of 237; 33%), and only a few generally assess the SLNs as one entire piece (seven of 237; 3%). Only a small number of the laboratories use one haematoxylin and eosin (HE) stained level for each block (28 of 239; 12%), but 16 of these units provide multilevel histology for larger SLNs by slicing the nodes into pieces. The remainder of the departments (211 of 239; 88%) indicated multilevel sectioning and assessment; 60 of 239 (25%) of the laboratories section the SLN blocks until extinction.

With regard to the number of sectioning levels, apart from an even step sectioning through the blocks (see above), the most common practice reported was the assessment of three levels (42 of 164; 26%), followed by the assessment of four or six levels (both in 15 of 164; 9%). Among the respondents using multilevel microscopic sectioning, tissue blocks are most frequently sampled by step sectioning the SLNs at 50 μm intervals (32 of 162; 20%); other common step sectioning distances include 150 μm (18 of 162; 11%), 250 μm

Table 3 Distances between sectioning levels of sentinel lymph nodes and their frequency

Distance between sectioning steps	Number of units reporting the given distances
2–10 μm/step	25
>10–50 μm/step	58
>50–100 μm/step	14
>100–250 μm/step	47
>250–500 μm/step	18
All	162

(14 of 162; 9%), and 100 or 200 μm (both in 13 of 162; 8%) (table 3).

The difference in the protocols involving multilevel histological sectioning and HE assessment can be illustrated by the most common protocol (six levels at 150 μm) reported from eight units; this means that on the basis of this survey, no identical histological protocol is used by more than eight departments. There were 123 different protocols reported. This may partly result from the free text format of reporting the number of levels and their distance, but the main cause is certainly the large divergence of the methods. The multilevel sectioning involving the smallest proportion of the SLN was two to five levels at 2 μm distance, and the most extensive sampling involves over 60 levels separated by 50 μm or around 100 levels at 40 μm/SLN reported by one laboratory each.

The use of immunohistochemistry

Most (165 of 234; 71%) of the departments use IHC in all cases negative by HE, including one department that uses IHC in all cases. Further laboratories (59 of 234; 25%) restrict the use of IHC to doubtful cases, including one that performs IHC for all cases of lobular carcinoma with negative HE findings. Some laboratories perform IHC staining on one level (83 of 226; 37%), whereas others assess multiple levels by IHC (143 of 226; 63%). The number of levels assessed varies considerably between laboratories using multilevel IHC staining, with the most common being the investigation of three levels in 29% of the cases, and the extreme being 10–15 levels done in nearly 5% of the departments in question.

The antibodies used were mainly raised against several types of cytokeratins (CKs), with the most frequently used being the AE1/AE3 antibody, which was used by 75 laboratories. Other frequently used antibodies are Cam5.2 (n = 38), MNF-116 (n = 33), and KL-1 (n = 29), whereas in some laboratories antibodies to CK7, CK8, CK22, epithelial membrane antigen, oestrogen receptor, progesterone receptor, CD68, and S-100 protein were also reported, either as the only antibodies used or as part of a combination with pancytokeratin antibodies.

The routine use of IHC, or more precisely its lack of use, shows a variation by country. Of those countries with more than 10 positive replies on SLNB specimens, IHC is routinely performed in over 90% of laboratories in Austria, France, and Spain, and in more than half of the laboratories in most other countries (Finland, Germany, Hungary, and Italy). Less than half of the respondents used IHC routinely in the UK (five of 20; 25%).

Reporting (section D)

Table 4 shows the use of reporting categories for small metastatic deposits. Although many definitions for micrometastasis (82%) were in accordance with previous or current TNM definitions,[3–7] 18% of the respondents used very heterogeneous definitions, such as: < 0.2 mm (n = 6), < 1 mm (n = 5), (small) subcapsular deposits (n = 4), < 3 mm (n = 3), small aggregates (n = 3), IHC detected nodal involvement (n = 2), and so on. The ITC category, although introduced by the TNM classification,[3–5] was less often used according to the TNM definitions (42%). Interestingly, a few replies referred to the TNM or AJCC definition of the submicrometastasis category, which does not exist.

Although not specifically assessed by the questionnaire, one reply commented that the measured size of the metastasis was reported instead of the categories targeted by the survey.

