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Updated pan-tumor guidelines for neoadjuvant scoring of pathologic response: a joint SITC and INMC effort

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Abstract

Background: Practice-changing clinical trials for novel therapeutic regimens administered in the neoadjuvant setting have been reported for multiple cancer types, bringing this treatment strategy to the forefront for patients with high-risk surgically resectable disease. Previously, tumor-type- or therapy-type-specific scoring systems were used for pathologic response assessment. The goal of this effort is to update, harmonize, and standardize the emerging system(s) for pathologic response assessment and data capture.

Materials and methods: Leaders in pathology, oncology, and surgery, including those from the Society for Immunotherapy of Cancer’s Pan-tumor Harmonization of Pathologic Response Assessment (PATHdata) efforts and the International Neoadjuvant Melanoma Consortium (INMC), convened to develop updated consensus guidelines for pathologic response assessment, including specimen handling and tissue submission, scoring, and reporting. This paper builds upon previous recommendations, which are updated based on histologic features associated with patient outcomes. Specific attention was paid to commonalities across tumor types, as well as tumor-type-specific considerations.

Results: A revised and standardized approach to tissue submission is recommended, including total submission of tumors ≤ 3 cm in size for histologic analysis. Additional guidance is provided for larger tumors. Pathologic response is quantified through assessments of percentage of residual viable tumor (%RVT), necrosis, and regression. Descriptions of histologic features to be scored are provided together with a standardized reporting template. Recommendations regarding

collecting additional key datapoints are also made, to allow continued, extended validation of this pan-tumor approach.

Conclusions: As pathologic response emerges as a surrogate endpoint for long-term clinical outcomes and to help inform adaptive adjuvant therapy decisions in routine clinical care, standardization is critical to facilitate consistent and reliable application. This pan-tumor approach to scoring and reporting supports robust stratification of patient outcomes, facilitates comparisons across clinical trials and tumor types, enhances data collection, and establishes a foundation for identifying additional, clinically meaningful %RVT cut points.

Keywords

pathologic response; %RVT; pan-tumor; neoadjuvant; melanoma; guidelines

INTRODUCTION

There has been tremendous progress over the past few years in treating patients with high-risk surgically resectable cancers using neoadjuvant and perioperative regimens. Many of these novel regimens include anti-programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1)-based immune checkpoint blockade (ICB). Benefits to neoadjuvant treatment include more effective priming of the antitumor immune response leading to a significant survival benefit when compared with the adjuvant setting, shorter treatment courses, and modified or smaller surgeries.^{1–13} Regulatory approvals have been secured based on demonstrated improvement in event-free survival (EFS), with confirmatory overall survival benefits now being reported in some tumor types.^{13,14} Additional approvals are anticipated with increasing frequency, given the growing annual growth rates of neoadjuvant clinical trial initiation.¹⁵

Objective response rate (ORR) based on the standard, pan-cancer RECIST 1.1 criteria serves as a critical endpoint for drug development in the advanced-cancer setting, often correlated with time-based efficacy endpoints of progression-free and/or overall survival (OS).^{16,17} Importantly, radiographic measurements underestimate therapeutic response in the neoadjuvant setting.^{1,18,19} Pathology serves as the gold standard for determining the amount of residual viable tumor (RVT) following surgical resection. Accordingly, pathologic response is gaining traction as an emerging surrogate endpoint.

Since many novel regimens include ICB, new scoring systems were developed in 2018 for both lung cancer [immune-related pathologic response criteria (irPRC)]²⁰ and melanoma [International Neoadjuvant Melanoma Consortium (INMC) (Figure 1)]²¹ to ensure that pathologic features of immune-mediated tumor regression were also captured and to support harmonized pathologic response assessment across trials. The similarity between the features of regression in these two tumor types prompted a broader review of >10 solid tumor types treated with ICB-containing regimens, as well as those treated with chemotherapy, radiotherapy, and/or targeted therapies in the neoadjuvant or advanced disease setting, to ensure the relevant features were captured in the scoring system.²² Additionally, comparisons of histologic features between pre- and on-treatment specimens were carried out, and the correlation of these histologic features with molecular studies

of tumor cell reduction fraction was also carried out.^{20,23,24} Collectively, these findings informed and motivated the initial pan-tumor pathologic response scoring proposal in 2020.²² Notwithstanding, some neoadjuvant/perioperative clinical trials had either started before these systems were developed, elected to use legacy pathologic response scoring systems based largely on the chemotherapy experience, or proposed scoring systems using many of the same histologic features without highlighting similarities to other tumor types.^{25,26}

The proliferation of pathologic response scoring systems is similar to the heterogeneity of PD-L1 immunohistochemistry (IHC) scoring, which remains a worldwide issue positioned at the boundary of cancer therapeutics and pathology practice.^{27–29} Similar to PD-L1 IHC, there are sometimes multiple pathologic response scoring systems utilized within an individual tumor type.^{20,25,30} The mounting complexity may be a source of confusion for providers and patients, leading us to develop a guiding principle:

‘The theoretical additive value of more detailed, elaborate or disease-specific approaches to scoring will have to be clearly superior with regard to predicting survival outcomes to outweigh the benefits of an efficient, robust and effective pan-tumor system for RVT assessment.’²²

The initial pan-tumor recommendations have been used in small clinical trials, by larger cooperative group trials, and in phase II/III trials leading to regulatory approvals (see Figure 1 and Literature Review below). Now that these initial guidelines have been in use for 6–7 years, we provide key terms and definitions (Table 1) and clarifications, and address common questions that have arisen since the initial publications. Questions include how much of the tumor resection specimen should be submitted for histologic studies; which histologic features should be emphasized while scoring; defining thresholds for a clinically meaningful pathologic response; how to handle specimens that include both primary tumor and regional lymph nodes; and the applicability of these guidelines across different tumor types and drug regimens. Additionally, clinical outcome data have matured, allowing for data-informed revisions to the guidelines and supporting the convergence of multiple scoring systems, including the alignment of INMC with the pan-tumor proposal.

