RESEARCH ARTICLE

The ever-evolving role of pathologists in the management of breast cancer with neoadjuvant treatment: recommendations based on the Spanish clinical experience

O. Burgués¹ · M^a. Á. López-García² · B. Pérez-Mías³ · P. Santiago⁴ · B. Vieites² · J. F. García⁵ · V. Peg⁶

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Abstract

Purpose To compare the current international standards for neoadjuvant systemic therapy (NAST) protocols, and establish consensus recommendations by Spanish breast pathologists; and to look into the Spanish reality of defining pathological complete response in daily practice.

Materials and methods A modified Delphi technique was used to gain consensus among a panel of 46 experts with regard to important issues about NAST specimens, with the objective of standardize handling and analysis of these breast cancer specimens. In addition, a survey was conducted among 174 pathologists to explore the Spanish reality of post-NAST breast cancer specimens handling.

Results Our survey shows that pathologists in Spain follow the same guidelines as their international colleagues and face the same problems and controversies. Among the experts, 94.1% agreed on the recommendation for a pre-treatment evaluation with a core needle biopsy, and 100% of experts agreed on the need of having properly indicated

information for the post-NAST surgical specimens. However, only 82.7% of them receive properly labelled specimens and even less receive specimens where markers are identified and the degree of clinical/radiological response is mentioned. Among participants 59.9% were familiar with the residual cancer burden system for post-NAST response quantification, but only 16.1% used it regularly.

Conclusions Active participation on breast cancer multi-disciplinary teams, optimal usage of core needle biopsy for timely and standardized procedures for the diagnostic analysis, and accurate diagnosis of pathological complete response and complete evaluation of the response to NAST need to become the standard practice when handling breast cancer specimens in Spain.

Keywords Breast cancer · Neoadjuvant treatment · Pathology · Recommendation

Introduction

Detailed and accurate histo-pathological analysis and description of cancer specimens are pivotal to any decisions taken regarding treatment options. In clinical oncology practice, planning of local or systemic treatment either pre-operatively or post-operatively is based on predictive and prognostic information extracted from histo-pathological and immunohistochemical data. Evidence-based treatment protocols tailored to each cancer characteristics can be elaborated by an in-depth understanding of the tumour's distinct pathologic features.

It has been shown that structured pathology reports with a standardized format significantly improve the data quality and completeness [1, 2] contributing thus importantly to the management of oncologic patients and simplifying the

✉ O. Burgués
burgues_oct@gva.es

¹ Servicio de Anatomía Patológica, Hospital Clínico Universitario, Avda. Blasco Ibáñez, 17, 46010 Valencia, Spain

² Servicio de Anatomía Patológica, Hospital Virgen Del Rocío, Seville, Spain

³ Servicio de Anatomía Patológica, Hospital Universitario Ramón y Cajal, Madrid, Spain

⁴ Servicio de Anatomía Patológica, Complejo Hospitalario A Coruña, A Coruña, Spain

⁵ Roche Farma S.A., Madrid, Spain

⁶ Servicio de Anatomía Patológica, Hospital Vall d'Hebron, Barcelona, Spain

auditing process at the same time. Standardized pathology reports have been implemented via publication of national guidelines and protocols for histo-pathological assessments of breast cancer specimens in USA [3], UK [4], Australasia [5], Belgium [6], The Netherlands [7] and Germany [8].

With the increasingly better understanding of breast cancer and the emergence of new treatments, the management of this disease becomes progressively adjusted to the patient's profile and tumour behaviour. A multidisciplinary assessment process combining pre-operative clinical findings with imaging results, percutaneous biopsy and surgical histo-pathological analysis is of fundamental importance in the delivery of a high quality care for the breast cancer patients.

Currently, an increasing number of early-stage breast cancer patients are treated with neoadjuvant systemic therapy (NAST) protocols with the aim to increase the possibilities of breast conservation, eliminate micro-metastases and also to measure efficacy of systemic therapy in vivo as assessed by means of pathologic response. Pathologic response after NAST is a significant prognostic indicator [9]; patients with a pathological complete response (pCR) have the best prognosis.

