Sentinel lymph node assessment in breast cancer—an update on current recommendations

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REVIEW AND PERSPECTIVES

Sentinel lymph node assessment in breast cancer—an update on current recommendations

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Abstract

Sentinel lymph node biopsy (SLNB) has become the preferred method of surgical pathological nodal staging of early breast cancer by the end of the nineties. As the most likely sites of metastasis, the SLNs allow a more precise staging, and indeed gross sectioning, step sectioning, immunohistochemistry, and molecular staging methods have been used to disclose metastatic involvement of these lymph nodes. This review summarizes the backgrounds of SLNB, trends in related surgery and pathology. It also gives an insight into European National recommendations related to SLN and divergent daily practices in European pathology departments, on the basis of replies to questionnaires from 84 pathologists from 38 European countries. The questionnaires revealed the post-neoadjuvant setting as an area where a significant minority of pathologists report less confidence in classifying residual nodal involvement into TNM categories. The review also summarizes the neoadjuvant therapy-related aspects of SLNB.

Keywords Breast cancer · Lymph nodes · Neoadjuvant treatment · Questionnaire · Sentinel lymph nodes

Introduction

This review deals with sentinel lymph nodes (SLNs) and their pathological assessment. (Supplementary material 1 includes a list of abbreviations and acronyms used in this review.) As it is often useful to know why something is done and why changes are later implemented, the clinical (surgical) and pathological approaches to these nodes are summarized first, to give an insight into current European recommendations and practices. The latter part of the review addresses some of the challenges of assessment of SLNs in the post-neoadjuvant treatment setting.

Surgical pathological nodal staging: surgery—a historical perspective and sentinel lymph node biopsy then and now

Although its strength as a prognostic factor and the need for prognosticators to plan treatment have been altered by the development of multifactorial prognostic models and predictive factor-based treatment planning, contemporary texts still acknowledge that nodal status is one of the most important prognostic factors in breast cancer. There are a number of methods for the assessment of regional (axillary) nodal status. These include multivariable models of prediction based on clinical and radiological features (ultrasound often being routinely used in this context), preoperative sampling by fine needle aspiration cytology or core needle biopsy, and surgical removal of the lymph nodes (LNs) for histopathological and/or molecular evaluation. Of these, surgical pathological staging has been accepted as the gold standard and is used as such even at the present time.

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Before the last decades of the last century, complete (level I to III) axillary lymph node dissection (ALND) was the general surgical technique to remove LNs, and its side effects were well recognized. With the introduction of breast cancer screening in many countries, breast cancers operated on became smaller and the proportion of node-positive disease has decreased. Surgeons were eager to recognize that the removal of negative nodes was overtreatment, and that ALND was the source of significant morbidity. More conservative axillary staging surgeries have been introduced, such as level I–II ALND [1] or 4-node-sampling [2]. The breakthrough came in the mid-nineties when a radio-guided, blue-dye-only, and a combined dual labeling method of lymphatic mapping and sentinel lymph node biopsy (SLNB) were described for breast cancers [3–5]. (These were later complemented with superparamagnetic iron oxide and fluorescent tracer-guided techniques [6, 7].)

Prospective randomized trials have established that SLNB is not less accurate than ALND for staging clinically node-negative (cN0) breast cancers. Long-term follow-up data corroborate the logical hypothesis that patients do not derive any benefit from ALND if their SLN is pathologically negative; the axillary recurrence rates are low [8–11]. Furthermore, the IBCSG-23–01 trial has convincingly supported the view that completion ALND is of no benefit to patients who have at most micrometastases in their SLNs [12]. Finally, the ACOSOG-Z0011 trial suggested that ALND was not needed for patients with 1–2 macrometastatic SLNs, when treated with breast conservation and adjuvant whole breast irradiation plus systemic therapies according to guidelines, since there was no survival benefit in those who underwent ALND [13]. Although there have been many criticisms of this trial, and several post-Z0011 trials have been initiated to clarify some of its problematic issues, Z0011 has changed surgical practice, and accordingly, it has also changed the pathologists' approach to SLN evaluation. For example, if up to 2 macrometastatic SLNs do not initiate ALND, there is no need to do intraoperative assessment if only 2 SLNs are removed. Furthermore, the AMAROS and OTOASOR trials provided evidence that radiotherapy was an alternative to completion ALND for patients with positive SLNs and had a better morbidity profile [14, 15].

Clinical trials like the SENTINA [16] and meta-analyses of data from several trials [17, 18] have also established that patients who are clinically node-negative (cN0) and receive neoadjuvant chemotherapy (NACT) can also have their axillary treatment based on the result of SLNB, as both the SLN identification rates and the false-negative rates (FNR) are comparable to the rates seen in patients with primary surgery. A major focus of investigation has been the role of SLNB after NACT in patients who have axillary nodal metastases at presentation and convert to ycN0 after treatment. The SLN identification rates are lower, and the FNR is generally above 10%, which is considered unacceptable. One arm of SENTINA included 592 women who were clinically node-positive (cN1) at baseline, converted to ycN0 after NACT, and underwent SLNB and ALND. The SLN identification rate was 80.1%, and the overall FNR was 14.2% [16]. Further analysis showed FNR of < 10% when three or more SLNs were identified. The ACOSOG Z1071 (Alliance) Trial evaluated 649 patients with cN1 disease who completed NACT and then underwent SLNB and ALND [19]. After NACT, 83% of patients were ycN0, the SLN identification rate was 92.9%, and the overall FNR was 12.6%. However, the FNR was 9% when three or more SLNs were obtained. The Sentinel Node Biopsy After Neoadjuvant Chemotherapy in Biopsy Proven Node-Positive Breast Cancer (SN FNAC) multicentre prospective study assessed 145 patients with node-positive breast cancer who had SLNB and ALND after NACT [20]. The SLN identification rate was 87.6%, and the overall FNR was 8.4%.