Molecular assessment (section E)

A positive answer for molecular assessment was reported by only 10 institutions (4%) (nine of these use less than half of the SLN for this purpose, whereas one uses half of the SLN). Only five answers mentioned the method used: quantitative real time reverse transcriptase polymerase chain reaction (RT-PCR), no primer specified (n = 1); quantitative RT-PCR for CK19 (n = 1); RT-PCR for mammoglobin (n = 1); and RT-PCR with no marker specified (n = 2). With regard to the consequences of a positive finding by the molecular assay, only four replies were available: in two laboratories this has no effect; in one, it results in the re-evaluation of microscopic specimens; and in another one, the positive CK19 assay may be taken as an indication for chemotherapy but not for axillary dissection.

Guidelines (section F)

Most laboratories (193 of 240; 80%) have their own guidelines for dealing with SLNs. National guidelines were acknowledged by 119 responders, and followed by 105. Some type of national guideline was acknowledged by all pathologists in Austria, Denmark, the Netherlands, and Sweden (100% each). Such guidelines were controversially recognised in Hungary (67%), in Germany (57%), in Italy (55%), in France (45%), and in the UK (32%). The recognition of national guidelines was even more controversial for other countries where most of the respondents were unaware of such guidelines or stated a lack of such guidelines, although a minority indicated the presence of some type of national guidelines. This last finding might have been the result of some regional guidelines in at least a few cases. The lack of national guidelines was widely recognised in the replies from Portugal (100%) and Belgium (92%).

DISCUSSION

Axillary nodal staging is traditionally recognised as one of the best single prognostic factors in breast cancer and has been established as such on the basis of standard histological assessment of lymph nodes removed by axillary lymph node dissection. This standard histological assessment generally consisted of the evaluation of a single HE stained slide of several lymph nodes. The prognostic profile of breast carcinomas has improved over the past few decades as a result of breast cancer screening programmes, better treatment, and increased awareness. As a part of this phenomenon, the proportion of cancers metastatic to axillary nodes has decreased.[8 9] Because total axillary clearance may be associated with relevant morbidity,[10 11] because axillary dissection is regarded by some surgeons as a pure staging procedure,[12] and also because many patients may undergo complete dissection of axillary nodes only to reveal the lack of regional metastases, alternative surgical staging procedures with less morbidity have been studied. These include limited (for example, level I, or levels I and II) axillary dissection,[13 14] axillary nodal sampling,[15 16] and more recently, SLNB. The last procedure has also been claimed to improve regional staging by allowing a concentrated pathological effort on one or a few selected lymph nodes, which are the most likely sites of regional nodal metastases.[1 17 18] SLNB has become a common nodal staging procedure for stage I and II, clinically node negative breast carcinomas, and is done as a primary surgical and pathological staging procedure in almost one third of the units dealing with SLN specimens that responded to our questionnaire.

Because many surgeons and oncologists feel that the finding of a positive lymph node on SLNB requires further axillary treatment, most often axillary dissection, intraoperative assessment has also become a requirement in several units (60%). It allows the completion of axillary operations in one step in at least a proportion of SLN positive cases. Both intraoperative cytology and frozen sections have advantages and disadvantages, and both methods are characterised by

Table 4 The use of reporting categories for small volume nodal involvement

Category	Proportion of respondents using it	No of different interpretations given for the category	Comments
Micrometastasis	222/240 (93%)	17	71/202 (35%) referring to or in keeping with the 6th edition of the TNM system (with 0.2 mm lower cutoff value)*[3–5] 76/202 (38%) using only the 2 mm upper limit*, in accordance with earlier TNM definitions[6 7] 18/202 (9%) referring to the TNM system without mentioning the edition (either using the 0.2 mm lower cutoff value or not) 37/202 (18%) using heterogeneous definitions not in accord with TNM definitions No definitions given by 20 laboratories
ITC	171/240 (71%)	10	65/155 (42%) referring to the 6th edition of TNM classification,[4 5] or using its definitions, or giving an upper limit of 0.2 mm† 49/155 (32%) stressing the isolated or single nature of the tumour cells in the definition, some requiring other criteria too (such as localisation in sinuses); 10 units from this last group defining ITC by "isolated tumour cells", others using different wording 14/155 (9%) stressing detection by IHC 9/155 (6%) defining ITC by the presence of the cells in the sinuses or afferent lymphatics 18/155 (12%) giving maximum number of cells that could fit in their category of ITC; these numbers demonstrated a wide variety, including up to 2, 3, 4, 5, 6, 10, or 20 cells No definitions given by 16 laboratories
Submicrometastasis	53/240(22%)	7	24/47 (51%) using an inclusive or non-inclusive upper limit of 0.2 mm‡ 7/47 (15%) reporting definitions close to the TNM definition of micrometastasis, which may represent misreading of the given category 16/47 (34%) giving very heterogeneous definitions, including IHC detected or confirmed cells, <1 mm, 10 cells to 2 mm, 50–100 cells, clusters, etc No definitions given by 6 laboratories