When we talk about NAST it does not necessarily mean chemotherapy schemes; it could equally be an anti-oestrogen treatment in combination with a biologic blocking agent or different combinations with anti-HER2 agents. In most institutions the decisions regarding NAST follow a multidisciplinary process and universally established criteria.

However, NAST might have an important impact for pathologists as handling and reporting of breast cancer specimens after NAST require specific considerations. Because of the complexity of NAST specimens, a multidisciplinary approach is essential before, during and after NAST. An accurate localization and sampling of the tumour bed is necessary for a complete evaluation of the original tumour. That makes gross pathologic methods the most important source for accurate definition of pCR [10] and emphasizes the need for a universally standardized protocol to evaluate the post-NAST specimen.

Multicenter breast cancer clinical trial studies have indicated that there is a huge variation in handling and reporting these specimens [11], due to the fact that guidelines are not always followed accurately [12]. Currently there are different classification systems with several relevant reviews [13–16], where recommendations for the assessment of pathologic response to NAST can be found. In recent time, NAST has been part of multicentre clinical trials and often recommendations for assessment of pathology specimens are elaborated during these trials [17, 18].

The pathologist's task in assessing post-NAST specimens could get even more complicated by the fact that the definition of pCR is not uniformly accepted creating thus further challenging issues with the interpretation and reporting of the data [19]. Bossuyt et al. and Provenzano et al. in their respective studies [17, 18] recommended that the post-NAST assessment and report should include information on pCR versus residual disease as defined by the FDA meta-analysis [9] (*ypT0/is ypN0*), AJCC/UICC *ypT* plus *ypN* stage and detailed quantification of residual disease (RCB system).

In this ever-changing era in the diagnosis and treatment of breast cancer, pathologists, the keepers and purveyors of excised tissues, have extended their role by employing new technologies to examine the molecular complexities of breast cancer relating thus its biological heterogeneity to prognosis and treatment, and issuing recommendations aiming to improve the handling and reporting of the specimens [20]. With this paper we aspire to contribute positively to this global effort of post-NAST breast cancer specimens reporting standardization by looking into the Spanish reality of daily practice of accurately defining pCR. We compare it with the current international standards and establish relevant recommendations elaborated by Spanish breast pathologists reaching consensus following a Delphi methodology enquiry with the aim to improve management and prognosis of this disease.

Materials and methods

The Delphi method

A modified Delphi technique was used to gain consensus among a panel of experts [21]. The Delphi method is a structured process used to gain consensus on a given question from a panel (Delphi panel) constituted by a range of experts. With this methodology, situations such as dominance of the panel by the views of few can be avoided [22].

A previously elaborated questionnaire containing assertions covering current controversial issues on the management of breast cancer patients with NAST in the daily Spanish practice and on handling and evaluation of post-NAST breast cancer samples was presented to a group of pathologists with special interest in breast cancer participating at the time in an interactive session to establish the role of the pathologist in the management of breast cancer with NAST. Each member of the group expressed their opinion to each assertion by voting anonymously. The degree of the participants' agreement or disagreement with the questionnaire's assertions was scored.

The responses' results from this first round of voting were subjected to statistical analysis to assess the degree of consensus or not for each assertion among the participants and subsequently were presented for discussion to the entire group giving thus the opportunity to each group member to reconsider their responses. In a second round of voting, ambiguous items with relevant proposals by comments of the first round were subjected to a further survey. The results from this second round were analysed once again to determine the items that reached sufficient degree of consensus among the participating experts, and which ones could be used to issue relevant recommendations.

Stages of the process

Following an extensive review of literature on the subject of pathological evaluation of post-NAST specimens of breast cancer, taking in account the experience from the Spanish clinical practice and paying special attention to the recently published recommendations of Provezano et al. [17] and Bossuyt et al. [18], two questionnaires, one containing assertions on relevant items of handling and analysing post-NAST breast cancer samples (consensus questionnaire) and the other questions about the Spanish daily breast cancer pathology practice (Clinical practice questionnaire) were designed by a committee of pathology experts on breast cancer to be discussed and subjected to consensual surveyance by the Delphi method.