Purpose of this guideline

The purpose of this guideline is to provide a method for standardized, quantitative pathologic assessment and reporting of response to neoadjuvant therapy in solid tumors. A Society for Immunotherapy of Cancer (SITC)-sponsored international reproducibility study—Pan-Tumor Harmonization of Pathologic Response Assessment for Standardized Data Collection in Neoadjuvant Trials (PATHData)—which is published concurrently, showed that this updated, pan-tumor scoring system is highly reproducible across pathologists for assessing %RVT in primary tumors, lymph nodes, and distant metastases.³¹

This guideline includes updates to previously published recommendations (summarized in Figure 2).^{20–22} The accompanying manuscript provides details of the associated reproducibility study carried out using these new guidelines, as well as tutorials and extended resources to support implementation.³¹ While it is anticipated that these

criteria will be broadly deployed, we recognize that clinical trials may have additional, individualized tissue submission and reporting requirements.

Intended audience

The main target audience includes pathologists, medical oncologists, surgical oncologists, and other providers involved in routine clinical care, as well as investigators and related stakeholders designing clinical trials. These recommendations are also relevant for the cancer surveillance and registry communities, as well as invested regulatory and government officials. Implementation partners, including those leading training and budgeting, may also benefit.

MATERIALS AND METHODS

Literature review

To identify studies that used the first version of irPRC,²⁰ INMC,²¹ or pan-tumor guidelines,²² the ‘Cited by’ feature in both PubMed and Google Scholar was used to retrieve all articles that referenced these studies. Additional references were identified by querying PubMed using the search terms (‘Immune-related pathologic response criteria’) OR (‘irPRC’) OR (‘immune-related PRC’) from 1 August 2018 through 31 January 2025. Articles describing human studies published in English were reviewed by two independent reviewers (KYC and JSD), who assessed eligibility criteria. Studies met inclusion criteria if they cited these papers as the method used for pathologic response assessment. When studies with the same national clinical trial number were identified with overlapping participants, the study with the largest population with pathologic response assessment carried out was included. Standalone abstracts were excluded. The co-authors were also surveyed to determine if there were additional publications that were not revealed by the PubMed search.

Guideline development

The 2023 and 2024 Society for Immunotherapy of Cancer, Immunotherapy Bridge, International Neoadjuvant Melanoma Consortium, and INNOVATE (neoadjuvant immunotherapy across cancers) meetings convened pathologists and medical and surgical oncologists from academic centers in multiple countries. Participants were invited to join the working group based on their experience and expertise from clinical trials, clinical care administering neoadjuvant or perioperative therapies, or participation in the PATHdata study.

The working group subsequently communicated in person, and through teleconferences and written communications. This document represents the consensus opinion of the participants and serves as a companion to an accompanying effort reporting reproducibility of pathologic scoring across 12 different tumor types [bladder, breast, cervical, colorectal, cutaneous squamous cell, esophageal, head and neck squamous cell, hepatocellular, Merkel cell, non-small-cell lung (NSCLC), and renal cell carcinomas and melanoma] from patients receiving neoadjuvant treatment using a pan-tumor scoring system.³¹ Panel recommendations are based upon literature evidence, as well as practical clinical and pathology experience, and represent the consensus opinion.

RESULTS

Literature review

Forty-nine clinical studies including patients with 12 different solid tumor types were identified that utilized the pan-tumor or INMC pathologic response systems. Forty-four of these were neoadjuvant/perioperative studies, and three used these studies to score on-treatment biopsies in patients with advanced, metastatic disease (Supplementary Table S1, available at <https://doi.org/10.1016/j.annonc.2025.10.018>).^{4,5,7,10–12,23,32–71}

Clinical information provided to the pathologist with the surgical specimen

Specimen handling and reporting from patients treated in the neoadjuvant setting requires additional considerations beyond most current standard College of American Pathologists (CAP), Royal College of Pathologists (RCPath), and other standardized protocols.^{72–74} It is imperative that the pathology team be made aware that the patient received neoadjuvant systemic therapy at the time of pathology specimen handling and tissue submission.

Gross examination and specimen handling

Resection specimens from patients treated with neoadjuvant therapy may include the primary tumor ± regional lymph nodes, a lymphadenectomy specimen only (as in melanoma), or sometimes regional soft tissue deposits or distant metastases. The largest dimension of the tumor directs the amount of sampling for both the primary tumor and lymphadenectomy specimens (see description below and example in Figure 3). We provide a handout that the surgical team can provide the pathology team together with the specimen and/or post in the pathology suite for quick reference (see Supplementary Material S1, available at <https://doi.org/10.1016/j.annonc.2025.10.018>). Notably, patients enrolled in certain clinical trials may have different specimen handling and tissue submission specifications, including additional grossing requirements. In such instances, this guideline should be supplemented with trial-specific instructions.

- A. The specimen should be handled according to standard grossing and tissue submission protocols, e.g. CAP cancer protocols. This includes fixation requirements per tumor-specific grossing recommendations,⁷⁵ followed by requisite sections for the assessment of margin status, the submission of lymph nodes, assessment for potential extranodal extension, and other parameters that support standard American Joint Committee on Cancer (AJCC) classification and staging [i.e. ypTNM (tumor–node–metastasis)].⁷⁶ The specimen should be sectioned to identify the tumor/tumor bed. Lesions should be measured and recorded in three dimensions. Whenever possible, photography or a sketch of the gross specimen is recommended to facilitate mapping tissue submission (Supplementary Material S1, available at <https://doi.org/10.1016/j.annonc.2025.10.018>).
- B. After tissue handling per routine pathology staging protocols, additional tissue submission should be performed as described below. The tumor/tumor bed submission from primary tumor, lymph nodes, and/or other metastases should include grossly obvious tumor/tumor bed, inclusive of fibrotic, necrotic, and

hemorrhagic areas. This is because gross measurements often do not correspond to the %RVT observed microscopically.²⁰

- i. Tissue submission for primary tumor specimens with greatest tumor dimension ≤ 3 cm

Tumor/tumor beds ≤ 3 cm should be submitted in their entirety.^{19,25,77,78} If lymph nodes are present with the specimen, please refer to sections (ii) and (iii) below.