*For ease, no distinction was made between replies with an upper limit of 2 mm not including this value (<2 mm) and those including this value (⩽2 mm).
†Definitions inclusive or non-inclusive of this value lumped together. ‡A few of these also giving some descriptive supplements such as location in the parenchyma or in afferent vessels or sinuses.
IHC, immunohistochemistry; ITC, isolated tumour cell.

similar sensitivities and specificities.[1] However, frozen sections seem to be more popular, probably because histopathologists are more used to this technique. Some laboratories can even afford a complete intensive investigation of the SLNs during surgery by frozen step sections,[2] although this is costly and is thought to be suboptimal because the quality of frozen sections is not as good as that of permanent sections.

> "Our survey identified two main areas to be addressed in formulating guidelines on the pathological investigation of sentinel lymph nodes: a minimum protocol aimed at the identification of all macrometastases, and guidance on reporting the findings"

Several current guidelines and recommendations suggest that immunohistochemistry is not required for the investigation of SLNs, and up to three HE stained slides for each slice of an SLN are sufficient for staging purposes,[19–21] whereas others recommend IHC and multiple sections for each block.[22 23] The use of these additional techniques (step sectioning and/or IHC) is tempting, and as a result, the routine assessment of SLNs, as demonstrated by this survey, is generally done through the examination of step sections (88%). In a few cases, multilevel assessment is the result of examining one HE stained section from several slices. IHC is also widely used as a routine staining procedure for SLNs negative by HE (71%). Several anti-CK antibodies are available and used for this purpose, but some of the antibodies used routinely (for example, antibodies to steroid hormone receptors) cannot identify all metastatic breast carcinoma cells in lymph nodes identified by antibodies to CKs. The additional use of antibodies to S-100 or CD68 in some doubtful cases, as reported to us, can help differentiate naevus cells and histiocytes from epithelial cells, but their use alone is of no help in detecting nodal involvement from breast cancer. The sampling of SLNs at multiple levels is very heterogeneous, and ranges from a complete step sectioning protocol (sectioning the blocks until extinction) to uneven sampling of a few levels from each slice. It has been shown that the examination of more levels identifies more SLNs containing tumour cells,[24 25] and this is also true for complete step sectioning protocols.[26] The addition of IHC to step sectioning also results in a higher detection rate of tumour cells within the lymph nodes,[1] although it has been suggested that a limited number of immunostained slides (three for each block) could be sufficient to detect most of these diagnostic events.[27] The practice reflected in our survey is not unique to Europe, because analysis of the survival epidemiology and end-results database has revealed an increase in the stage II node positive subset of patients since 1995, reversing the favourable trend towards the decreasing number of these patients seen before 1995.[28] This seemingly unfavourable effect is certainly not the result of biological parameters, but parallels the introduction of SLNB for staging breast cancers, and can be explained by a more detailed pathological assessment of these nodes. These events have encouraged a change in the nomenclature of metastases and led to the introduction of the term ITC.