Clinical practice questionnaire was presented to a group of pathologists who were participating in a training meeting that included the Delphi method questionnaire (see below) and to 126 pathologists participating in training sessions throughout Spain (Valencia, Madrid, A Coruña, and Sevilla). In total, 174 pathologists answered the clinical practice questionnaire.

Consensus questionnaire was presented to a group of pathologists (30 specialists in breast cancer, 16 general pathologists), who were participating at the time in an interactive session regarding the role of the pathologist in the management of breast cancer treated with NAST. The items of the consensus questionnaire were scored by means of a Likert-type ordinal scale from 1 to 9 points (minimum 1: complete disagreement, maximum 9: complete agreement) as it is described by the UCLA-RAND Corporation [21]. The responses were classified into three groups of answers (1–3: disagree, 4–6: neither agree nor disagree and 7–9: agree). An item was regarded as consensual in agreement if the median of the scores fell within the {7–9} range group. On the contrary, it was considered consensual in disagreement if the median fell within the {1–3} range group. Items with medians within the {4–6} range group should be subjected to a second round of voting. The

questions of the clinical practice questionnaire were subjected to general voting.

The answers to the questionnaires were analysed by external reviewers. Although consensus was reached for all items of the consensus questionnaire during the first round of voting, items that reached consensus between 70 and 80% were subjected to a second round of voting after presenting and discussing the results of the first round of voting. At the end of this round consensus was reached for all items. The final results were presented to the participants for further discussion and comments, which were used to compose the recommendations document by a scientific committee, whose members reviewed and approved the final draft unanimously.

Results

Consensus was defined a priori as greater than 70% agreement on all items with the same ranking according to the recommended quality indicators for a Delphi study [23]. The consensus questionnaire contained 18 items addressing 8 current and controversial issues in the handling and analysis of the post-NAST breast cancer pathology specimens (Table 1). As it has been mentioned already consensus was reached for all of the items during the two rounds of voting (100%), and the detailed results can be seen in Table 1. During the ensuing discussion at the end of the voting there was general agreement by all the participants regarding the results of the voting and no concerns were expressed with regards to the consensus reached.

The results/recommendations of the consensus questionnaire, which are very much in line with the current international recommendations, are summarized below:

1. For the initial evaluation of treatment a core needle biopsy (CNB) is recommended and an unequivocal diagnosis of infiltrating breast cancer with histological type, grade (Nottingham/Scarff-Bloom) and biomarkers [oestrogen receptor (ER), progesterone receptor (PR), HER2, Ki-67] should be included. The tumour should be marked during the biopsy.
2. For the evaluation of the axilla during the diagnostic process it is recommended: axillary ultrasound (US) for all those patients that undergo CNB for suspected breast cancer, with a fine needle aspiration biopsy (FNA) or a CNB in the case of suspicious lymph nodes detection. It is recommended the evaluation of sentinel lymph node (SLN) biopsy after treatment, including positive lymph nodes at the moment of diagnosis, which become negative post-NAST. In the case of

Table 1 Consensus questionnaire (with Delphi results)