- ii. Tissue submission for primary tumor specimens with greatest tumor dimension > 3 cm

In addition to following standard grossing protocols for assessment of margin status, and the requirement to submit one section per 1 cm of tumor, *at a minimum*, one complete cross-section of tumor/tumor bed from the longest dimension of the tumor should also be submitted for embedding. When possible, the interface of tumor with surrounding normal tissue should also be included.

For tumors that have a plaque-like growth pattern that is not amenable to a representative cross-section along the long axis, e.g. mesothelioma, it may be necessary to submit the entire tumor. If this will require an excessive number of blocks, e.g. more than ~ 20 blocks, systematic sampling of every second or third section while ensuring the capture of areas with variable gross appearance is recommended. Similarly, even for the non-plaque-like larger tumors that would require much more than 20 blocks to submit a full-thickness section from the greatest dimension, a modified approach of submitting every other section or even every third section across the largest cross-sectional diameter may be considered. For pathology laboratories that use macrosections, there may be efficiencies in the number of blocks generated.

This recommendation is supported by data showing that in both NSCLCs and melanomas > 3 cm, it is not necessary to submit the entire mass for an accurate determination of complete pathologic response (pCR, defined as 0% RVT).^{79,80} Specifically, in NSCLC after a full-thickness cross-section is submitted, additional sampling of ≤ 20 blocks total of the tumor/tumor bed provides an accurate reflection of pCR if no residual tumor is detected. This block count of 20 may be inclusive of the additional one/1 cm sections taken in larger tumors.

Gross specimen photography and/or sketch is particularly useful when the entire sample is not being submitted.

- iii. Tissue submission for lymphadenectomy specimens with greatest tumor dimension ≤ 3 cm

All identified lymph nodes should be sampled for histologic evaluation per standard staging protocols. In addition, each tumor deposit ≤ 3 cm

should be entirely submitted, including any grossly evident extranodal extension or matted nodes.

- iv. Tissue submission for lymphadenectomy specimens with greatest tumor dimension >3 cm

Each lymph node with a tumor/tumor bed deposit >3 cm in size should be submitted similarly to a primary tumor of this size [described in (ii) above]. In brief, *at a minimum*, one complete cross-section of tumor/tumor bed from the longest dimension of the tumor/tumor bed should be submitted for embedding. As for primary tumors, regular subsampling may be considered for particularly large lesions or, alternatively, more complete sampling may be dictated by a specific clinical trial protocol.

Adequacy assessment

All slides generated from a pathology specimen should be submitted when pathologic response assessment is conducted in consultation (slides submitted for expert review by a different institution). If the anticipated tissue sampling is not carried out per the guidelines above or expected slides are not received, the originating site should be directed to submit more tissue/slides for review. If it is not possible to submit more tissue, the specimens can still be assessed for %RVT, but a note should be included in the pathology report indicating the potential limitations. Suggested verbiage is ‘Please note that due to insufficient gross sampling of the lesion, the results of pathologic response assessment may not be fully representative of treatment response’. See Supplementary Material S2, available at <https://doi.org/10.1016/j.annonc.2025.10.018> for additional guidance for adequacy assessment as a part of research studies and clinical trials.

Microscopic assessment of primary tumor

The foundational concept of pathologic response assessment is that the %RVT is determined by the proportion of viable tumor after therapy in relation to the largest extent of the tumor before therapy (Figure 4):

$$\%RVT = \frac{\text{Surface area of residual viable tumor on the slide}}{\text{Surface area of total tumor bed on the slide}} \times 100$$

Historically, individual tumor types and/or scoring systems designed to assess response to distinct therapeutic modalities have used different histologic components, especially in the denominator, when determining this ratio. Stated another way, some systems differ in the histologic features used and/or how they are assessed to identify the ‘surface area of total tumor bed’. A goal of this guideline is to harmonize, whenever possible.

The components that constitute the tumor bed and should be scored include: RVT, necrosis, and regression (Figure 4 and Supplementary Material S3, available at <https://doi.org/10.1016/j.annonc.2025.10.018>). The total percent surface area(s) of each of the three components is estimated across all slides containing tumor/tumor bed. It is recommended

that, when possible, pathologists use slide marking pens on glass slides or annotate on digital sections to circle the three tissue classes of RVT, necrosis, and regression. When all slides are marked, it is possible for a pathologist to reliably estimate the %RVT across all slides visually, which obviates the need to perform direct on-slide measurements with a micrometer or image analysis.⁸¹

When estimating the surface area involved by tumor, *in situ*/noninvasive disease is not included in the calculation. If multiple foci of residual tumor are present, these are added together for the RVT surface area, provided they are located in a single tumor bed. When multiple invasive primary tumors are identified, they should be scored individually for response. Comedonecrosis should be considered part of the 'viable tumor' surface area, while larger, broad areas of geographic necrosis should be counted in the necrosis category. IHC may be used at the pathologists' discretion in challenging cases to help identify residual tumor. However, it is not recommended as a reflexive test. Routinely generating and examining multiple slide levels from a single block is also not necessary nor recommended.⁸²

Regression stroma/bed is characterized by a constellation of co-localized features identified in the background of fibrosis and neovascularization, i.e. features associated with wound healing, which is most commonly seen adjacent to tumor (save for instances of pCR) and/or necrosis. Other features that are most often present include plasma cells, foamy macrophages, and lymphocytes. In many cases, tertiary lymphoid structures (TLSs) are present and cholesterol clefts in areas of tumor clearance may also be seen. The proportion of each of these features may vary, depending on the phase of regression, with more TIL seen in actively regressing lesions and more macrophages seen in the tumor bed of tumors that have already regressed.