In summary, in patients presenting with node-positive disease and converting to ycN0 status after NACT, clinical trials demonstrate that SLNB is acceptably accurate when ≥ 3 sentinel nodes are obtained. However, many of these patients will not have three or more SLNs identified, potentially limiting the number of patients who may benefit from this approach [21]. Only 56 and 34% of the total clinically node-positive study population had ≥ 3 SLNs in the ACOSOG Z1071 and SENTINA trials, respectively [16, 19]. This has led to refinements of the technique of surgical nodal staging, the introduction of so-called SLNB-plus (SLNB +) methods, in an attempt to decrease FNR in this setting. First, it is accepted that when more than 2 SLNs are identified (in the minority of patients), the FNR is below 10% [16, 18, 19]. Using post-treatment ultrasound to select the best candidates for axillary re-staging with SLNB may decrease FNR [22]. In addition, pre-treatment labeling of biopsy-proven positive LNs, e.g. with clips, followed by targeted removal of the labeled LNs also decreases the FNR, and it seems that with these techniques, the limited axillary surgical staging is feasible and acceptable [23–25] (Fig. 1). Despite these favorable results, there are still unresolved questions relating to reproducibility of these techniques and resources required to implement them. Ongoing clinical trials in Europe (GANEA 3, ATNEC, TAXIS) will further investigate the use of targeted axillary dissection [26–28].

All these changes have affected pathology practices and this evolving area presents a challenge for multi-disciplinary teams making recommendations to breast cancer patients.

