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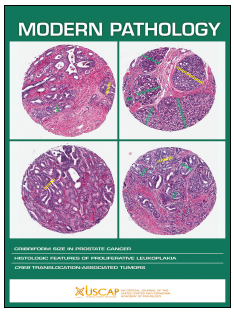

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A Worldwide Survey on Pathological Measurement of Residual Breast Cancer After Neoadjuvant Therapy: Different Interpretations of the ypTNM Classification

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Abstract

The extent of residual disease after neoadjuvant chemotherapy (NAC) in breast cancer (BC) patients holds prognostic value. However, current practices for reporting post-NAC BC specimens according to the ypTNM classification vary. This study aimed to map these practices and provide recommendations for standardization. A survey was developed and globally circulated to pathologists with a special interest in BC through personal networks and working group mailing lists. The survey included general questions about tumor diameter assessment, as well as graphical scenarios presenting different distributions of tumor cells. We did not provide definitions mentioned in reporting guidelines to capture unbiased current real-world practices. A total of 208 pathologists from 35 countries completed the survey. Almost all responding pathologists (97.1%) report the ypTNM in daily practice. Despite self-reported strict adherence to the 8th edition of the international ypTNM classification, we found substantial variation in practice concerning the application of this staging system, particularly in cases with an uneven distribution of scattered residual disease. Notably, 57.2% of respondents reported measuring the largest 'continuous cluster of tumor cells', but the interpretation of this definition varied widely. This international survey identifies the challenges and the practice heterogeneity in the current application of the ypTNM staging system, which hampers the value of ypTNM reporting in daily practice. To enhance reproducibility and to provide more reliable post-NAC risk stratification, we recommend adopting standardized reporting with clearer pattern-based definitions of the ypTNM guidelines, supplemented with the elements of the Residual Cancer Burden system.

Keywords: breast cancer; neoadjuvant chemotherapy; pathology; pTNM classification; residual disease; residual cancer burden

Introduction

Neoadjuvant chemotherapy (NAC) allows monitoring of treatment response in breast cancer (BC) patients as well as the potential for breast conserving surgery in some patients. Residual disease is often considered a dichotomous outcome, distinguishing between pathological complete response (pCR) or no pCR. Achieving a pCR is a strong predictor of improved survival outcomes,[1-4] and guides post-NAC therapy approaches.[5, 6] Furthermore, several studies have also reported that the extent of residual disease after NAC significantly correlates with prognosis, which highlights the relevance of quantifying residual disease.[7-9] The KEYNOTE-522 trial revealed that the benefit from adjuvant pembrolizumab in triple-negative BC varied significantly with the amount of residual disease.[10] These findings emphasize that moving beyond the distinction between pCR and no pCR is necessary for refining risk-stratification and enabling more personalized treatment strategies.

Currently, several systems exist to quantify residual disease post-NAC, with the tumor-node-metastasis (ypTNM) staging system, adapted from the pretreatment clinical (c)TNM staging framework, and the Residual Cancer Burden (RCB) index being commonly employed. The pathologist plays a central role in quantifying the amount of residual tumor in the breast (ypT) and lymph nodes (ypN), while the M stage is usually determined clinically and on imaging. The ypTNM is recommended by both the Union for International Cancer Control (UICC)[11] and the American Joint Committee on Cancer (AJCC)[12]. The post-NAC diameter of the residual primary tumor (ypT), in both the 8th edition of the ypTNM of the AJCC and the UICC, requires measurement of the largest contiguous focus of residual tumor as post-NAC diameter (Figure 1A).[11, 12] The AJCC definition further specifies a cluster as a group of tumor cells without intervening fibrosis.

In contrast, the RCB determines residual tumor size based on the two greatest dimensions of the residual invasive tumor area, including intervening stroma (Figure 1B). The RCB score combines these tumor dimensions with the cellularity across the entire tumor area, the number of positive lymph nodes and the size of the largest regional lymph node metastasis.[7]

The International Collaboration on Cancer Reporting (ICCR) recommends reporting both the ypTNM and the RCB.[13] However, the ICCR recommends taking the growth pattern of the BC into account when determining what to consider the largest continuous focus for ypTNM staging and further distinguishes between even and uneven tumor distribution. If residual invasive carcinoma cells are evenly distributed over a fibrotic area, the ICCR prefers to consider this as a single focus.[13] If the distribution of residual invasive carcinoma cells is more uneven, the ICCR considers these as separate foci and recommends measuring the largest.