In cases where it is possible to distinguish between a desmoplastic tumor stroma (which lacks neovascularization and other key components of bona fide regression) and regression bed, the surface area of the tumor stroma should be included in the surface area for viable tumor, rather than as part of the surface area of fibrosis associated with regression. See Supplementary Material S3, available at <https://doi.org/10.1016/j.annonc.2025.10.018>, for an extended discussion regarding distinguishing regression from intratumoral stroma, for example, in NSCLC. The reader is also referred to the companion manuscript for an extended discussion regarding histologic features scored, including a few tumor and treatment-specific notations.

Microscopic assessment of excised lymph nodes

All lymph nodes in the resection specimen should be examined for features of viable tumor, necrosis, and regression. The histologic features of regression are consistent enough that it is possible to distinguish a normal lymph node that was never involved by a well-established tumor deposit (i.e. more than isolated tumor cells in parenchyma or those confined to a subcapsular sinus) from one that was involved and has undergone a pCR, even without a pretreatment biopsy demonstrating nodal involvement.^{20–22,52} Hyalinized granulomas, sinus histiocytosis, and anthracotic macrophages must be distinguished from features of regression, as these do not reflect tumor clearance.²⁰

Similar to the primary tumor, surface area measurements are added across all slides from all lymph nodes in the specimen to generate %RVT, %necrosis, and %regression for the lymph node compartment. Histologically unremarkable, normal lymph nodes that were never involved by tumor are not included in the surface area calculation for %RVT assessment. As noted in the preceding text, the %RVT of the lymph node compartment is determined separately from the primary tumor. Additional future studies will be required to determine whether there is additional prognostic benefit to assessing lymph node response by station or anatomic level.⁸³

Assessment of specimens containing both primary tumor and lymph nodes

For cases where there is a primary tumor and regional lymph node deposit, it is recommended that %RVT for both are captured and reported as discrete variables, since the relative contribution to clinical outcomes for the %RVT in the primary tumor and %RVT in the lymph node compartment is not yet known. Such an approach will also allow for studies to determine the prognostic significance of mixed responses between anatomic compartments, including the relative significance of residual primary versus metastatic tumor. While the optimal combination is yet to be determined, if a global value (taking into account all tumor deposits at multiple sites, including distant metastases, if present) is provided, it should be: (i) provided in addition to %RVT in each compartment (primary tumor, regional lymph nodes); and (ii) an aggregate surface area measurement, rather than a strict average of %RVT from the different locations.

Defining pathologic response and associated reporting recommendations

It is recommended that %RVT, %regression, and %necrosis are each measured and reported at 10% intervals (0%, followed by rounding to the nearest 10%, 20%, 30%, 40%, etc.). In instances where %RVT is between 1% and 5%, single percentages should be recorded. If any tissue class has a value in the 1%–5% range, the other tissue classes may not have values that are a factor of 10, as the total values of the three tissue classes must sum to 100%. Collecting data in this manner will inform future data-driven assignment of pathologic response categories, including how best to combine response assessments from different anatomic sites, e.g. primary tumor and lymph nodes. A sample template for reporting is shown in Figure 5. The rationale for capturing the full spectrum of %RVT is provided below:

A continuum of pathologic responses from 0% to 100% may be observed and inversely correlates with improved patient outcomes in many tumor types.^{18,83–87} In one study, each 1% of RVT in the definitive resection specimen was associated with a 0.017 increase in hazard ratio for EFS in patients with NSCLC.¹⁸ Identification of discrete categories or clinically meaningful ‘bins’ in the context of particular disease types and associated therapy is an area of active investigation and may be established in the future. Some currently used categories include pCR and major pathologic response (MPR, defined as $\leq 10\%$ RVT). Some systems have also advocated for $>10\%$ to $\leq 50\%$ RVT and $>50\%$ RVT cutpoints,^{21,88,89} or so-called ‘partial pathologic response’ and ‘pathologic nonresponse’; however, now that long-term patient outcomes are maturing, these latter categories are currently being re-examined.⁹⁰ It should be noted that many studies only captured and

reported pathologic response categories, precluding a more refined investigation of data-driven, clinically relevant %RVT thresholds.⁹¹

For clinical trials. The reporting of patient-level data is recommended for any study and specifically in phase II/III clinical trials, facilitating future meta-analyses (Supplementary Table S2A, available at <https://doi.org/10.1016/j.annonc.2025.10.018>). If individual patient-level data are not provided, at a minimum, summarized data at 0%, 1%–5%, 10%, and increasing 10% RVT increments should be provided along with key survival metrics (Supplementary Table S2B, available at <https://doi.org/10.1016/j.annonc.2025.10.018>).⁹²

Interpathologist reproducibility

Initial reproducibility studies using this approach to score %RVT in NSCLC specimens scored by four pathologists at a single institution showed an intraclass coefficient (ICC) of 0.98 [95% confidence interval (CI) 0.96–0.99] when assessing %RVT in the primary tumor at 10% intervals.²⁰ Similar results for interobserver reproducibility by four pathologists for scoring %RVT were obtained in melanoma with an ICC of 0.965.⁹⁰ A more recent study that included 12 different tumor types and an international, multi-institutional group of 14 pathologists demonstrated an ICC of 0.85 (95% CI 0.76–0.92) and 0.89 (5% CI 0.78–0.96) for primary tumor and lymph node assessments, respectively.³¹ High concordance has also been observed between local pathologists and central pathology review.^{11,93}

Assessment of resected metastases other than regional lymph nodes

Some patients with resectable metastases are being treated with neoadjuvant therapy. Resected metastases should follow the guidance above for primary tumors and lymph nodes with regard to tissue submission and microscopic assessment, and should be included in the surface area calculation if a ‘global value’ for %RVT is generated. Brain metastases are an exception to this guidance, as these criteria have not yet been studied for that anatomic site.