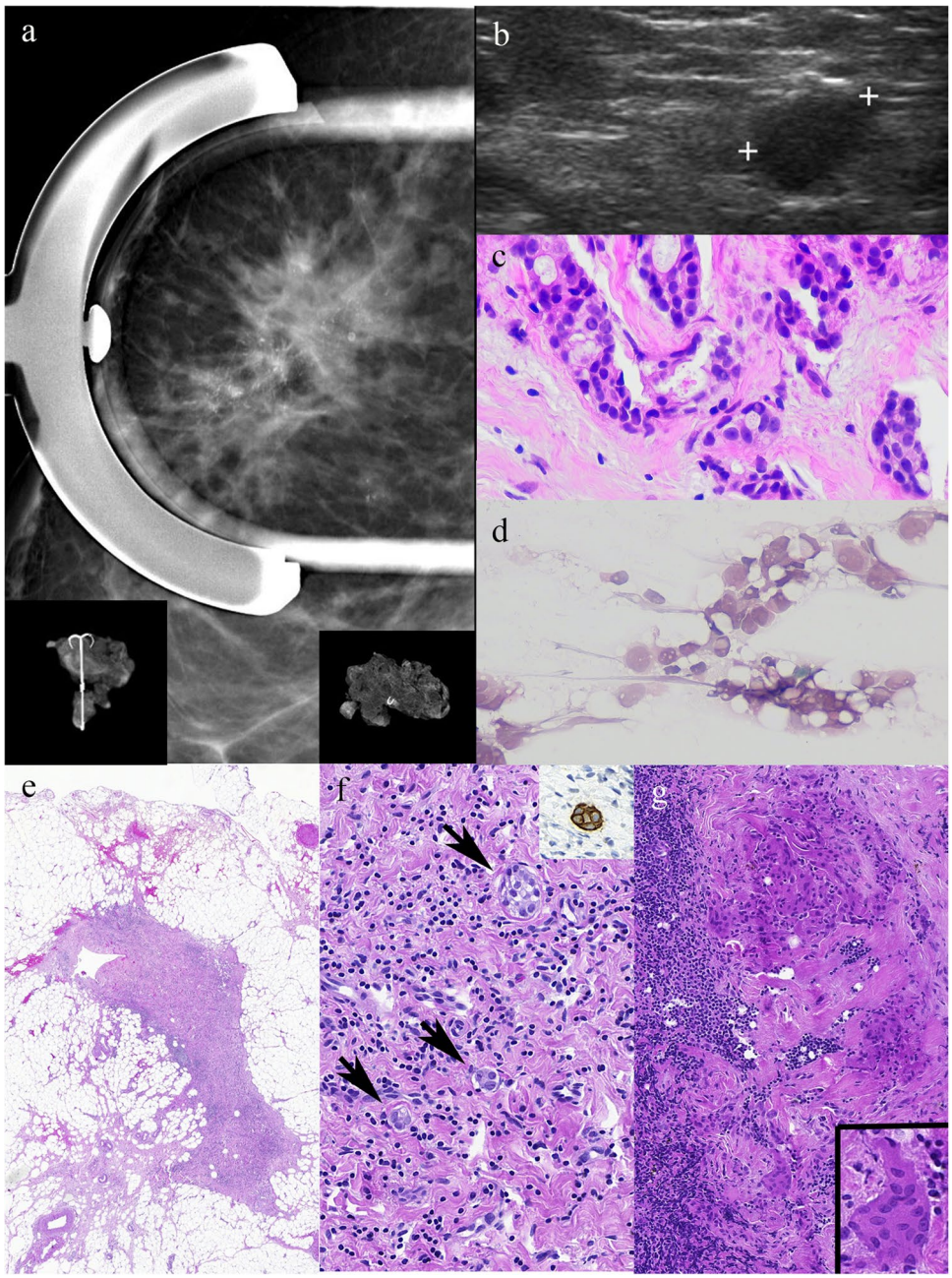

Fig. 1 Sentinel lymph node biopsy and targeted axillary surgery following neoadjuvant systemic treatment. **a** Pre-treatment mammography (mediolateral magnified view) demonstrates a 7-cm-large tumor with microcalcification (bottom left inset, tailored axillary surgery with wire-labeled lymph node removal—the wire containing lymph node coincided with the non-blue but radioactive SLN, but this surgery failed to remove the clip inserted at the time of pre-treatment lymph node biopsy; bottom right inset, following radiography of the wire containing SLN, axillary fat tissue containing a firm palpable lymph node was also removed, the clip was identified in the lymph node); **b** Pre-treatment axillary ultrasound highlights an enlarged and rounded pathological lymph node; **c** Core needle biopsy of the primary tumor prior to treatment demonstrates a histological grade II breast carcinoma of no special type, which proved to by HER2 positive by IHC—not shown (HE, ×40); **d** Fine needle aspiration cytology of the pathological lymph node demonstrated tumor cells; the biopsy was followed by the insertion of a clip (see bottom right inset of part **a**) (Papanicolau, ×40); **e** Low power view of the SLN (also illustrated on the bottom left inset of part **a**); the primary tumor showed complete regression without residual tumor, and the SLN at low power also seemed completely regressed (HE, ×2); **f** At higher power, a few tumor glands (arrows) corresponding to ITCs could be identified in the same SLN (HE, ×30); inset: cytokeratin IHC confirming the epithelial nature of the cells detected on HE (×30); **g** Histology of the clip containing lymph node disclosed no residual tumor, but the giant cell reaction depicted corresponds to the clip site (HE, ×15); inset: a multinucleated giant cell at higher power (HE, ×40)

Surgical pathological nodal staging: pathology—a historical perspective and sentinel lymph node biopsy then and now

The gold standard of nodal staging by histopathology was and is still subject to variability. The pathological nodal status for an ALND depends on the surgical procedure (level I and II versus level I to III dissection), on how thoroughly this is carried out [29], on the pathologists retrieving the LNs from the axillary fat [30], and on the method of investigating these LNs. For a long time, LNs of ALND specimens have been assessed by a single (generally central plane) cross-section histological slide for larger LNs, and a more tangential section for smaller ones, but many institutions have realized how superficial this method may be, and introduced gross sectioning of larger LNs with multiple slices for microscopic analysis. Depending on how thorough the work-up of LNs was, small-size metastases and occult metastases (not detected by the "standard" assessment) often falling into the micrometastatic category (first labeled as such with a 2 mm arbitrary cut-off size by Andrew Huvos et al. [31]) were more and more commonly discovered.

As early as 1995, it was proposed that a more thorough investigation of SLN(s) provided more precise staging information than the traditional methods of assessment, used to examine LNs from an ALND. This led to a substantial increase in the rate of detection of micrometastases [32]. Pathologists started to look for tiny nodal tumor burden in the SLNs, something which was not practical in case of ALND specimens containing numerous LNs. There was tremendous heterogeneity in how SLNs were subjected to pathology analysis. Even molecular methods were introduced to further improve the precision of staging. In a survey on European pathology practice, most laboratories reported an enhanced histopathology for SLNs, including routine immunohistochemistry to detect epithelial cells (used in 71% of the labs). There were 123 somewhat different SLN protocols used in the 240 pathology departments replying to the questionnaire. The most common method was examination of 6 levels separated by 150 μm, used by 8 units only [33]. Not surprisingly, the detection of low-volume "occult" metastases and upstaging rate of SLNB was also very variable, and ranged between 9 and 47% in the early reports [34]. With such a sudden increase in the node-positive-rate of breast cancers, without any changes in the overall survival of the disease, a stage migration took place virtually improving the outcomes of both the (cleaned) node-negative and the (diluted) node-positive cases [35]. To overcome this phenomenon, the TNM staging system introduced the misnamed isolated tumor cell (ITC) classification as a subset of the pN0 (node-negative) category [36]. ITC was later also referred to as isolated tumor cells/clusters, and had reproducibility problems among pathologists [37, 38]; it required further refinements to reach acceptable reproducibility [39–42].

Meanwhile, data have accumulated and have suggested that neither ITC nor micrometastases impact greatly on survival [43, 44] or warrant further axillary [12] or systemic treatment [45, 46].

As the identification of micrometastases and ITCs no longer appears to alter clinical management, use of enhanced pathology protocols to search for this very low volume of nodal disease may not be indicated. The main aim of SLN assessment has become the identification of a pN0 category without macrometastases [47, 48].

The changes in surgical practice have also greatly impacted on the need for intraoperative assessment of SLNs. At the beginning, there was much emphasis on identifying patients who have SLN metastases, to allow a one-step completion ALND, and even intraoperative molecular tests have been introduced to cover this need. However, the scenario has changed. Up to 2 macrometastatic SLNs are still not a general indication for ALND and axillary radiotherapy is still a valid option to reduce regional recurrences after a positive SLN finding. The rate of intraoperative SLN assessment has dropped significantly, to zero at some centers.

The area where a more thorough assessment of SLNs might be warranted and classification of nodal lesions may be problematic is the neoadjuvant setting, which is dealt with in more detail in the last section of this paper.

Current guidelines in Europe and daily practice

We assessed the availability of SLN-related pathology guidelines in a number of geographically European countries by means of correspondence (with professional friends, friends of friends, and colleagues identified through the internet) and a questionnaire (Supplementary material 2). We also tried to gain insight into current practices dealing with SLNs with another questionnaire (Supplementary material 3).