In tumors showing a scattered response pattern to NAC, the measurement of the largest contiguous focus of residual invasive carcinoma according to the ypTNM becomes challenging. Such scattered response patterns are frequently observed in luminal BC subtypes, whereas concentric shrinkage patterns are more common in triple-negative breast cancer (TNBC).[14, 15] Scattered versus concentric patterns were shown to carry prognostic significance in TNBC.[16] The variability in ypTNM assessment can compromise the reliability of risk stratification and response monitoring in the post-NAC setting, potentially leading to inconsistent and suboptimal adjuvant therapy decisions.

The aim of this study is therefore to map the current practices of post-NAC BC specimen reporting according to the ypTNM and provide recommendations for the standardization of post-NAC breast resection specimen assessment.

Materials and methods

Survey development and circulation

The study design is outlined in Figure 2. The survey was implemented in CastorEDC and pilot-tested by its developers and the central pathologist group. Subsequently, the questionnaire was globally distributed to pathologists with a special interest in BC through personal networks and working group mailing lists from February 4, 2025, until April 27, 2025. Participation was voluntary and anonymous. Respondents could optionally provide an email address to receive the study results after publication.

The questionnaire (Supplementary File 1) included general questions regarding the processing and staging of primary tumor resection specimens and resected lymph nodes, as well as graphical scenarios. In these schematic scenarios, participants indicated how they would measure residual disease diameter in different distributions of tumor cells or clusters. We did not provide information about any of the reporting guidelines, to capture personal definitions in daily practice. The questions concerning the intervening stroma used the values of 1 mm (an empirical value based on a previous report by Harter et al.[17]) and 5 mm (based on the College of American Pathologists (CAP) guideline, UK standards and ICCR for reporting of primary breast cancer[18-20]).

Data analysis

We screened the list of collected email-addresses for duplicates and analyzed the similarity of the given answers to identify duplicate responses. The data were analyzed using the Pandas package (Python 3.12). As all continuous variables showed non-parametrical distribution (through the Shapiro-Wilk test), results are reported as

median and interquartile range (IQR). Categorical variables are reported as absolute frequencies and their corresponding percentages.

Results

Characteristics of respondents

We received a total of 208 unique fully completed responses from 35 different countries, including those from the central pathologist group (n=19). Based on the number of times that the Castor link was used, and the approximate number of emails circulated, we estimate the response rate to be around 20%. Most responses were received from the United Kingdom (19.2%), followed by the United States of America (13.9%) and The Netherlands (12.0%). The geographical distribution of the received responses is provided in Supplementary Table S1. Of the respondents, 59.6% worked in academic hospitals. Respondents had a median of 15 years of professional experience (IQR: 9-25). The median number of annually examined breast specimens was 200 (IQR: 100-400) with a median of 50 post-NAC specimens (IQR: 25-100).

Post-NAC specimen handling

While markers are used in 78.8% of surgical specimens, only 28.4% of respondents use x-ray imaging to perform targeted sampling.

Pathological assessment of lymph nodes varies by node type: sentinel lymph nodes (SLNs), nodes marked with radioactive iodine (MARI, a potential SLN, that is marked with a radioactive iodine seed before neoadjuvant chemotherapy), and non-sentinel nodes (NSLNs).

For SLNs, sectioning practices are diverse. Most responding pathologists (59.1%) prepare multiple H&E sections whilst 36.6% assess only a single H&E section. 43.3% of respondents routinely include cytokeratin immunostaining in their panel.

MARI nodes are processed similarly: nearly half (49.1%) undergo multiple sectioning and one-third (33.7%) are processed with a single H&E section. Among responding pathologists, 40.4% routinely include cytokeratin staining on MARI nodes.

NSLNs receive the most conservative approach, with most respondents (69.2%) using a single H&E section and 25.5% using multiple H&E sections. Only 16.3% use immunohistochemistry (IHC) routinely, in addition to either a single or multiple H&E sections. IHC represented at least one slide for immunohistochemical analysis, as it was not specified whether respondents used IHC on multiple levels.

Application and reproducibility of ypTNM staging

Almost all respondents (202/208, 97.1%) report the ypTNM in daily practice (Figure 3A) and 72.6% also report the RCB. All respondents who report the RCB also report the ypTNM. 48.3% follow the AJCC version, 39.4% the UICC version and 12.3% were unsure (Figure 3B). Respondents from North America almost exclusively adhered to the AJCC version (97.1%), while 30.7% of European respondents adhere to UICC, and 53.6% to AJCC.