For certain cutaneous malignancies, patients with in-transit metastases may also receive neoadjuvant therapy. As these may represent intralymphatic deposits in some instances, it is not yet clear whether they will manifest the full spectrum of histologic features described above. Data such as whether in-transit metastases are present and whether regression is observed (%RVT over surface area of lesions aggregated, same as for multiple lymph node deposits) should be collected. A composite %RVT value for ‘regional metastases’ that includes both in-transit metastases and regional lymph nodes may also be generated.

Assessment of pretreatment biopsies

Pretreatment specimens are not required to assess pathologic response in on- or post-therapy specimens, although such material may assist with identification of residual tumor in morphologically challenging cases. Pretreatment biopsies may also facilitate the distinction of tumor-associated stroma from treatment effect (Supplementary Material S3, available at <https://doi.org/10.1016/j.annonc.2025.10.018>).

Assessment of on-treatment incisional biopsies

In certain clinical scenarios, response assessment performed on incisional biopsies may be used to guide subsequent treatment decisions. This is an active area of investigation that has the potential to be tissue and organ sparing, for example, through response-adaptive surgical planning.^{6,7,94} A recent study demonstrated that pathologic response assessment performed on a biopsy specimen taken 2 weeks after neoadjuvant treatment initiation was reflective of treatment response/resistance in the subsequent definitive surgical resection specimen.⁹⁵ While outside of the scope of this current effort, pathologic response assessment performed on core needle or punch biopsies of early, on-treatment tumors from patients with advanced, metastatic disease may also be used to predict long-term outcomes.²³ Best practices regarding tissue procurement strategies (biopsy versus subtotal or complete resection) and the associated adequacy for performing robust pathologic response assessments are still being defined.

DISCUSSION

A pan-tumor system for assessing and reporting pathologic response is possible and desirable (Figure 6). Pathologists, oncologists, and regulatory specialists have expressed interest in such a system for routine clinical practice. It is also important for clinical trials, as it avoids having different scoring systems arise within individual studies that are then difficult to cross-compare or subsequently implement in routine clinical practice (akin to the PD-L1 IHC biomarker). Our guideline recommendations provide a robust framework for neoadjuvant scoring of pathologic response and facilitate future, direct comparisons of relative therapeutic efficacy across different trials and cancer types. They may also lead to revised (either pan-tumor or tumor-specific) clinically meaningful and patient-centered %RVT thresholds beyond pCR alone for predicting EFS and/or OS, and informing personalized, response-directed treatment decisions, especially in the context of increasing ICB use in the perioperative setting, e.g. as performed in the NADINA trial in melanoma (MPR patients received no adjuvant therapy).¹¹

Radiology underwent a similar convergence of scoring systems with the establishment of RECIST. Forty years ago, advocates for the development of a universal system noted “We believe that the adoption of standard criteria of response should be given high priority... Uniform criteria of response should not be chosen on the basis of popular opinion, but because they meet standards of reliability and validity. Thus, the criteria must be reproducible and should correlate with other measures of patient benefit such as quantity and quality of survival”.⁹⁶ The pan-tumor pathologic response system described herein achieves these goals for pathology and addresses a large unmet need in the field of neoadjuvant therapy.

Using this pan-tumor system, %RVT is highly reproducible among pathologists and meets United States Food and Drug Administration criteria for an endpoint supporting accelerated regulatory approval (i.e. it is “reasonably likely to predict clinical benefit”).^{97,98} %RVT also meets the more stringent criteria for surrogacy: (i) the treatment intervention must be associated with the surrogate, (ii) the surrogate must be associated with the outcome, and (iii) the surrogate manifests the overall treatment effect on the clinical outcome.^{99,100}

Initial pathologic response protocols used in neoadjuvant clinical trials are often conservative, requiring large volumes of tumor/tumor bed submitted for histopathologic analysis.^{12,21} Such practices do not translate readily to routine clinical practice and are perceived to be overly burdensome to the laboratories and pathologists carrying out pathologic response analyses (Supplementary Figure S1, available at <https://doi.org/10.1016/j.annonc.2025.10.018>). This is an area of active investigation, with studies ongoing to further examine grossing recommendations in tumors >3 cm as they relate to maturing patient outcomes data. In the absence of data supporting a need for exhaustive tissue submission, our guidelines for grossing (amount of tissue submitted for slides) and reporting (essential variables) optimize the balance between raising the amount of tissue examined to a uniform minimum standard to determine %RVT versus expending unnecessary medical resources for diminishing returns with regard to predicting clinical outcomes. Nonetheless, it may sometimes be of value to submit more tumor/tumor bed tissue than these guidelines recommend to support extended, translational research studies. Extended tissue submission may also be of value for some treatment modalities or tumor types where pathologic response has not yet been well characterized, e.g. intratumoral injections or central nervous system tumors.

One of the critical steps toward further implementation of these guidelines in routine practice is inclusion in CAP, AJCC, RCPATH, and European Organisation for Research and Treatment of Cancer (EORTC) cancer staging systems and practice guidelines/protocols, as it will prompt individual pathologists to complete pathologic assessments in contemporary fashion. The training materials in the accompanying manuscript are provided to support pathologist education and associated implementation.³¹ Appropriate reimbursement that supports the workload for pathologists who perform the requisite tissue submission and quantitative microscopic analyses for %RVT will also increase compliance with these recommendations. To that end, it may also be prudent to develop a new reimbursement code for this specific pathology procedure that is more extensive than currently deployed staging protocols. In the United States, there is precedent in IHC stain interpretation for having quantitative versus qualitative Current Procedural Terminology (CPT) reimbursement codes. Here, a similar construct could be used where a new CPT code is developed for providing quantitative %RVT assessments versus existing, more qualitative assessments for staging resection specimens. Standardization may also likely advise and support inclusion of %RVT and other key variables in registries such as the Surveillance, Epidemiology, and End Results (SEER) database and National Cancer Database (NCDB).