Pathologists from 45 European countries/sovereignties were approached by e-mail to respond to the 2 questionnaires. We got replies from 38 countries. The daily practice questionnaire was returned by 84 pathologists from these 38 countries, 1–7 per country, the expected target having been 1–4 per country.

On the basis of the survey, SLN-related national guidelines or recommendations exist in 18/38 of the countries evaluated, and these have been from or last updated between 2005 and 2020; i.e., some do necessarily not

incorporate newer data based alterations. Recommendations were, broadly speaking, divided into those which advise only gross sectioning (e.g., at 2 mm intervals, aiming at the potential identification of all macrometastases, as proposed by the International Collaboration on Cancer Reporting (ICCR) or the College of American Pathologists (CAP) recommendations [42, 49]; those advising further step sectioning (i.e., more thorough sampling), those adding routine IHC (a more sensitive method), and those also allowing for molecular assessment of the SLNs (in the intraoperative setting)) (Fig. 2). The majority recommend intensive metastasis search that enables pathologist to identify a higher rate of micrometastasis, too (Fig. 2). For comparison, as a frequently quoted set of recommendations, that of the American Society of Clinical Oncology recommends a single HE-stained level examination per slices not thicker than 2 mm [50]. A few of these national guidelines have specific recommendations for the neoadjuvant setting (6/18), 4 advising routine IHC for HE-negative SLNs with regressive changes, and 1 advising this when the HE findings are suspicious. When no national guidelines were reported, other recommendations were sometimes listed as examples to follow, most commonly the ones by the CAP [49].

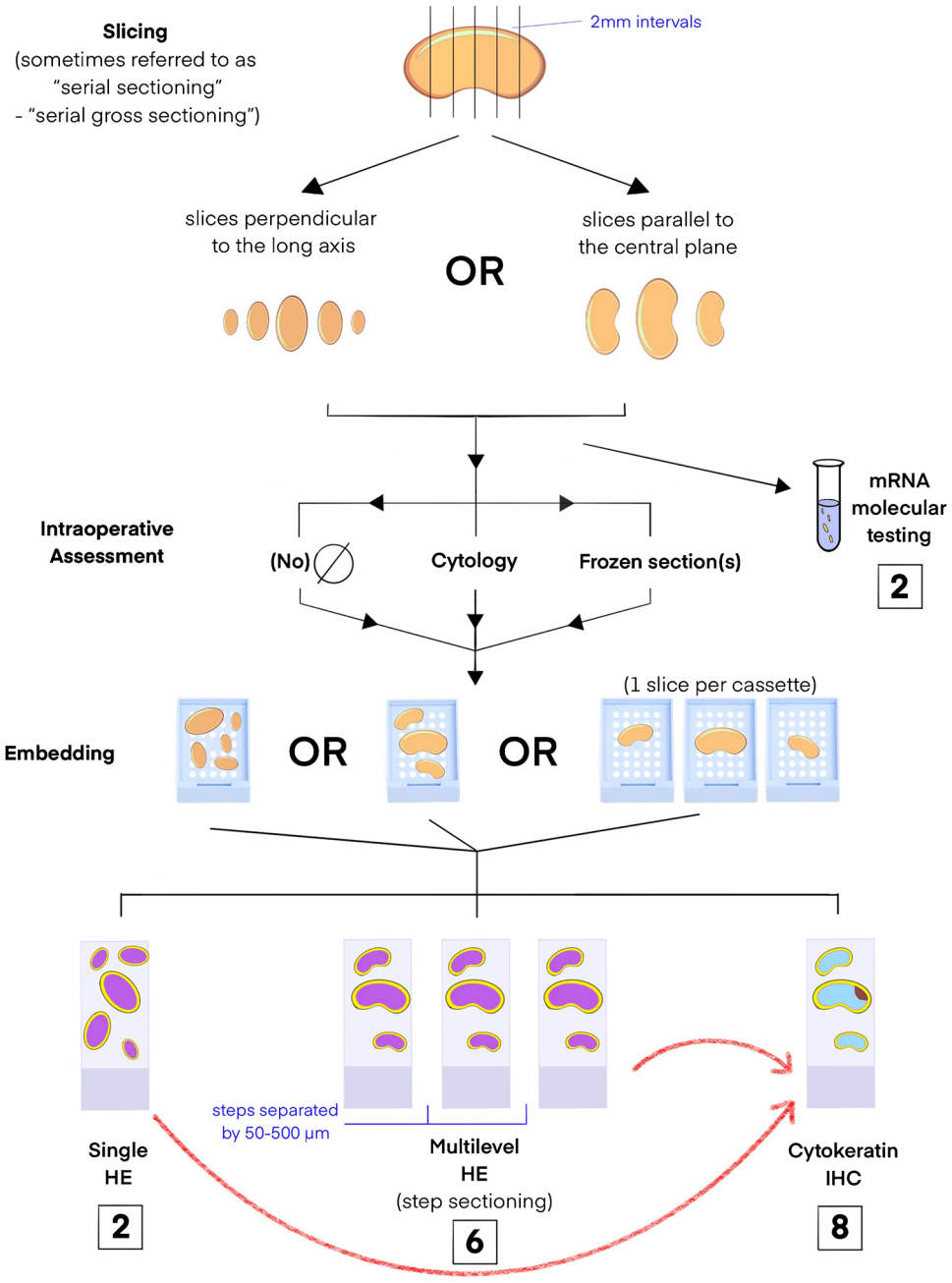

Fig. 2 Protocols of SLN assessment reflected in the questionnaire-based survey. Numbers in squares reflect the number of national guidelines reported (n = 18 in total) allowing or recommending the given details of evaluation. HE, hematoxylin and eosin; IHC, immunohistochemistry; mRNA, messenger ribonucleic acid