Respondents found lymph node assessment (ypN) to be more reproducible than breast tumor assessment (ypT); 53.8% reported reproducible measurements in lymph nodes versus 46.6% in breast tissue. This was further reflected in the difficulty scores (scale 1-10, where a score of 1 indicates ‘not difficult at all’ and a score of 10 ‘very difficult’), which were 5 (IQR: 3-7) for ypT, and 3 (1.25-6) for ypN (Figure 3C). Those who did not find the ypT reproducible indicated the need for a clear definition of a tumor

cluster (80.2%) or provided a free-text answer. Recommendations centered on: 1) clarifying the handling of multiple tumor clusters within a single tumor bed, including the role of intervening stroma/fibrosis; 2) harmonizing the measurement approach with the RCB methodology, which incorporates tumor cellularity across the full tumor bed, rather than solely relying on maximum diameter; and 3) providing standardized guidelines and schematic examples to improve variation in individual practices. In the lymph node, these recommendations focused on: 1) harmonizing ypN assessment with RCB methodology, specifically regarding the inclusion of intervening fibrosis when measuring residual tumor extent within lymph nodes; 2) clarifying the definition of tumor clusters and incorporating cellularity into the assessment.

The use of the 'm' (multiple) modifier for the ypT was inconsistent: 42.3% apply it when multiple residual tumor foci are observed after NAC, regardless of the pre-NAC imaging, 34.6% if there are multiple tumors on imaging pre-NAC, 21.2% never use the 'm' modifier and 1.9% use it when there is one tumor before NAC with multiple residual tumor foci identified post-NAC.

Finally, most participants reported that they commented on tumor bed and marker clip reactions in their pathology reports (82.2%) and almost all participants (93.3%) requested the formulation of a standardized post-NAC reporting template.

Definitions of the extent of residual disease used in daily practice

Most respondents reported strict adherence to the 8th edition of the ypT in breast specimens and ypN in lymph nodes (both 84.6%) in daily practice. Responders who do not strictly adhere to the ypTNM reported that this was mainly because of both an unclear definition of a tumor cell cluster, as well as the concern of underestimating the extent of residual tumor. While the substantial majority reported strict adherence to the

ypTNM, inconsistencies became apparent in the follow-up questions. For instance, although the 8th edition of the TNM emphasizes measuring the 'largest contiguous focus', a significant percentage (35.1%) of pathologists measure the post-NAC diameter in breast specimens as the complete tumor area, including all intervening stroma. Moreover, while 57.2% stated that they use the largest continuous cluster of tumor cells, the definitions of a cluster varied (Table 1). For both breast and lymph nodes, most respondents define a continuous cluster as 'Tumor cell clusters with a limited amount of intervening stroma, irrespective of signs of regression (52.4% and 44.2%, respectively). When specifying limited stroma, 51.4% used two criteria, depending on the distribution of the tumor cells: 1) in tumors with an even distribution of tumor cells in a fibrotic area, measure this as one focus and 2) in tumors with an uneven distribution of tumor cells, measure these as separate continuous foci and use the largest focus for ypTNM staging system.

Assessment of residual disease in graphical scenarios

After the questions about definitions and practices, pathologists were asked to define the diameter of residual disease in scenarios with an even distribution or with an uneven distributions of tumor cells or tumor cell clusters on both a background of normal breast tissue and reactive stroma.

Even distribution of residual disease

In graphical scenarios with an even distribution of tumor cells, respondents predominantly chose to define the full diameter of the residual disease as the ypT, irrespective of the background (89.9%; Figure 4A versus 89.4%; Figure 4B). In the case of an even distribution of tumor cell clusters, again, the maximum extent was predominantly used to determine the diameter (76.0% and 75.5% in normal breast

(Figure 4C) and reactive stroma (Figure 4D), respectively). The diameter of the largest cluster of touching cells was used by 24.0% and 21.2% of respondents (for normal breast tissue and reactive stroma, respectively).

Uneven distribution of residual disease

In scenarios with an uneven distribution, the measurement preference shifted from the diameter of the largest focus to the overall maximum tumor extent as the tumor density increased (Figure 5). This pattern was present regardless of the background. For example, with tumor cell clusters in normal breast tissue, preference for measuring maximum extent increased from 30.3% in the sparsely distributed scenario to 77.9% in the densest configuration (Figure 5C).

Discussion

This large world-wide survey aimed to map current practices and challenges in reporting post-NAC breast and lymph node specimens using the ypTNM staging system. Based on input from 208 pathologists across 35 countries, we confirm that while the ypTNM system is widely used (97.1% of respondents), reproducibility is limited, particularly for primary tumor (ypT) assessment, due to the lack of clear, standardized definitions, especially regarding the handling of cases with an uneven distribution of scattered tumor cells or clusters.