In summary, here we present updates to a common scoring and reporting system for pathologic response to neoadjuvant systemic therapy, which is independent of tumor type and treatment and empowers future study design. The implementation of a unified scoring approach and systematic data capture reporting system for 0%–100% RVT recognizes the dynamic nature of the field by providing a foundation for evaluation (and re-evaluation) of %RVT thresholds for different therapeutic regimens as our understanding evolves and new data emerge.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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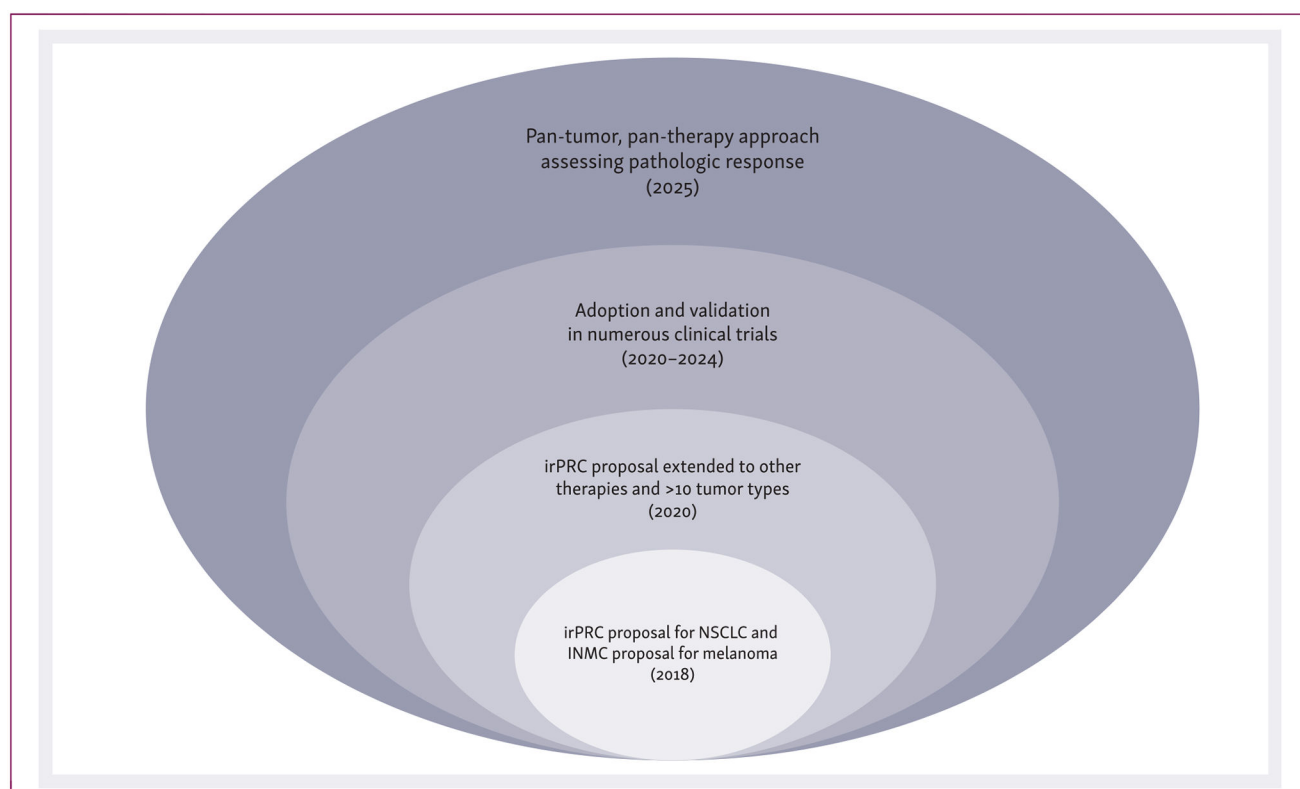


Figure 1. The evolution of a pan-tumor, pan-therapy approach to pathologic response assessment.

The initial description of irPRC for NSCLC was published in 2018, concurrent with the INMC proposal for pathologic response assessment in melanoma. Since that time, the two proposals have merged, expanded to include numerous other solid tumor types and therapeutic modalities, and are updated herein to provide a pan-tumor, pan-therapy scoring system.

INMC, International Neoadjuvant Melanoma Consortium; irPRC, immune-related pathologic response criteria; NSCLC, non-small-cell lung carcinoma.

Number	Title	Type of change	Description
1	Tissue submission guidelines (Figure 3)	Addition to pan-tumor ^{20,22} ; revision of INMC ²¹	Specimens ≤ 3 cm should be submitted in their entirety for histological analysis; sampling of specimens > 3 cm is defined
2	Adequacy criteria for slide review	Addition to pan-tumor and INMC	'All' slides generated from the specimen (including 'normal' lymph nodes) should be reviewed when assessing pathologic response for clinical care and for clinical studies where pathologic response is associated with survival outcomes
3	Histologic parameters/tissue classes that are scored (Figure 4)	Clarification of INMC	Tumor necrosis and regression are scored to assess %RVT
4	%RVT reported at 10% intervals (except for values $< 10\%$)	Revision/clarification of both pan-tumor and INMC	A threshold of pPR versus pNR at 50% is not specifically endorsed
5	Reporting templates (Figure 5)	Modification to both pan-tumor and INMC	Unified and simplified reporting template for pathologists, facilitating consideration for adoption into CAP and AJCC cancer staging protocols
6	Pre-treatment biopsy	Revision of INMC	May be helpful, but not required

Figure 2. Summary of recommended changes and updates.

The following summarizes updates to the original irPRC/pan-tumor and INMC pathology response assessment guidelines.^{20–22}

%RVT, percentage residual viable tumor; CAP, College of American Pathologists; INMC, International Neoadjuvant Melanoma Consortium; irPRC, irPRC, immune-related pathologic response criteria; pPR, partial pathologic response; pNR, pathologic nonresponse.