Pre-treatment diagnosis	Agreement (%)	Result %
For the pre-treatment evaluation a core needle biopsy (CNB) is recommended	94.1	First round agreement
The pre-treatment evaluation should include	100	First round agreement
Unequivocal diagnosis of invasive cancer		
Histological type (OMS 2012)		
Histological grade (Nottingham Scarff-Bloom)		
Biomarkers: ER-PR-HER ₂ -Ki67		
During the biopsy a marking clip should be left	94.4	First round agreement
<i>Axillary evaluation at diagnosis</i>		
It is recommended	97.2	First round agreement
US axillary evaluation for all the breast cancer suspected patients who undergo CNB		
Perform FNA or CNB for morphologically abnormal nodes		
Sentinel lymph node biopsy (SLNB) is recommended post-treatment including positive nodes at diagnosis	79.3	Second round agreement
<i>Required information on the request form for post-NAST surgical specimen</i>		
The request form should indicate clearly that NAST was done	97.3	First round agreement
The request form should include information regarding site, number and size of the tumour/s pre-treatment	100	First round agreement
The following information should be indicated	100	First round agreement
Presence and type of markers (clips, tattoos etc.)		
Pre-treatment nodal status		
Clinical/radiological grade of response (breast and axilla)		
Characteristics of the primary tumour (type, HG, ER, PR, HER ₂ , Ki67)		
<i>Macroscopic analysis post-NAST</i>		
A systematic sampling of the specimen and the creation of schematic map, using imaging or individual drawings.	100	First round agreement
If the tumour/tumour bed are detectable macroscopically their presence and size should be indicated	100	First round agreement
The sampling should include both macroscopic lesions and the suspected areas affected by the tumour pre-treatment	100	First round agreement
All lymph nodes should be evaluated histologically and they should be included in 1–2 mm slices	96.4	Second round agreement
The post-NAST histology report should include	100	First round agreement
Grade and histological type: Multiple tumours with different histological type or grade and clearly separated by adipose tissue should be reported separately		
Size and extension: The following two options are recommended for inclusion in the report; two dimensions of the tumour area including not only the dispersed residual tumour foci but also the tumour bed among all of them, or according to the AJCC (7th ed) the size (<i>ypT</i>) is established based on the biggest adjacent invaded area. It should be indicated that the tumour is multifocal		
Cellularity: If the evaluation system is based on cellularity reduction (Miller-Payne, Pinder), then it should be compared with the CNB at diagnosis		
Tumour bed: detectable or not, and its position regarding the margins		
Lymphovascular invasion: its presence excludes pCR		
Nodal metastasis: the presence of cancer cells in lymph nodes is not pCR		
Treatment response: presence or absence of treatment response and number of nodes with regressive changes		

Table 1 continued

Pre-treatment diagnosis	Agreement (%)	Result %
<i>Post-NAST sentinel node selective biopsy (SLNB)</i>		
For the evaluation of sentinel node post –NAST techniques that allow for treatment response assessment should be used	81.5	Second round agreement
<i>Post-NAST biomarkers evaluation</i>		
Repeated evaluation of biomarkers post-NAST in residual invasive cancer specimens (breast or nodes) should be reserved for cases that	100	Second round agreement
The pre-NAST result was negative		
The pre-NAST result was inconclusive		
In case of tumours without any response to treatment		
In case of heterogeneous tumours or multifocal ones with different morphology		
<i>Pathologic complete response (pCR)</i>		
pCR is defined by the absence of infiltrating residual cancer not only in the totally excised breast specimen but also in all sampled regional nodes post-NAST completion	96.7	First round agreement
The presence of carcinoma in situ only is considered to be pCR	93.8	First round agreement
<i>Response valuation system</i>		
For the post-NAST response evaluation the RCB (residual cancer burden) system from MDACC (Symmans) is recommended	92.9	Second round agreement

positive lymph node detection in the axilla, axillary lymphadenectomy is recommended.

3. The requesting form for the histological evaluation of post-NAST specimens should clearly indicate that the specimen is a post-NAST one. The pathologist must have information regarding the number and size of the tumour/s before treatment, the existence/types of markers, nodal status before treatment, characteristics of the primary tumour (type, histological grade (HG), ER, PR, HER2, Ki67) and the clinical/radiological response grade in both breast and axilla after treatment.
4. With regards to the macroscopic examination of the post-NAST specimen, the recommendations consist of systematic sampling and mapping of the specimen using a photograph, X-ray or a draw sketch of the slices (the sampling should be extended to include the entire suspected tumoural area before the treatment as well), localization and measurements of the tumour/tumour bed (if and when they can be identified) and histological evaluation of all included lymph nodes (in 1–2 mm slices) (Fig. 1).
5. The pathology report should include the following information: histological type and grade (in the case of multiple tumours with different types/grades a separate report for each one of them should be issued), size and extension of the neoplasm (either a two-dimensional calculation in mm of the neoplastic area including not only the dispersed tumour infiltrated residual areas but the tumoural bed between them as well known as residual cancer burden RCB estimation [24], or

according to the AJCC [25] the size ypT of a multifocal tumour is established based on the biggest adjoining invaded area), the percentage of tumour cellularity, margin evaluation (including invasion by the tumour bed), lymphovascular invasion, number of lymph nodes showing metastases indicating the size of the biggest one and finally the presence or not of post-treatment changes in the lymph nodes.