Systematic sampling is crucial for accurate post-NAC pathological assessment. However, only 28.4% of the responding pathologists use radiological imaging to guide targeted sampling, and 21.2% report that no marker is used by their clinical team to identify the tumor bed, potentially risking missing residual disease in near complete or complete responders to NAC.

Assessment of ypN was considered more reproducible than ypT, likely reflecting pathologists' familiarity with the measurement of scattered nodal metastases in the non-NAC setting, already defined as isolated tumor cells, micro- and macrometastases. The processing of lymph nodes varies widely. While the AJCC acknowledges that multiple sectioning with H&E levels in combination with IHC will identify additional tumor deposits,[12] the clinical significance of such occult metastases remains unclear.[21, 22] The UK Royal College of Pathologists Reporting and the CAP guidelines recommend bread-slicing lymph nodes at 1-2mm intervals and examining a single H&E section.[18, 19] Further levels and cytokeratin IHC are performed on selected cases at the discretion of the reporting pathologist. The guidelines support that ITCs following NAC represent chemotherapy-resistant residual disease and are therefore more significant than in the non-NAC setting.[23] The variability in both breast and lymph node processing may contribute to inconsistent detection of minimal residual disease, however, standardized protocols should balance diagnostic yield and clinical relevance.

Measurement approaches varied considerably: 35.1% of pathologist respondents measure the complete area including intervening stroma, while 57.2% measure the 'largest continuous cluster' of tumor cells. Furthermore, the definition of 'continuous cluster' lacks consensus. Graphical scenarios revealed additional complexity: responding pathologists consistently measured maximum spread for *evenly* distributed residual disease but showed substantial inter-observer variation for *uneven* distributions. This variation highlights the need for clearer definitions. The definition of 'continuous cluster' with the least interobserver variation is likely "cells that are touching one another", in line with the definition used to distinguish between isolated tumor cells and micrometastatic disease in the non-NAC setting. However, since most untreated

invasive cancers already have some stroma between the tumor cells, this definition is unlikely to accurately reflect the prognosis. The current AJCC version and the upcoming 9th edition of the UICC ypTNM also defines the largest continuous focus of residual cancer without treatment-related fibrosis. It should be highlighted that the distinction between normal stroma and treatment-related fibrosis is often not well defined and varies between tumors.

To determine the largest tumor diameter according to ypTNM, we suggest a pattern-based approach. An even distribution should be defined as relatively uniform scattering of tumor cells with consistent spacing, while uneven distribution shows clustering in certain areas with variable spacing. For the evenly scattered patterns, measure the full extent of the tumor encompassing all tumor clusters. For uneven patterns, define the largest concentration of residual cancer that includes intervening stroma, in line with the ICCR approach.[13] Finally, when presented with multiple residual tumor foci following NAC, we recommend using the 'm' modifier, regardless of whether pre-treatment findings showed multiple tumor foci or a single tumor. This is in line with the current ypTNM guideline.[24] The variety in the use of the 'm' post-NAC, as shown in this survey, suggest that this point should be further clarified in the next version of the ypTNM.

Pathologists recognize that measuring only the largest contiguous focus in scattered disease patterns may underestimate total residual burden.[25] Harter et al. confirmed this concern, showing that strict adherence to the 8th edition of the AJCC guidelines resulted in smaller tumor sizes and lower ypT categories compared to routine practice.[17]

Most (93.3%) respondents indicated the need for a standardized reporting template, suggesting that current templates need to be improved. We therefore recommend the

standardized dual reporting of both the ypTNM and the RCB, including the separate elements of the RCB system: full tumor size in two dimensions, estimated overall residual cancer cellularity, number of positive lymph nodes and size of largest metastasis.[7] This approach is increasingly supported by international guidelines (ICCR and the 9th edition of the TNM classification[13, 24]) and The Breast International Group-North American Breast Cancer Group (BIG-NABCG).[26, 27] This standardized data collection would also facilitate research into subtype-specific element weighting, validation of the RCB components for neoadjuvant treatments other than chemotherapy (e.g. endocrine or immunotherapy) and integration with other biomarkers, such as Ki-67 and the number of tumor-infiltrating lymphocytes to further refine risk-stratification for BC patients with residual disease.[28-30] In future versions of the ypTNM, clearer definitions, potentially using a pattern-based approach with illustrated examples are required to decrease the current degree of inter-observer variability. We expect good correlation between the ypTNM values and the RCB values in tumors with a concentric shrinkage response pattern. In cases with a fragmented shrinkage (scatter) pattern, the values are likely to show greater variation. We believe that standardized reporting of both systems will be complementary in determining prognosis. The full set of values may be used in a prognostic model.