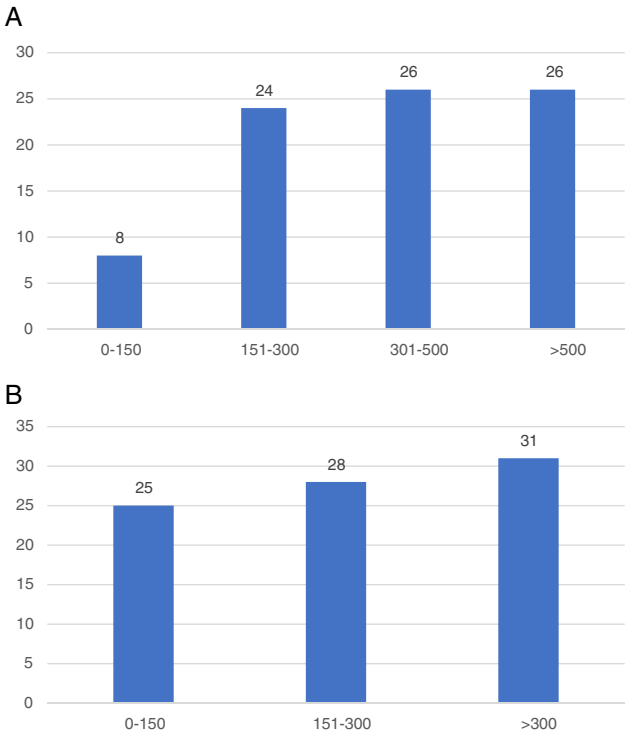

Fig. 3 Breast cancer (**A**) and SLNB (**B**) caseloads of the responders to the questionnaire

With regard to the daily practice reports, the majority of the answers came from institutions with considerable annual case numbers of breast cancers and SLNBs (Fig. 3, Supplementary table 1) and most responders followed the national recommendations when available, with only few exceptions doing more than requested by national guidelines.

Intraoperative assessment was routinely performed (in all or most cases) in a substantial number of institutions 36/84 (43%), was restricted to selected cases in 30/84 (36%), and was not performed at all in a minority, 18/84 (21%). The latter two options reflect the changes in surgical policies mentioned previously, whereas the first probably reflects the fact that at many places, surgeons still base their decision about further axillary surgery on intraoperative findings and their practice was not greatly affected by the Z-0011 trial. Frozen sections were the major means of intraoperative assessment (57/66), but intraoperative cytology was also used alone or in combination with other methods in a minority (18/66) with rapid IHC added to the intraoperative assessment in some places. Molecular assessment with one-step nucleic acid amplification (OSNA) was also reported from 6 hospitals from 4 countries (Supplementary table 1).

Routine step sectioning was reported from 53/84 (63%) institutions, with variable distances, and including exhaustive sectioning till the extinction of the tissue blocks. As micrometastases and ITCs have lost of their prognostic importance, it is interesting to see that many laboratory protocols are still devised to find such volume of nodal involvement, and that IHC is still part of routine assessment of the SLNs in a considerable number of units [48] (Supplementary Table 1), either from all HE-negative SLNs (17/84) or from HE-negative SLNs of patients without identified metastasis in other nodes (16/84). Of course, IHC may make the recognition of any metastasis easier, and this might be the argument for maintaining its use for metastasis detection. However, macrometastases are seldom identified by IHC only, and this occurs principally in cases of lobular carcinomas [51]. Metastases greater than 2 mm in size (macrometastases) can generally be identified with a single HE section per 2-mm-thick gross slices [47–50], and a few step-sections deeper into the blocks can compensate for the uneven or > 2 mm thickness of gross slices. If micrometastases turn up in the last section of a limited sampling protocol, one cannot be certain that the block does not harbor a larger metastasis; therefore, some laboratories have introduced the addition of deeper sections to clarify this situation, and this policy was reported from a significant number of places, but not all. The selective use of IHC was generally included in laboratory practices when findings were suspicious of metastasis on HE; the primary carcinoma was of lobular type or the SLNs showed signs of regression without obvious metastatic involvement (Supplementary table 1).

The majority of the responders (73/84; 87%) indicated that it was part of their daily routine to receive SLN specimens after neoadjuvant therapies. Most responders identified themselves as being confident in the classification of nodal involvement as ITC or micrometastasis or macrometastasis after primary surgery; however, 30/84 (36%) expressed some degree of uncertainty about this classification following primary systemic treatment. These results suggest that the rules for classifying lymph node involvement into TNM defined categories are less straightforward in the post-neoadjuvant setting. This is not surprising, as discussed in the last section.

SLNB after neoadjuvant treatment, the pathologists' perspectives

Assessment of post-treatment nodal status is an important determinant of overall and disease-free survival, independent of response in the breast [52, 53]. Approximately 40% of patients treated with neoadjuvant chemotherapy will have pathological complete response (pCR) in the axilla [54, 55]. Patients with triple-negative and HER2-positive breast carcinomas are most likely to have a pCR, including no residual carcinoma in LNs.

The approach to the clinical management of the axilla, including the feasibility of SLNB, in the neoadjuvant setting,

depends on whether the patient is clinically node-negative (cN0) or clinically node-positive (cN1), at presentation. This has been explored in clinical trials described in the introduction.