6. Biomarkers in residual invasive breast cancer specimens (breast or nodes) post-NAST should be assessed in cases where the results before the treatment were not conclusive or were negative, in tumours with minimal response to treatment and in heterogeneous tumours or in multifocal cancers with different morphologies.
7. Post-NAST pCR is defined by the absence of residual invasive cancer not only in the totally resected surgical specimen but also in all of the sampled lymph nodes following the completion of NAST as well. Lymphovascular invasion and/or isolated tumour cells (ITC) in the nodes are not considered as pCR. The presence of in situ carcinoma solely is classified as pCR. The use of the RCB system is recommended for the evaluation of the post-NAST breast cancer response [24].

The analysis of the results of the clinical practice questionnaire is summarized on Table 2. It is worth noting the percentage of the panellists that regularly participate in the multidisciplinary breast cancer meeting, which was around 70%. Almost all of the participants (97.9%) responded that the axilla is evaluated during the diagnostic

Fig. 1 Mastectomy specimens in which a complete mapping of the tumour bed or suspected areas with residual tumour has been carried out to assess pathological response to the neoadjuvant treatment. Alternatively to specimen photographs, X-rays or diagrams may be used

process and FNA or CNB is performed for cancer suspicious nodes. Regarding the sentinel lymph node 44.8% thought that a biopsy should be done pre-NAST, 30.7% post-NAST and only to patients with negative nodes at diagnosis, 17.5% post-NAST, including patients with positive nodes at diagnosis as well, 5.6% pre-and post-NAST and 2.1% said that there is no need for selective sentinel lymph node biopsy. 42.6% use the OSNA method intra-operatively to evaluate the sentinel lymph node, 24.1% imprint cytology or frozen section intra-operatively and 33.3% evaluate the lymph nodes at later stage (not intra-operatively).

Among the participants, 59.9% were familiar with the RCB system [24, 26] for the quantification of the post-NAST response, but this system was used as the method of choice only by 16.1% of them, whereas 62.7% were using the Miller-Payne classification system [27]. 16.1% were using both systems. With regards to the definition of the

pCR, 59.1% responded non-invasive cancer and *ypT0/ypTis ypN0*.

Discussion

The last few years NAST is offered more and more often to patients with early breast cancer and it has almost become routine for patients to receive systemic therapy [11, 28]. However as a result of NAST, the correlation of clinico-pathological and radiological response with residual tumour could not be defined accurately [29], although with the introduction of magnetic resonance the accuracy in discriminating residual disease versus pCR has improved [30]. Pathologic evaluation of the tumour is still regarded as the gold standard in optimizing the knowledge required for the design of any breast cancer therapy. Pathologists have an important role in providing this information, standardizing existing classification schemes and developing new schemes for ongoing trials [15].

Post-NAST breast cancer specimens reporting standardization recommendations for clinical trials are key for accurate data collection during these studies; however, we believe that these recommendations should be applied to any post-NAST breast cancer specimens in routine clinical practice in an effort to standardize pathological response reporting.

Every health carer that participates in a multidisciplinary team for neoadjuvant-treated breast cancer patients has to deal with critical issues and the pathologist is not an exception to this concept. Handling of surgical breast cancer specimens can be challenging, because of a number of histo-pathological changes in the post-NAST tumour and adjacent breast tissues [31]. However, only minimal guidelines regarding specimen handling do exist [32]. Frequently, pathologists in their daily routine practice have to deal with specimens where important parameters for reporting are missing. The neo-tAnGo trial revealed large variations in handling and reporting of post-NAST breast cancer specimens [11].