Our large international survey-based study provides a valuable overview of real-world practice. Inherent to all survey-based research, this study also has some limitations. Firstly, the findings may be influenced by non-response bias. Secondly, a response bias may be present, as respondents might provide desirable answers, rather than reflecting their actual practice. Furthermore, more than half of the respondents work in academic hospitals, where practices might be different to non-academic hospitals. While achieving broad international reach, countries in Asia, Africa and South America

were underrepresented. Finally, we chose to avoid an overly lengthy questionnaire by including the even and uneven distributions separately, in order to establish an understanding of how pathologists interpret these distinct scenarios. This may not have fully captured the real-world complexity of assessing resection specimens. Future research should focus on the clinical implications of the different interpretations of the ypTNM classification. We acknowledge that even with the proposed definitions, some interobserver variation will remain, although illustrated examples of even and uneven distributions will likely enhance the reproducibility. Further, the use of digital pathology supported by image processing or artificial intelligence algorithms, may support the pathologist by objectively delineating the extent of the tumor area, identifying tumor clusters and determining cellularity.

In conclusion, this international survey highlights substantial practice heterogeneity in the application of the 8th edition of the ypTNM staging system, which limits its value, particularly in cases with an uneven distribution of scattered residual disease. To enhance reproducibility and to provide more reliable post-NAC risk stratification, we recommend the adoption of standardized dual reporting of the complete ypTNM and RCB system. This approach leverages the strengths of both methods and should be accompanied by clearer pattern-based definitions within the ypTNM guidelines.

Author contributions

Conceptualization: CHMVD

Methodology: CHMVD, MRVB, AS

Formal analysis: KK

Investigation: CHMVD, KK

Data Curation: KK, CHMVD

Writing - Original Draft: KK, CHMVD

Writing - Review & Editing: CHMVD, MRVB, AS, EB, GC, IOE, MPF, SBF, ZBH, AJ, SJ, SEP, EP, CMQ, EAR, WAR, PHT, GMT, ZV and HYW

Visualization: KK, CHMVD

Supervision: CHMVD

Data Availability Statement

The dataset generated during the current study are not publicly available due to the inclusion of anonymized professional practice data from individual respondents but are available from the corresponding author upon reasonable request.

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Declaration of Competing Interest

ZBH reports lecture honoraria and advisory boards from MSD, Abbvie, Gilead, Stemline and Daiichi Sankyo. SJ is consultant for Astra Zeneca and Daiichi Sankyo. All other authors have no relevant disclosures to make related to this paper.

Ethics Approval and Consent to Participate

Research ethics approval was not applicable as no patients were involved. The questionnaire only collected professional opinions and practices without gathering sensitive personal information.

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References

1. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014;384(9938):164-172. https://doi.org/10.1016/s0140-6736(13)62422-8.

2. Mackelenbergh MTv, Loibl S, Untch M, et al. Pathologic Complete Response and Individual Patient Prognosis After Neoadjuvant Chemotherapy Plus Anti–Human Epidermal Growth Factor Receptor 2 Therapy of Human Epidermal Growth Factor Receptor 2–Positive Early Breast Cancer. *Journal of Clinical Oncology.* 2023;41(16):2998-3008. https://doi.org/10.1200/jco.22.02241.

3. Spring LM, Fell G, Arfe A, et al. Pathologic Complete Response after Neoadjuvant Chemotherapy and Impact on Breast Cancer Recurrence and Survival: A Comprehensive Meta-analysis. *Clin Cancer Res.* 2020;26(12):2838-2848. https://doi.org/10.1158/1078-0432.Ccr-19-3492.

4. Yee D, DeMichele AM, Yau C, et al. Association of Event-Free and Distant Recurrence-Free Survival With Individual-Level Pathologic Complete Response in Neoadjuvant Treatment of Stages 2 and 3 Breast Cancer: Three-Year Follow-up Analysis for the I-SPY2 Adaptively Randomized Clinical Trial. *JAMA Oncol.* 2020;6(9):1355-1362. https://doi.org/10.1001/jamaoncol.2020.2535.

5. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. *N Engl J Med.* 2017;376(22):2147-2159. https://doi.org/10.1056/NEJMoa1612645.