It must be realised that none of the histopathological protocols reported in this study, and none of the protocols reported in the literature to date can identify all tumour cells in the SLNs.[28 29] The identification of single tumour cells is

just a random side effect of a more detailed investigation; some are revealed whereas others certainly remain hidden. The importance of occult metastases is unclear,[1] and strong evidence that they are associated with a poor prognosis is lacking. Many of the occult metastases (defined here as nodal involvement not seen on initial examination and disclosed by the examination of further sectioning levels and/or immunostained levels) identified in SLNs are micrometastases or ITCs.[26] It is also obvious that the term micrometastasis has been used with different definitions,[30] but none of these definitions has considered that micrometastases may also be heterogeneous, and that metastasis size is also a continuous variable.[31–33] Although the studies on the prognostic relevance of micrometastases are also inconclusive,[1] it has been suggested that micrometastases larger than 1 mm in greatest dimension are more often associated with non-SLN metastases than are smaller micrometastases.[32] Therefore, reporting the size of the metastasis identified might be relevant in some cases. The new TNM classification has introduced the category of ITC[3–5] to label single tumour cells or small clusters of tumour cells not larger than 0.2 mm, because it was felt that the smallest degree of nodal involvement that can be demonstrated does not merit the name of metastasis, with the associated prognosis and treatment implications. Some of the ITCs may be the result of artefactual tumour cell dislodgement and not the result of a genuine metastatic process, and hence may never give rise to true metastases if left in situ. ITCs have also been associated with some qualitative features, such as the lack of a stromal reaction, the lack of proliferation, and the lack of invasion through vascular channels, or lymph node sinuses. A subjective interpretation was reflected in some of the replies we received (for example, isolated tumour cells equalling single tumour cells), and we interpreted this as a disadvantage of the ITC term. A synonymous category has been called ''submicrometastasis'' by others, and implies a nodal load of ''0.2 mm or less in size''.[21] The limit of 0.2 mm is just as arbitrary as the limit of 2 mm for the definition of micrometastasis, but seems to be relatively easy to measure as a fixed proportion of the high power field diameter of most microscopes. For staging purposes, ITCs are not considered to be metastases, and when they are identified in a lymph node, they are designated pN0(i+), where the (i+) however indicates the presence of a minimal number of tumour cells. Clearly, many of these ITCs (often revealed by IHC only) were included in the node positive group earlier, and categorised under micrometastasis, resulting in an artefactual stage migration.

Such a stage migration artefact can result in a seemingly better prognosis in both the node negative group of patients (having somewhat fewer patients with significant occult metastases) and the node positive group (having more patients with insignificant nodal positivity).[34] Because the phenomenon has been explained by the changes in pathological practice of nodal assessment as a result of the introduction of enhanced pathological evaluation of the SLNs,[28] it is important to have common terms and a relatively uniform reporting system. Our survey disclosed that, in addition to the variable histological protocols used, this is probably the most controversial issue relating to the histopathology of SLNs. A uniform reporting system is essential if researchers need to compare treatment outcomes. It is clear that different protocols will give rise to different tumour stages.

The definitions of the TNM categories are commonly used in several European countries and form a common background for staging malignant diseases. Therefore, we recommend the use of these definitions, even if the TNM staging system itself is not used, and also advise as much adherence to the categories as possible. This would enable people involved in breast cancer care to use a uniform language, as pointed out by a recent editorial.[35] Because the evidence on the poor prognosis associated with nodal involvement that is available to date is related to macrometastases, it is reasonable to mandate that all these should be identified in the SLNs. Some of the protocols reported to us do not reach this aim, and the European guidelines will have to address this issue, by recommending a histopathology protocol that will identify all metastases > 2 mm as a minimum aim (for example, macroscopically slicing the SLNs or step sectioning them at appropriate intervals). It is obvious that smaller metastases will incidentally be identified, and reporting these unequivocally is important. At present, for the purposes of staging, small metastases should be divided into micrometastases, which are not larger than 2 mm in greatest dimension, but are larger than 0.2 mm (therefore, theoretically, a step sectioning protocol with 200 μm intervals would enable their identification), and ITCs (or submicrometastases, if one prefers this less contradictory term), defined previously; the first will continue to be considered as metastasis, the second will not be included as metastasis. Optimally, all metastases should be recognised, and for this, a protocol aimed at the recognition of micrometastases should also be considered. Hopefully, with time, follow up studies will enable us to refine these categories further. The use of the ITC category is probably acceptable to most pathologists, who would be reluctant not to report seeing something in a lymph node, and are happy to have a name for it. Although there is no evidence that ITCs have a prognostic disadvantage, the issue of further nodal involvement associated with them is unsolved.[1] It is obvious that IHC will identify more ITCs than HE stains, but IHC may also identify micrometastases. This is a well recognised phenomenon in cases of lobular carcinoma, but can also be the case in ductal carcinomas. Many of us have found the routine use of IHC helpful in some cases of micrometastasis, and therefore it would be unwise to discourage the use of IHC in the examination of SLNs if the resources permit this. In contrast, the use of IHC cannot be recommended as mandatory in the investigation of SLNs. It must be stressed that the identification of ITCs is not an aim of the histopathological evaluation of SLNs, so that the very extensive histopathological protocols reported to us by a few laboratories do not seem to be justified on the basis of current knowledge. Because of the heterogeneity of the histological protocols used, reporting the protocol itself is recommended.