SLNB may be carried out before or after NACT in cN0 patients. Contemporary clinical practice is moving towards post-NACT SLNB for cN0 patients as it appears to be more beneficial [56-58]. SLNB prior to chemotherapy provides information on axillary nodal status without the confounding effects of treatment and may allow more accurate initial staging and be helpful for treatment planning. However, it involves the patient having two separate surgical procedures. Time required for wound healing, which may delay initiation of NACT, is another disadvantage [57]. Potentially valuable prognostic information about post-treatment LN status is not obtained. The pre-treatment LN data are not valid for calculation of residual cancer burden (RCB), which is increasingly used to quantify residual disease in the neoadjuvant setting, correlates with survival outcomes, and influences decisions regarding further treatment. Pre-NACT SLNB does not exploit the potential down-staging effect of treatment and patients with a positive SLN prior to NACT may be committed to ALND. Repeat SLNB after NACT is not recommended, as SENTINA reported a low identification rate of 60% and false-negative rate (FNR) of 50% [16].

Patients who present as cN0 with a negative SLN after NACT do not require any further axillary surgery [56]. There is a paucity of evidence regarding the optimal approach to management of patients who present as cN0 and have unexpected histological evidence of previous node positivity after NACT. UK guidelines advise that until there is an improved evidence base for this group of patients (ypN0 on post-NACT SLNB), they should be offered axillary radiotherapy [56]. Two current ongoing randomized clinical trials may provide more information on the longer-term safety of SLNB after NACT and the optimal management of these patients. NSABP B-51/Radiation Therapy Oncology Group 1304 (NRG 9353) and Axillary Management in Breast Cancer Patients With Needle Biopsy Proven Nodal Metastases After Neoadjuvant Chemotherapy (ATNEC) are specifically addressing axillary management following NACT in patients with proven ALN metastases who convert to ypN0(sn) [27, 59].

ALND rather than axillary radiotherapy alone remains the standard of care for patients with a positive SLN after NACT, regardless of the volume of residual disease [56]. Axillary radiotherapy only may be considered in individual cases but the evidence that it is equivalent to ALND for ypN1 patients is not established. Current trials will hopefully elucidate this as they examine whether axillary radiation is as effective as ALND.

To date, studies suggest that low-volume axillary nodal disease present after NACT is associated with a worse outcome and even low-volume residual metastatic carcinoma in a post-NACT SLN may indicate a higher likelihood of non-SLN metastases [60, 61]. Further study is required and outcome data from randomized trials should help define the clinical and prognostic significance of low-volume residual nodal disease. The Italian NEONOD2 is one such trial which aims to study 130 ypN0mi patients to determine if ALND can be omitted in patients with micrometastases in the post-NACT SLN [62].

Although SENTINA, ACOSOG Z1071, and SN FNAC inform us about the performance of SLNB after NACT, the clinical significance of leaving metastatic disease behind after NACT is not addressed in these trials. The extent to which locoregional therapy should be modified based on the response to NACT is also an unresolved question. Ongoing randomized clinical trials are investigating these issues. As mentioned above, the NSABP B-51/Radiation Therapy Oncology Group 1304 (NRG 9353) and the ATNEC trials will evaluate the benefit of addition of regional nodal irradiation in patients who have axillary nodal pCR [27, 59]. The Alliance A011202 trial also seeks to define the optimal management of the axilla in patients with a positive post-NACT SLN and randomizes patients to axillary dissection versus axillary radiotherapy after the completion of NACT [63].

De-escalating the extent of axillary treatment is a "hot topic" in clinical management of breast cancer patients having NACT. SLNB after NACT in patients with biopsy-proven node-positive breast cancer requires careful patient selection. Kantor et al. developed a model based on 19,115 node-positive patients undergoing NACT registered in the American National Cancer Data Base and found that young age, grade, intrinsic subtype, tumor histology, clinical N stage, and primary tumor response were predictive for pN conversion [64]. All patients with node-positive breast cancer should be re-discussed at the multi-disciplinary team meeting on completion of NACT, where clinical and radiological features and known tumor biomarker profile can be considered. Some patients may not be suitable for an attempt at SLNB after NACT, e.g., those with extensive clinical or radiological axillary nodal involvement at presentation.

Pathological evaluation of SLNs following NACT

Evaluation of SLNs from patients who have had NACT can be challenging for the pathologist. While low-volume SLN metastatic disease does not always mandate completion ALND in primary surgical patients, the optimal management of low-volume disease in post-NACT SLNs is still being investigated and completion ALND is often required. In the post-neoadjuvant setting, the presence of ITCs

(ypN0(i+) category) excludes pCR [41, 42]. The extent of LN involvement provides important data for calculation of RCB which is an independent factor for prognosis after NACT [65, 66]. Furthermore, if residual axillary disease is identified, patients with triple-negative tumors and HER2-positive tumors can be selected for additional adjuvant treatment with capecitabine or trastuzumab emtansine (T-DM1), respectively [67, 68].

As there are no sufficient data so far demonstrating that SLNs should be evaluated differently in post-NACT cases, they should be assessed in the same way as non-neoadjuvant cases. All LNs should be sectioned at 2-mm intervals and entirely submitted for histologic evaluation. It is important to note if a clip was placed in a previously biopsied LN and to locate the clip in the specimen with the help of a specimen X-ray, if necessary.

The total number of LNs, the number of LNs with metastatic carcinoma, the size of the largest metastatic deposit, and the presence of extracapsular extension should be reported. The histological reaction to clip/clip site or tattoo ink associated with pre-treatment biopsy should be documented. The number of LNs with treatment-related changes (usually fibrosis) and no viable carcinoma should also be reported as it is a reflection of pre-treatment nodal burden.

Of note, decisions regarding the extent of radiation therapy may be based on the combination of nodes with viable metastatic carcinoma and the number of nodes with features indicative of "regressed" metastatic carcinoma [56, 69]. The International Collaboration on Cancer Reporting (ICCR) recommends reporting of treatment effect and states treatment effect is best reported separately for lymph nodes with residual metastatic carcinoma and for lymph nodes without residual metastatic carcinoma [42].