The results of the clinical practice questionnaire showed similar results; only 70% of the participants attend the breast cancer MDT, 82.7% of them receive properly labelled specimens and even less receive specimens where markers are identified and the degree of clinical/radiological response is mentioned, whereas with the Delphi process there was consensus that the histological evaluation requesting form should contain information such as whether or not the specimen is a post-NAST one, number and size of the tumour/s before treatment, the existence/types of markers, nodal status before treatment, characteristics of the primary tumour (type, HG, ER, PR, HER2, Ki67) and

Table 2 Clinical practice questionnaire. The total number of participants was 174, not all participants answered all questions

Question	Responses (%)	N
Participation in multidisciplinary breast cancer meeting by the participant or any other pathologist from the team (yes)	70.7	174
<i>Regarding the information provided in post-NAST surgical specimens</i>		
Specimens are properly marked as post-NAST (yes)	82.7	168
<i>Information accompanying the post-NAST surgical specimens</i>		
Tumour location and size before treatment (yes)	78.8	170
Radiological clips are identified (yes)	74.3	167
Degree of clinical and radiological response (yes)	64.9	168
Information regarding about tumour features before treatment (type and histological grade, ER, PR, HER2, Ki-67) (yes)	88.4	172
<i>Regarding the evaluation of the axilla and sentinel lymph node</i>		
Routine evaluation of axilla at the time of diagnosis (with sentinel lymph node biopsy in uncertain cases)	97.6	163
Routine sentinel lymph node biopsy in NAST patients		143
Pre-NAST	44.8	
Post-NAST only in patients with negative lymph nodes at diagnosis	30.7	
Post-NAST for all patients regardless of lymph node status at diagnosis	17.5	
Pre- and Post-NAST	5.6	
Not done	2.1	
Method used to assess sentinel lymph node		162
Imprint cytology or frozen section intra-op	24.1	
OSNA method	42.6	
Post-surgery evaluation	33.3	
Familiar with the RCB system (YES)	59.9	167
<i>Regarding the evaluation of the specimens</i>		
Method used for quantification of the post-NAST response		174
Miller-Payne	62.6	
RCB	16.1	
Both	16.1	
Other	1.7	
None	3.5	
Definition of pCR		154
Absence of residual invasive cancer (with or without DCIS) and negative lymph node (ypT0/ypTis ypN0)	59.1	
Absence of residual invasive cancer (with or without DCIS) regardless of axillar lymph nodes (ypT0/ypTis)	16.9	
Complete absence of cancer in the breast (no invasive cancer nor DCIS) and negative lymph nodes (ypT0 N0)	19.5	
Complete absence of cancer in the breast (no invasive cancer nor DCIS) regardless of axillar lymph nodes (ypT0/ypTis)	4.6	
Analysis of biomarkers on surgical specimens after TNA		158
No, never	12.0	
Yes, usually	53.2	
Yes, sometimes	34.8	

the clinical/radiological response grade (breast, axilla) post-treatment.

Following the Delphi inquiry in the ensuing discussion among the participants, the consensual questionnaire and clinical practice questionnaire results were analysed.

During the pre-treatment assessment a percutaneous image-guided CNB is necessary to determine unequivocally the existence or not of invasion, histological type and grade of the tumour and the relevant biomarkers (ER, PR, HER2, Ki-67) [33] used to evaluate the necessity for NAST

[34]. Tumour size is usually estimated by clinical examination and radiological tests. At the same time, biopsies could be taken for research purposes [35] and most importantly clips should be placed to mark the site of the tumour which are extremely useful especially in those cases with pCR post-NAST [36].

Axillary status at diagnosis plays an important role in breast cancer patients when decisions regarding local or systemic treatment are taken. The consensus for the evaluation of the axilla during the diagnostic process was that axillary US should be performed to all breast cancer suspected patients that undergo CNB and in the case of suspicious lymph nodes detection, a biopsy (FNA or/and CNB) of them should be performed [37] with concomitant placement of a radiological marker into the biopsied node. This was in agreement with the current recommendations [17, 18] and the results of our consensual and clinical practice questionnaire.

Sentinel lymph node biopsy (SLNB) before NAST is not always indicated because an excision-biopsy of a positive sentinel lymph node might complicate the evaluation of nodal response to NAST and thus it invalidates the *yp* stage and the calculation of RCB. It should be reserved for cases where the pre-NAST axillary status is required for local or systemic treatment decisions [38]. In our survey the conclusions of the consensus questionnaire with reference to the SLNB were similar, whereas the results of the clinical practice ones were inconclusive (see the results section).