> ''Molecular sentinel lymph node staging continues to be a research area, and it is widely agreed at present that treatment decisions should not be based on its results''

Molecular techniques for the examination of SLNs from patients with breast cancer, particularly RT-PCR methods, are not specific enough despite their increased sensitivity.[1] Only a few departments use RT-PCR on SLNs, and the results influence treatment in only one institution. Molecular SLN staging continues to be a research area, and it is widely agreed at present that treatment decisions should not be based on its results.

In conclusion, our survey disclosed heterogeneity in almost all aspects of SLN pathology assessed by the questionnaire. It identified two main areas to be addressed in formulating guidelines on the pathological investigation of SLNs: a minimum protocol aimed at the identification of all macrometastases, and guidance on reporting the findings, as put forward in this article. The considerable variability in the methods of assessment and in reporting the results highlights

Take home messages

- Our questionnaire revealed that the pathological examination of sentinel lymph nodes throughout Europe varies considerably and is not standardised
- The European guidelines urgently need revising and should focus on standardising examination
- They should recommend techniques that identify metastases > 2 mm as a minimum standard
- Uniform reporting of additional findings may also be important, because micrometastases and isolated tumour cells may in the future be shown to have clinical relevance

the urgent necessity of formulating the next revision of the European guidelines.[36]

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The appendix is available online at http://www.clinpath.com/supplemental.

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ECHO

Perinatal postmortems: professionals, parents, and clinical trials

Please visit the *Journal of Clinical Pathology* website [www.jclinpath.com] for a link to the full text of this article.

Attitudes towards perinatal postmortem examinations (PMs), especially in the context of clinical trials, have been explored in a series of articles.

There is concern about falling PM rates both in general and in perinatal pathology. Perinatal PMs are seen as having particular advantages in that they might provide genetic information for parents and by clarifying the cause of death might also provide 'closure'. They are also useful for audit and research. When babies in clinical trials die, asking for consent for PM may be seen as more difficult because it might be interpreted as being of benefit only to the trial rather than to the parents. Added to that the whole subject of consent for perinatal PM has become more complex in the wake of UK controversies about organ retention and about consent in perinatal trials. Researchers in London and Cambridge, UK have analysed the views expressed by neonatologists, pathologists, and parents who participated in one or both of two neonatal trials, one of nitric oxide against standard care and one comparing two surfactant preparations.

Twenty six neonatologists (ages 30–54 (mean 37 years), 23 men, 11 consultant grade) participated in semistructured, tape recorded interviews. Many of them expressed a feeling of conflict between their duty of care to the parents and their responsibility to the trial. Less senior neonatologists in particular tended to be less aware of the pathology aspects of the trial and to feel that PM had little to offer. Some neonatologists, however, regarded their responsibilities to the trial and to parents as of equal importance and felt little sense of conflict. A few worried that participation in the trial might lead them to apply pressure to reluctant parents and some resolved the dilemma by giving priority to parental feelings and withdrawing immediately if they detected resistance. Asking parents to consent to PM because the research might benefit others was looked on by some as emotional blackmail and the suggestion that PM might be necessary to monitor for possible harm could raise questions in the parents' minds about the safety of the trial. The detailed nature of present PM consent forms could on the one hand increase family distress and on the other hand make their decisions clearer and more informed. Five pathologists expressed their views in writing or by telephone. They expressed concern about the state of perinatal pathology and the sharp fall in the number of PMs. They agreed about the importance of PM studies within clinical trials and thought that clinicians should try to persuade parents of that importance.