6. Geyer CE, Jr., Untch M, Huang CS, et al. Survival with Trastuzumab Emtansine in Residual HER2-Positive Breast Cancer. *N Engl J Med.* 2025;392(3):249-257. https://doi.org/10.1056/NEJMoa2406070.

7. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol.* 2007;25(28):4414-4422. https://doi.org/10.1200/jco.2007.10.6823.

8. Yau C, Osdoit M, van der Noordaa M, et al. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. *The Lancet Oncology.* 2022;23(1):149-160. https://doi.org/10.1016/S1470-2045(21)00589-1.

9. Park H, Kim H, Park W, et al. Oncological outcomes in patients with residual triple-negative breast cancer after preoperative chemotherapy. *Radiat Oncol J.* 2024;42(3):210-217. https://doi.org/10.3857/roj.2024.00087.

10. Pusztai L, Denkert C, O'Shaughnessy J, et al. Event-free survival by residual cancer burden with pembrolizumab in early-stage TNBC: exploratory analysis from KEYNOTE-522. *Annals of Oncology.* 2024;35(5):429-436. https://doi.org/10.1016/j.annonc.2024.02.002.

11. Brierley JD, Gospodarowicz MK, Wittekind C. *TNM classification of malignant tumours.* 8 ed: John Wiley & Sons; 2017.

12. Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual.* 8 ed: Springer; 2017.

13. Bossuyt V, Provenzano E, Symmans WF, et al. A dedicated structured data set for reporting of invasive carcinoma of the breast in the setting of neoadjuvant therapy: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Histopathology.* 2024;84(7):1111-1129. https://doi.org/10.1111/his.15165.

14. Wang M, Du S, Gao S, et al. MRI-based tumor shrinkage patterns after early neoadjuvant therapy in breast cancer: correlation with molecular subtypes and pathological response after therapy. *Breast Cancer Res.* 2024;26(1):26. https://doi.org/10.1186/s13058-024-01781-1.

15. Pastorello RG, Laws A, Grossmith S, et al. Clinico-pathologic predictors of patterns of residual disease following neoadjuvant chemotherapy for breast cancer. *Mod Pathol.* 2021;34(5):875-882. https://doi.org/10.1038/s41379-020-00714-5.

16. Laws A, Pastorello R, Dey T, et al. Impact of the Histologic Pattern of Residual Tumor After Neoadjuvant Chemotherapy on Recurrence and Survival in Stage I-III Breast Cancer. *Ann Surg Oncol.* 2022;29(12):7726-7736. https://doi.org/10.1245/s10434-022-12054-6.

17. Harter D, O'Connor SM, Hertel JD, Calhoun BC. Pathological measurement and staging of residual breast cancer after neoadjuvant chemotherapy. *Histopathology.* 2023;83(3):453-464. https://doi.org/10.1111/his.14966.

18. College of American Pathologists *Protocol for the Examination of Resection Specimens from Patients with Invasive Carcinoma of the Breast* 2024.

19. The Royal College of Pathologists *Dataset for histopathological reporting of breast disease in surgical excision specimens of breast cancer*2024.

20. Ellis I, Webster F, Allison KH, et al. Dataset for reporting of the invasive carcinoma of the breast: recommendations from the International Collaboration on Cancer Reporting (ICCR). *Histopathology.* 2024;85(3):418-436. https://doi.org/10.1111/his.15191.

21. Loya A, Guray M, Hennessy BT, et al. Prognostic significance of occult axillary lymph node metastases after chemotherapy-induced pathologic complete response of cytologically proven axillary lymph node metastases from breast cancer. *Cancer.* 2009;115(8):1605-1612. https://doi.org/https://doi.org/10.1002/cncr.24173.

22. Ai D, Arrey EN, Postlewait LM, Gao Y, Li X. The prevalence and clinical significance of residual occult breast cancer after neoadjuvant chemotherapy: reassessing surgical pathology in cases initially described as pathological complete response. *Histopathology.* 2025;86(7):1112-1120. https://doi.org/10.1111/his.15417.

23. Wong SM, Almana N, Choi J, et al. Prognostic Significance of Residual Axillary Nodal Micrometastases and Isolated Tumor Cells After Neoadjuvant Chemotherapy for Breast Cancer. *Ann Surg Oncol.* 2019;26(11):3502-3509. https://doi.org/10.1245/s10434-019-07517-2.

24. Brierley JD, Giuliani M, O'Sullivan B, Rous B, Van Eycken E. *TNM classification of malignant tumours.* 9 ed: Wiley; 2025.