With regards to the handling and macroscopic and microscopic examination of the post-NAST breast cancer specimen the achieved recommendations' consensus (Table 1) was in the same lines with the recently internationally published guidelines [17, 18] taking into account that a post-NAST specimen has special features that are different from a non-NAST specimen [13]. The pathologic evaluation of the post-NAST specimen should be done keeping in mind that adequacy of surgery is achieved, prognostic factors are assessed and provisions were made for the collection of research specimens. Collection of research tissue should be done according to previously published guidelines [35].

The microscopic examination should give information regarding the type and the grade of the tumour, the extent and the cellularity of the tumour, the margins and the existence of lymphovascular invasion. Particular attention should be given to the estimation of cellularity as it can be profoundly affected by NAST. The effect of NAST on tumour cellularity can be heterogeneous. Several scoring systems for grading response are based on comparisons between pre- and post-NAST cellularity [13, 27, 39, 40] and frequently they can not deal with this heterogeneity which can be addressed by the RCB system, which does not use pre-treatment cellularity [26], is easily reproducible

[41], can be satisfactorily used in a prospective manner and contributes to the standardization of macroscopic and microscopic methods. It is worth noting the results of the clinical practice questionnaire with regards to the RCB system; although 59.8% of the participants were familiar with it, only for 16.1% was the method of choice in assessing cellularity and 16.1% were using it in combination with the Miller-Payne system.

Post-NAST axillary nodal status is an important predictor of survival independently of breast response [10, 28, 42–44], however the value of SNLB post-NAST is still under a lot of investigation [38, 45]. Various parameters predict worse survival: the number of affected nodes, the size of the largest metastasis and the existence of micro-metastasis and isolated tumour cells (ITCs). The presence of ITCs (*pN0i+*) precludes pCR. The current recommendation in clinical trials [17, 18] is to use a technique that allows the assessment of treatment response and the measurement of the diameter of the metastases (as this measure is used to calculate RCB). Currently in Spain there are trials to assess the validity of the one step nucleic acid amplification (OSNA, Sysmex, Kobe, Japan) in the assessment of SLN post-NAST.

The issue of testing for biomarkers in residual invasive breast cancer specimen post-NAST remains controversial [46]. In our survey, there was consensus that it should be assessed when the pre-NAST CNB is inconclusive or negative, in non-responding to NAST tumours and in heterogeneous or multifocal ones. Of interest is the result of our clinical practice survey, where 53.2% stated that biomarkers are checked routinely in the post-NAST specimen. Special attention should be given in the determination of Ki67 expression, which correlates well with long-term outcome [47] and although the analytical reproducibility of Ki67 measurements is of concern [48], it is used frequently for basic risk assessment and is part of some post-NAST multivariate prediction models [49].

Pathologic complete response is defined by the absence of residual invasive cancer not only in the totally resected breast surgical specimen but also in all of the sampled lymph nodes following the completion of NAST as well (the presence of cancer solely in situ is classified as pCR): either *ypT0/isypN0* or *ypT0ypN0* [50]. However, the significance of residual carcinoma in situ remains controversial as it is shown in various studies [19, 51]. In our clinical practice questionnaire 76% responded correctly with regards to the US FDA pCR definition.

As for other consensus approaches, vocal members in the panel could influence decisions; in our study, rating was anonymous and took place before an expert debate. For the clinical questionnaire, results were not only collected from the interactive meeting attended by experienced pathologist, but also from several training sessions; results from

the interactive meeting and training sessions were similar regarding clinical practice.

In conclusion, without a doubt pathologists are playing a fundamental role in the management of post-NAST breast cancer. As the histological changes of post-NAST breast cancer specimens become even more complex, it is clear that pathologists have a demanding task to standardize handling and analysis of breast cancer specimens to enable the usage of pCR as an indicator to novel therapies. Our survey shows that pathologists in Spain follow the same guidelines with their international colleagues and face the same problems and controversies as well. The way forward is active participation to the breast cancer multidisciplinary teams, optimal usage of CNB for timely and standardized procedures for the diagnostic analysis (type, histological grade and biomarkers) of the breast cancer specimen and finally accurate diagnosis of pCR and complete evaluation of the response to NAST.

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Compliance with ethical standards

Conflict of interest J. Francisco García is an employee of Roche Farma Spain, all other authors declare no conflict of interest.

Ethical statement The study has been performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent statement Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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