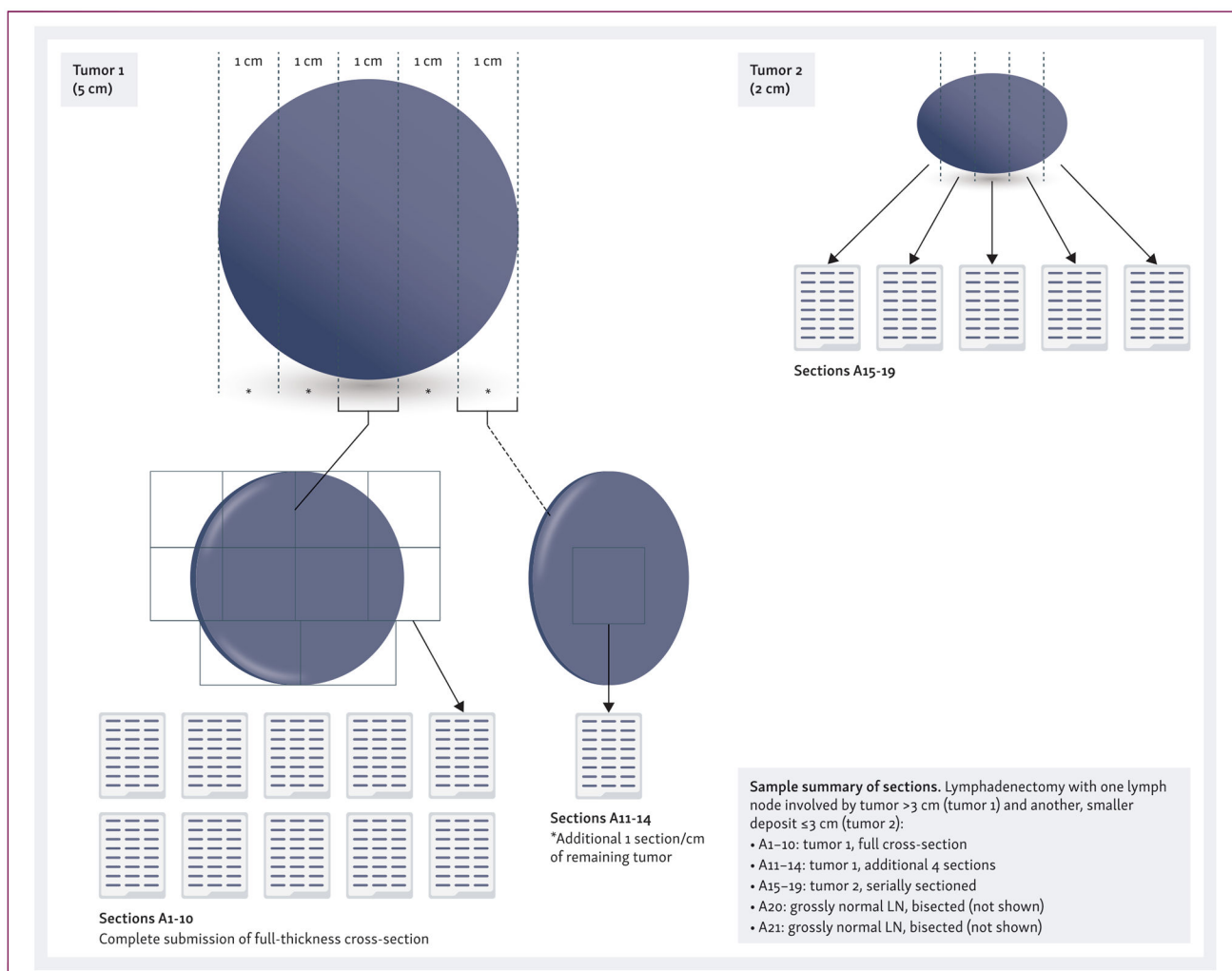


Figure 3. Example of grossing and associated summary of sections for a lymphadenectomy specimen containing two tumor deposits of different sizes.

One of the deposits is 5 cm in greatest dimension, and one is 2 cm in greatest dimension. As such, after standard sections are taken for staging purposes, the minimum additional tissue submission should include one complete cross-section of tumor/tumor bed from the longest dimension of tumor for the tumor >3 cm in size, with an additional one section/cm of tumor for the remainder of the specimen. This complete cross-section should include areas of hemorrhage and necrosis, if present. The tumor deposit ≤3 cm in size should be submitted in its entirety. Certain clinical trial protocols may have additional tissue submission requirements.

LN, lymph node.

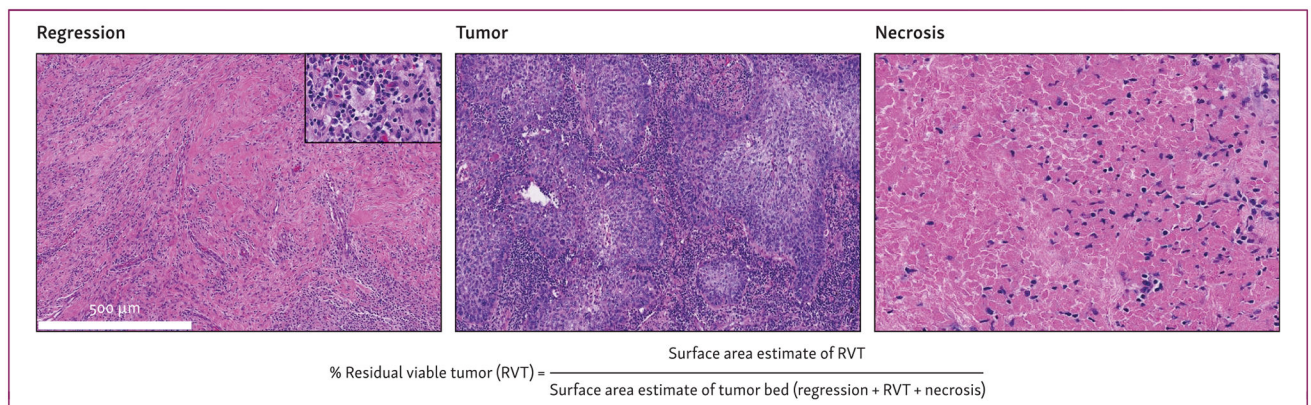


Figure 4. The calculation of percentage residual viable tumor (%RVT) is the surface area of RVT divided by the surface area of tumor bed.