25. Naidoo K, Pinder SE. The importance of histological assessment after neoadjuvant therapy and the need for standardisation. *Clinical Radiology.* 2018;73(8):693-699. https://doi.org/10.1016/j.crad.2018.01.005.

26. Bossuyt V, Provenzano E, Symmans WF, et al. Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical

trials of breast cancer by the BIG-NABCG collaboration. *Ann Oncol.* 2015;26(7):1280-1291. https://doi.org/10.1093/annonc/mdv161.

27. Provenzano E, Bossuyt V, Viale G, et al. Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. *Mod Pathol.* 2015;28(9):1185-1201. https://doi.org/10.1038/modpathol.2015.74.

28. Kim JY, Oh JM, Lee SK, et al. Improved Prediction of Survival Outcomes Using Residual Cancer Burden in Combination With Ki-67 in Breast Cancer Patients Underwent Neoadjuvant Chemotherapy. *Front Oncol.* 2022;12:903372. https://doi.org/10.3389/fonc.2022.903372.

29. Campbell JI, Yau C, Krass P, et al. Comparison of residual cancer burden, American Joint Committee on Cancer staging and pathologic complete response in breast cancer after neoadjuvant chemotherapy: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). *Breast Cancer Res Treat.* 2017;165(1):181-191. https://doi.org/10.1007/s10549-017-4303-8.

30. Sejben A, Hegedűs F, Almási S, Berta M, Oláh-Németh O, Zombori T. Good practice: The experiences with the utilization of residual cancer burden-A single institution study. *Thorac Cancer.* 2023;14(11):963-968. https://doi.org/10.1111/1759-7714.14826.

Figure 1: Definitions of residual tumor as used by the Union for International Cancer Control (UICC), the American Joint Committee on Cancer (AJCC) and the residual cancer burden (RCB). Both the AJCC and UICC use the largest contiguous cluster of residual tumor, in one dimension (diameter A). The RCB uses two dimensions of the total extent, including intervening stroma (B).

Figure 2: Study overview showing survey development involving feedback from a central panel of 19 pathologists. After finalization, both the personal networks of the central pathologists, as well as national working group mailing lists were used to facilitate worldwide distribution.

Figure 3: Pathologists responses on post- neoadjuvant chemotherapy (post-NAC) staging systems and measurement reproducibility. A: Post-NAC reporting systems used in clinical practice; B: TNM version used by respondents. Within the bars, the geographic region of the respondents are given; C: Difficulty scores for primary tumor and lymph node assessment, with scores ranging from 1 (least difficult) to 10 (most difficult).

Figure 4: Respondents determination of the residual tumor diameter with an even distribution of single tumor cells (A and B) and tumor cell clusters (C and D), in a background of normal breast (A and C) and reactive stroma (B and D). The scenarios in this figure relate to items 4.1 – 4.8 of the questionnaire (Supplementary File 1).