In a separate study 10 interviews were conducted with 16 parents of 12 babies who had died during one or other of the two randomised controlled trials. The parents of five of the babies had agreed to PM. None of the parents criticised the manner in which consent for PM had been sought and none had felt pressurised. While some found a PM too much to accept, others wanted one both to provide information for themselves and because of the possibility that the knowledge gained might help others.

In a commentary a pathologist describes a system in which deaths in clinical trials are often referred to the coroner. The issue of PM is raised with parents by the neonatologists but the pathologist discusses the details of the procedure with the family before it is carried out.

This Echo piece relates to:

▲ *Archives of Disease in Childhood Fetal and Neonatal Edition* 2004;**89**:F198–F199.
▲ *Archives of Disease in Childhood Fetal and Neonatal Edition* 2004;**89**:F200–F203.
▲ *Archives of Disease in Childhood Fetal and Neonatal Edition* 2004;**89**:F204–F207.
▲ *Archives of Disease in Childhood Fetal and Neonatal Edition* 2004;**89**:F208–F211.

Questionnaire on current practice with sentinel nodes (SN) in breast cancer

(Please underline and complete dotted areas of the text)

Institution:		Country:	

Your name: .....

Date of completion: .....

General

Profile: <100 breast cancers/year 100-200 BC/year 201-500 BC/year >500 BC/year

Part A (SN biopsy technique relevant to pathology)

A1. Is SN biopsy performed in your institution for staging breast cancer?

Yes No Only in some of the affiliated hospitals

A2. Is backup (routine) axillary dissection performed at present time?

Yes Yes, in some affiliated hospitals No No, but backup sampling yes

A3. What method is used for SN biopsy? Vital dye Radioguided Combined Any of the 2 or 3 methods

Part B (Intraoperative assessment)

B1. Do you perform intraoperative assessment of SNs?

No Yes (imprint cytology/IC) Yes (frozen sections/FS) Yes (IC and FS)

B2. Please, specify the number of levels used for intraoperative assessment.

(Assessment of both sides of a bisected node is considered 1 level here) 1 level Multiple levels

B3. Do you perform immunohistochemistry on intraoperative specimens? Yes No

Part C (Final histology)

C1. Is your final histology evaluation the same as the intraoperative assessment (Yes, if no paraffin embedded material is examined)? Yes No

C2. Is the whole SN used for pathological evaluation, or only a part (e.g. half) of it is used for this purpose?

Whole SN Part of the SN

*C3. Which of the protocols below better describes (in general) your current practice of final SN assessment (**slicing**)?*

Entire (unsliced) SN in one block Bivalving the SN Macroslicing (multiple slices) of SNs>5-10 mms

C4. *Which of the protocols below better describes (in general) your current practice of final SN assessment (**levels**)?*

1 level HE Multilevel HE Multilevel till extinction of the blocks (for negatives only)

If multilevel, specify number of levels for HE: ..... *distance between levels:* ..... *microns*

C5. Is immunohistochemistry performed during final histological assessment?

No Only in doubtful cases In all negative cases

What antibody/antibodies do you use: .....

C6. Specify the number of levels investigated by immunohistochemistry? 1 level multiple levels

In case of multiple levels, specify if possible: .....

Part D (Interpretation issues)

D1. Do you report the following nodal involvements separately?(Do you distinguish between them?)

Micrometastasis	No	Yes	If yes, your definition:
Submicrometastasis	No	Yes	If yes, your definition: .....
Isolated tumour cells	No	Yes	If yes, your definition: .....

Part E (Molecular investigations)

E1. Is molecular analysis performed on SNs at your institution?

No Yes-half node Yes-smaller than half portion of the SN

E2. What is your molecular assessment (RT-PCR, flow cytometry; please specify markers)? .....

.....

E3. Please specify consequences of identifying nodal involvement by molecular methods in histologically negative SNs:

.....

Part F (Guidelines)

F1. Do you have an "in house" protocol designed for routine investigation of SNs? Yes No

F2. Are you aware/Do you have national guidelines for the assessment of SNs?

No guidelines I am not aware Yes Yes, but I do not use them