The tumor bed is comprised of three tissue classes: regression (i.e. where tumor used to be), viable tumor, and necrosis. Regression is characterized by a constellation of co-localized histologic features including lymphoplasmacytic inflammation, fibrosis and neovascularization, and evidence of cell death, i.e. interstitial foamy macrophages, cholesterol clefts, and multinucleated giant cells. Given its role in the denominator of the calculation, accurate recognition of regression is key in determining %RVT.

Assessment of primary tumor components ^a	
Percent residual viable tumor:	_____ %
Percent necrosis:	_____ %
Percent regression:	_____ %

Assessment of lymph nodes components ^b	
Percent residual viable tumor:	_____ %
Percent necrosis:	_____ %
Percent regression:	_____ %

^aThese values represent an estimated % surface area across all slides of the specimen. *In situ* disease is not included in the RVT surface area calculation. The percentage of each of these three components must sum to 100%.

^bIf only primary tumor or lymph nodes are present in the specimen, these values are only reported for the appropriate compartment. If there are multiple primary tumors or lymph node tumor deposits, they should be combined when scoring to one total surface area value.

Figure 5. Recommended reporting template for pathologic response assessment.

In addition to standard College of American Pathologists (CAP) and American Joint Committee on Cancer (AJCC) reporting protocols, the histologic parameters/tissue classes that should be reported include (i) tumor, (ii) necrosis, and (iii) fibroinflammatory regression (including foamy macrophages, which in melanoma specimens are often represented by melanophages). Reporting of residual viable tumor, necrosis, and regression at 10% intervals is recommended, except when the value is $\leq 5\%$, at which point, single digits should be reported. There is no specific current recommendation for cut-point thresholds to describe partial pathologic response or pathologic nonresponse until more data are gathered to define the most clinically meaningful thresholds.

Pan-tumor	
• Generalizable to other tumor types, anatomic locations and treatment settings	☒
Pathologist ability/interest	
• Can perform scoring reproducibly in both primary tumor, lymph nodes, and distant metastases	☒
• Interest of system implementation for routine practice	☒
Surrugate measure of survival outcomes	
• Associates with treatment	☒
• Associates with outcome	☒
• Manifests overall treatment effect on the clinical outcome	☒

Figure 6.

A pan-tumor approach to pathologic response assessment is possible, is of interest to pathologists and can be reproducibly carried out, and meets criteria as a surrogate of patient outcomes.

Table 1.

Key terms, abbreviations, and definitions for assessing pathologic response to neoadjuvant therapy using hematoxylin and eosin (H&E)-stained slides (revised and updated from Cottrell et al.²⁰)

Term	Description
Fibrosis	Fibrous connective tissue representing a reparative response following tumor clearance. It may be proliferative (fibroblast nuclei are prominent) or hyalinized (homogeneous, acellular) in appearance. This should not be confused with normal structures such as lymph node capsule or hilum or other fibrosing pathologies such as pleural plaque in the lung.
Foamy macrophages	Lipid-laden macrophages that have phagocytosed cholesterol from the plasma membrane and other organelles after cell death. When there is too much cholesterol for macrophages to ingest, the result may be cholesterol clefts in the adjacent tissue. When melanomas regress, these macrophages often contain melanin, and are designated 'melanophages', and when grouped the term 'tumoral melanosis' may be used. To be considered part of the regression bed, the foamy macrophages and cholesterol clefts, when present, should be interstitial in location and co-localized with other features. They should not be confused with alveolar macrophages in lung or Kupffer cells in the liver.
Lymphoid aggregate	Discrete collection of >100 lymphocytes that does not demonstrate architectural organization or mixture of cell types that characterize a TLS.
MPR	Major pathologic response. ≤10% RVT (inclusive of 0%, pCR) remaining in on- or post-therapy pathology specimen.
Near pCR	>0% and ≤10% RVT remaining in on- or post-therapy pathology specimen.
Necrosis	Cell death characterized histologically by a lack of nuclear detail and typically showing an irregular, patchy geographic shape within a larger tumor nodule. If focal comedonecrosis is observed, it is scored as part of the surface area for viable tumor.
Neovascularization	Newly formed small blood vessels, most often seen in a background of tissue repair in this context.
pCR	Pathologic complete response. 0% RVT remaining in the on- or post-treatment pathology specimen.
Regression bed	Area previously occupied by tumor with characteristic histologic features of tumor clearance. This includes a mix of fibrosis, neovascularization, foamy macrophages, plasma cells, TIL, and lymphoid aggregates/TLS. ²⁰⁻²² This should be distinguished microscopically from other inflammatory pathologies, e.g. postobstructive pneumonia.
RVT	Residual viable tumor in the on- or post-treatment pathology specimen. Most often expressed as a percentage of the tumor bed surface area.
TIL	Tumor infiltrating lymphocyte.
TLS	Tertiary lymphoid structure. Ectopic, organized lymph node-like structure that includes both T and B lymphocytes. Mature TLSs have germinal centers and high endothelial venules that can be identified on H&E stains.
Tumor-associated stroma	Noncancerous tissue that is often fibrotic and is interlaced with malignant tumor cells. It is distinct from surrounding normal tissue, and can also typically be differentiated from tumor regression (see Supplementary Material S3, available at https://doi.org/10.1016/j.jannonc.2025.10.018).