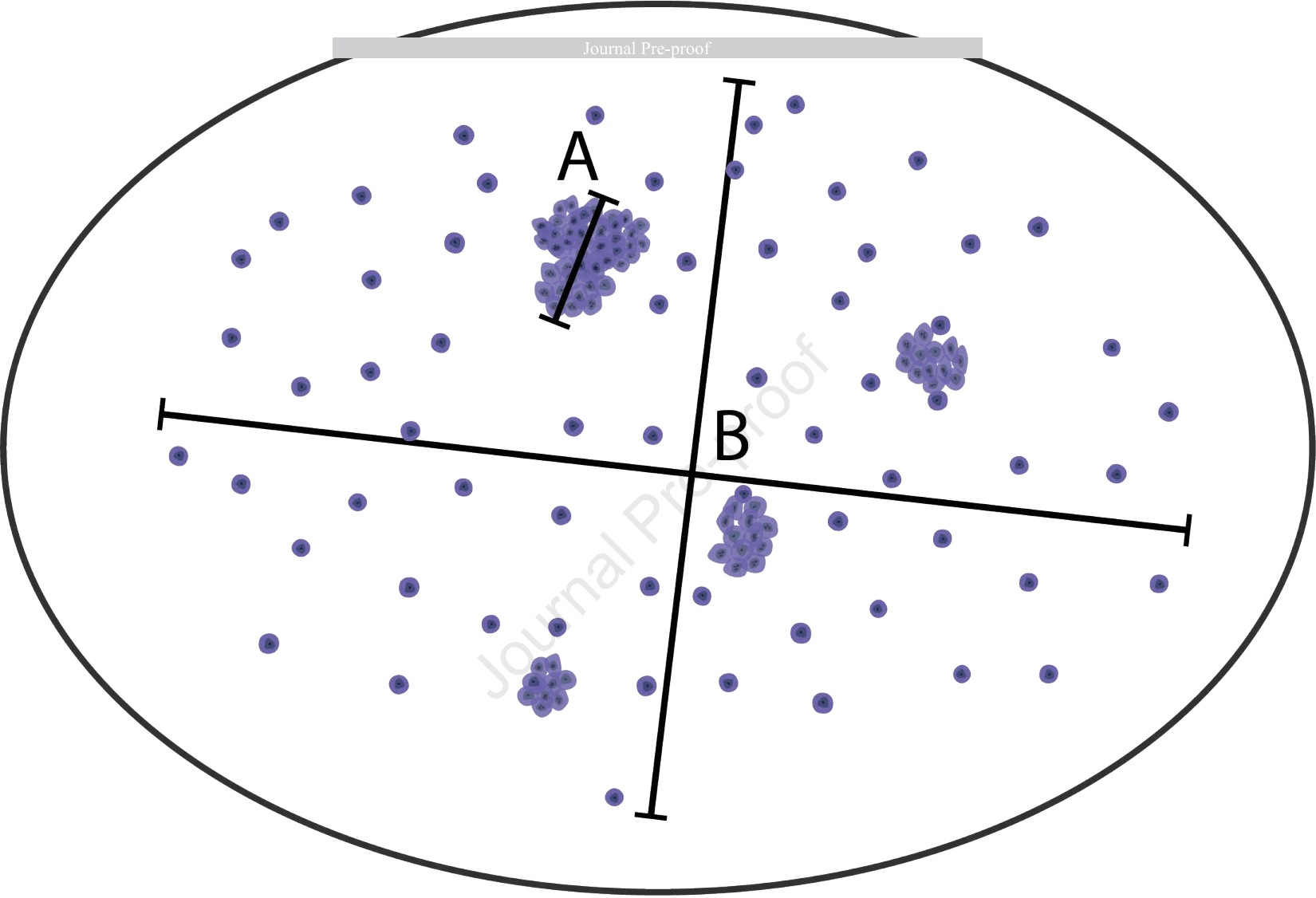
Figure 5: Respondents determination of the residual tumor diameter with an uneven distribution of single tumor cells (A and B) and tumor cell clusters (C and D), in a background of normal breast (A and C) and reactive stroma (B and D). Each case started with several separated tumor foci, with the second and third variation adding two quantities of intervening tumor. The flow charts show how individual respondents

changed their preferred diameter throughout the three scenarios. The percentages show the proportion of respondents selecting diameter D_1, D_2, D_3 or D_4. The scenarios depicted in this figure relate to items 4.9 – 4.32 of the questionnaire (Supplementary File S1).

Table 1: Definitions used regarding the ypTNM. The first rows present the method of measuring the diameter for the ypT. The question regarding continuous tumor cluster definition is then presented, followed by specifications for respondents who selected options involving 'limited amount of intervening stroma'. For those who defined limited stroma based on cell distribution, additional criteria specifications are shown. Percentages represent the proportion of respondents selecting each option for breast and lymph node assessments.

Definition/specification	**Breast**	**Lymph node**
Definition of diameter used for ypT		
Complete area, including all intervening stroma	35.1%	-
Largest continuous cluster of tumor cells	57.2%	-
Other	7.7%	-
Definition of a continuous tumor cluster		
Tumor cells that are touching each other	13.0%	17.8%
Tumor cell clusters with a limited amount of intervening stroma showing evidence of regression	12.0%	14.9%
Tumor cell clusters with a limited amount of intervening stroma, irrespective of signs of regression	52.4%	44.2%
Tumor cell clusters with all intervening stroma showing evidence of regression	9.1%	10.1%
Tumor cell clusters with all intervening stroma, irrespective of signs of regression	13.5%	13.0%
Specification of "Limited amount of intervening stroma"		

< 1 mm	22.4%	35.6%
< 5 mm	26.2%	8.9%
Depends on the distribution of cells	51.4%	55.6%
Specification of cell distribution		
In an uneven distribution, measure separate foci and use the largest	9.1%	16.0%
In an even distribution in a fibrotic area, measure this as one focus	10.9%	8.0%
Both options	80.0%	76.0%



A: largest contiguous tumor cluster
B: diameters of the total tumor extent