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ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

EDITORIAL

Optimizing pathological response assessment after neoadjuvant immunotherapy: linking clinical practice to drug development

Immune checkpoint blockade (ICB) has transformed our understanding of cancer therapy and rendered cures a regularly attainable goal. The basic concept of training the host's immune system to reject cancer demonstrated its curative potential first in the advanced disease setting. However, the neoadjuvant setting offers a unique opportunity to harness the power of ICB while delivering the *coup de grâce* through surgical extirpation of localized tumor. This double-pronged approach has demonstrated its overwhelming superiority over surgery followed by adjuvant therapy in melanoma (NADINA and S1801)[1,2] and other cancers, already showing an overall survival benefit in breast cancer (KEYNOTE-522).[3,4]

While traditional neoadjuvant therapy aimed at eliminating every last cancer cell, with pathological complete response (pCR) being the ultimate goal, neoadjuvant immunotherapy (NAT-IO) appears to benefit patients even if pCR is not achieved, reflecting the biological impact of igniting an antitumor immune response.

The rapid integration of NAT-IO into the treatment paradigm for solid tumors, particularly melanoma, marks a watershed moment in oncology, elevating pathological response assessment (PRA) to an ultimate determinant of therapeutic success. The neoadjuvant setting allows a detailed assessment of tumor response superseding radiographic assessments such as RECIST. In addition, the experienced pathologist can offer a nuanced assessment of different response features, allowing more accurate prognostication and deeper translational insights into mechanisms of response and resistance.

This issue of the *Annals of Oncology* provides a timely and necessary reflection on this transformation with two key papers that address the fundamental pathological challenges: efficiency in specimen handling and standardization in scoring across tumor types.

The editorial contributions by Rawson and colleagues[5] and Deutsch and colleagues[6] are not merely academic exercises; they represent an essential, evidence-based refinement of the pathologist's protocol in the age of IO. Together, they guide the transition from a morphology-centric evaluation to an integrated, clinically essential biomarker assessment, ensuring that the critical task of PRA scoring is both robust and practical. Importantly, harmonizing the definitions of assessment and reporting would allow for more consistently interpretable results and better evaluation of therapeutic efficacy correlating short-term measurements with long-term outcomes such as overall survival.

Rawson et al. tackle critical, real-world pathological challenges: the sheer volume of tissue generated by extensive surgical resection following NAT-IO.[2,7] The successful use of IO regimens in stage III melanoma often leads to significant tumor regression within a large residual tumor bed (TB).[1] Historically, exhaustive submission protocols were often mandated to ensure accurate quantification of the percentage of residual viable tumor (%RVT), a crucial prognostic factor guiding subsequent adjuvant therapy.[8]

Rawson and colleagues demonstrate, through a rigorous analysis of 134 specimens, that revising the prior International Neoadjuvant Melanoma Consortium (INMC) pathology guidelines and protocols can result in an evidence-based protocol recommendation that preserves accurate PRA for clinical response even with a substantially reduced examination of the TB.[5] Their findings support a streamlined protocol—specifically, recommending a cap on the number of slides examined (e.g. at 20) and a modified approach to lymph nodes >3 cm. The authors should be commended for a rigorous methodology utilizing the original INMC criteria as ground truth, developing seven different protocols, meticulously evaluating their comparative performances, and demonstrating that a significant reduction in slides examined is possible without compromising the classification of major pathological response (MPR) or the overall pathological response category.[5]

From a pathologist's perspective, this is a monumental contribution to sustainability and clinical effectiveness. By providing empirical validation for a streamlined sampling protocol, Rawson et al. offer a vital tool for laboratories to manage increasing NAT-IO caseloads recognizing the challenge inherent in identifying minute foci of residual tumor within vast, fibrotic, and heavily inflamed fields of immune-mediated regression—a unique post-IO feature.[9]

While the study by Rawson et al. refines how much tissue needs to be examined in melanoma, the paper by Deutsch et al. addresses the equally urgent need for standardization of what is being scored across the entire spectrum of solid tumors treated with NAT-IO.[6] As IO expands beyond melanoma into lung, breast, bladder, and colorectal cancers, there is an absolute moral imperative to understand IO across cancers in the neoadjuvant setting by harmonizing the reporting and assessment criteria in an evidence-based scalable manner to facilitate

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cross-trial comparisons and accelerate the validation of PRA as a robust surrogate endpoint for overall survival.

The updated pan-tumor guidelines, a joint effort between the Society for Immunotherapy of Cancer (SITC) and the INMC, build upon prior foundational work to create a unified scoring framework.[10] This consensus strongly reinforces the central role of %RVT quantification and provides practical, shared guidelines on the key histological features that define the immune-mediated regression bed, such as the presence of foamy macrophages, prominent lymphoplasmacytic infiltrate, and mature fibrosis.[6] The use of %RVT as a continuous variable with 10% increments can be critically impactful as it allows a transition from empirical cut-offs (e.g. INMC criteria for pPR and MPR) to data-driven categorization of response patterns. In addition, this could help better refine the identification of patients who do not experience benefit and are in need of novel approaches. Importantly, the guidelines offer practical solutions for managing the inherent morphological and biological heterogeneity seen across different tumor types and therapeutic regimens.

There are still some open issues to solve, including the proper significance and classification of intratumoral subtypes of necrosis, the added predictive value of immune cell densities within necrotic foci, and the role of other biomarkers. Longitudinal biospecimen collection will be essential to assess the temporal changes of histopathological features over time.

The publication of these two articles together in a single issue perfectly encapsulates the dual pressures and opportunities of modern surgical pathology: efficiency (Rawson et al.) and standardization (Deutsch et al.).

As NAT-IO continues to advance, the challenges for the pathologist will only increase, requiring the validation of more nuanced pathological metrics and the incorporation of computational pathology and artificial intelligence tools to achieve near-perfect reproducibility in %RVT scoring. However, the foundational steps laid out by Rawson et al.[5] and Deutsch et al.[6], streamlining workflow without sacrificing accuracy and standardizing criteria across all tumor types, are arguably the most important steps for ensuring that pathological response can be elevated to an essential measure of IO efficacy, guiding clinical practice in the NAT-IO era and beyond. Most importantly, this also represents a call to our industry colleagues and investigator community to change how we collect and report data so that we can build the body of evidence necessary to change the standard of care. A rigorous approach to assessing pathological response consolidates the neoadjuvant setting as a critical drug development tool, accelerating the evaluation of the clinical and biological impact of novel IO agents and providing a solid basis for regulatory approvals in oncology.

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