After NACT, LNs are often smaller in size and can appear lymphocyte-depleted. In most cases, complete response is evident in the form of fibrosis and aggregates of foamy macrophages without viable carcinoma cells, similar to the histological features seen in the primary tumor bed [69, 70]. Barrio and colleagues identified treatment effect in 94% of nodal specimens in patients with documented metastases pre-treatment who had nodal pCR [71]. Residual metastatic carcinoma cells may be scant, with single scattered malignant cells and small clusters of cells within areas of treatment effect such as fibrosis, aggregated macrophages, or mucin pools (Fig. 1). Routine levels and IHC are generally not recommended, although cytokeratin IHC may be required to confirm suspicious morphology in selected cases. Despite the lack of recommendations for routine IHC in these cases, our survey suggests that many pathologists use IHC regularly before establishing a complete SLN regression statement. Changes associated with neoadjuvant treatment cannot always be distinguished from biopsy site changes or reactive changes in LNs that may be unrelated to treatment. In some cases, the histological evidence of prior tumor involvement is very subtle and some previously involved LNs can look histologically unremarkable after treatment.

It is essential to be aware of the pre-treatment nodal status (Fig. 4). The lack of finding a LN with regressive changes and the knowledge of a previous biopsy proven cN1 or higher nodal status should prompt a further search for such reactions (deeper levels), or should raise the suspicion that the originally positive lymph node has not been removed.

Classification and measurement of nodal metastases post-treatment poses some difficulties. The ICCR, World Health Organization, and Royal College of Pathologists regard small nodal metastases and ITCs as evidence of an incomplete response [42, 72, 73]. Similarly, the AJCC TNM staging system states that ITCs may represent minimal nodal disease that did not respond to NACT, or residual macroscopic nodal disease with a partial response [41]. Although TNM states that the presence of ITCs precludes classifying the patient as having pCR, it still recommends classifying these cases as ypN0(i+). While this uniform approach allows standard definitions of N staging to be maintained, it can be a source of confusion. In some institutions, due to concerns about potentially misleading clinicians, the terms ITC and micrometastases are not used. The size and description of the largest post-NACT metastatic carcinoma are reported without use of these terms. The ypN categories used for NACT are the same as the pN categories applied to untreated cases, but the clinical significance differs. Our survey suggests that pathologists' confidence in classifying nodal burden into TNM defined categories post-NACT is also weaker.

The measurement of residual carcinoma in the post-neoadjuvant therapy setting is a subject of debate and guidance on measurement varies in different classification systems. The current AJCC TNM staging manual states that the largest focus of residual carcinoma in the lymph nodes is used for ypN categorization. Treatment-induced fibrosis between adjacent foci of residual carcinoma is not included in the size measurement [41]. However, for the purpose of calculating the RCB score, the largest extent of lymph node involvement by carcinoma cells including intervening treatment-induced stromal fibrosis is used as the size of largest metastasis (Fig. 5) [74].

Pathological evaluation of SLNs after NACT remains challenging, with conflicting guidance on measurement of residual metastatic disease. It is hoped that further international collaboration will aid standardization of approach to SLN assessment in the future.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00428-021-03128-z.

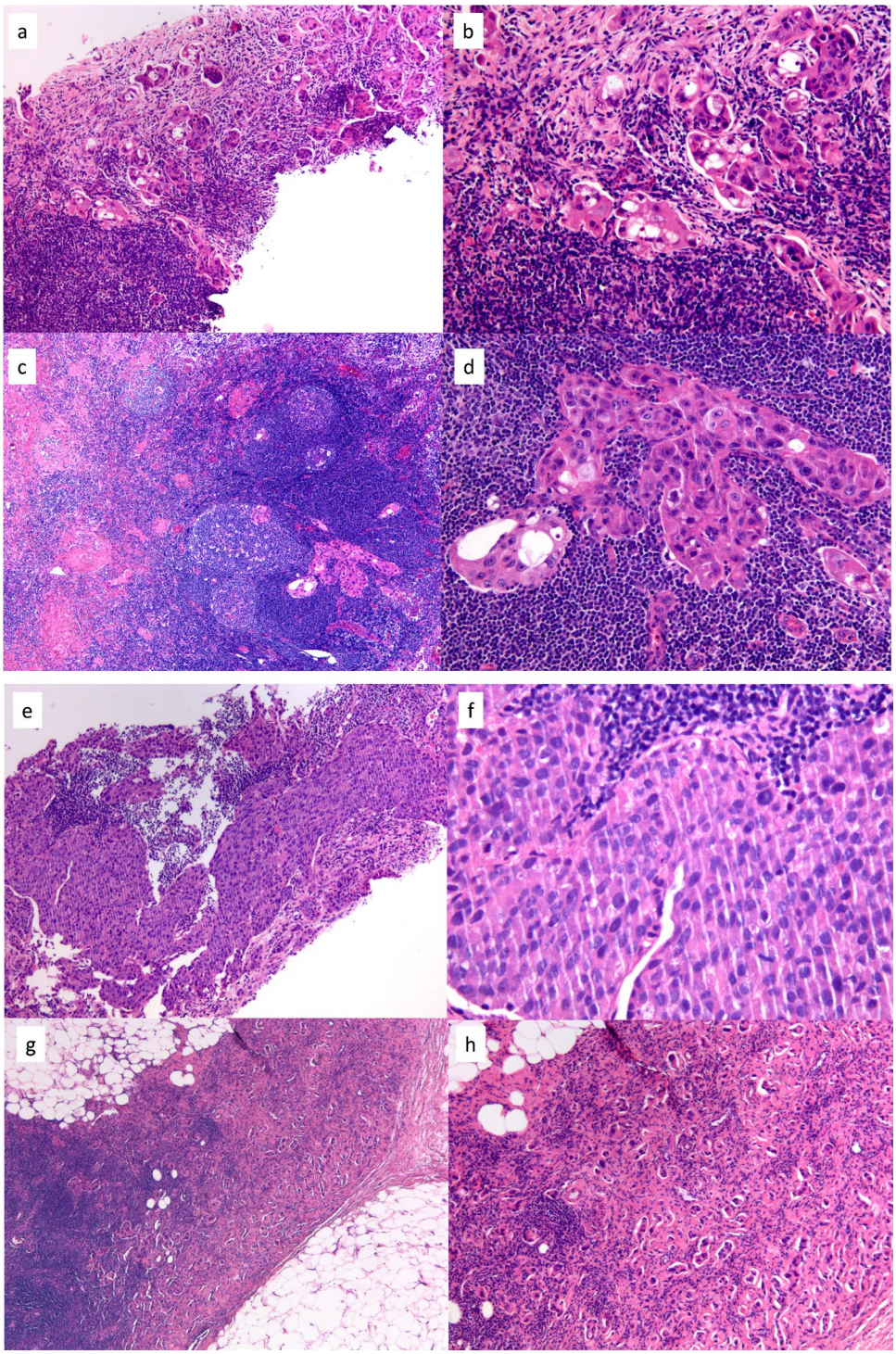

Fig. 4 Examples of core needle biopsy proven nodal metastases with signs of regression after NACT. Patient A had lymph node involvement of a triple negative tumor demonstrating some fibrosis initially, making the assessment of regression more difficult after treatment (**a** HE×10, **b** HE×20). Following NACT with 4 EC + 12paclitaxel, the lymph node showed treatment-related fibrosis (left side of **c** HE×5) and a residual micrometastasis with possible cytopathic effect but no surrounding fibrosis (right side of **c**, and **d** HE×20). Patient B had biopsy proven lymph node metastasis from her HER2-negative luminal B-like tumor (**e** HE×10, **f** HE×40). Following NACT with 4 EC + 12paclitaxel, the lymph node still harbored a macrometastasis with obvious signs of fibrosis suggestive of regression (**g** HE×5, **h** HE×20)

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Author contribution G.Cs. and A.M. have drafted the manuscript; G.Cs., A.M., and S.B. have contributed the figures; all authors have contributed in answering and spreading the questionnaires; all authors have commented the draft manuscript on multiple occasions, and approved the final version submitted.

Data availability The results of the questionnaire-based survey are submitted (therefore available) as Supplementary material.

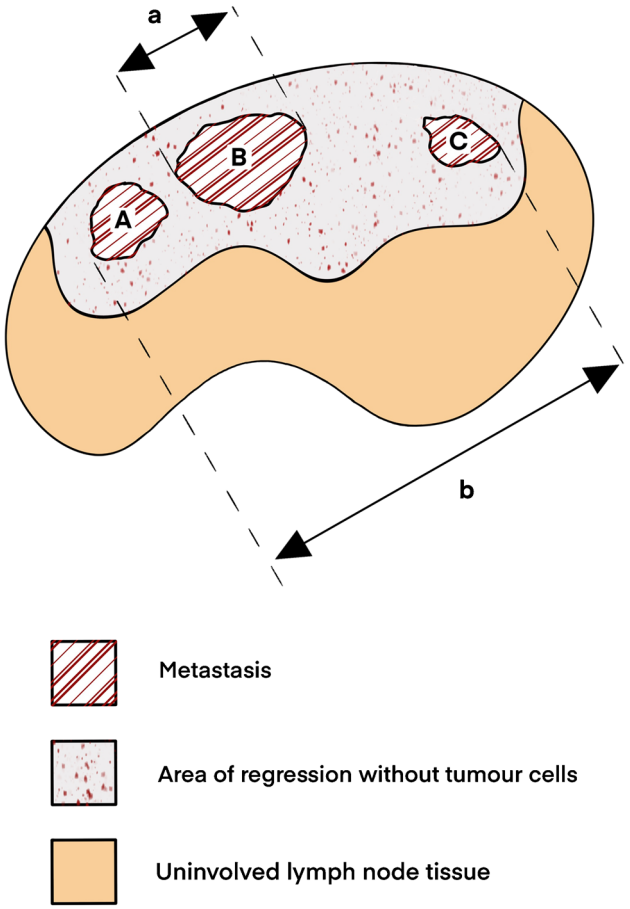

Fig. 5 Metastasis measurment issues after neoadjuvant treatment. According to the AJCC criteria, the metastasis size and the ypN category are defined by the largest size of the largest contiguous focus of residual cancer, without treatment-related fibrosis between the foci or adjacent to the foci being included; as B > A > C, the size of the residual metastasis will be the size of cluster B, i.e., segment "a" on the drawing [41]. While calculating the RCB [74], the size of the tumor-involved residual metastasis bed is taken into account as metastasis size, segment "b" on the drawing. A similar policy is used in some neoadjuvant trials, where the guidance is to give the size as tumor + space + tumor + space + tumor for the given example. A further source of confusion may stem from the fact that the Royal College of Pathologists' guidance on reporting breast diseases suggests to measure foci separated by less than 5 mm as a single lesion for the primary tumor, but no similar statements for the metastasis size measurement [72]

Declarations

Ethics approval No ethical approval was deemed necessary for this review.

Consent to participate Not applicable.

Consent for publication There is no item requiring such a consent.

Conflict of interest The authors declare no competing interests.

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