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EDITORIAL – MELANOMA

Melanoma Surgery in the Emerging Era of Effective Neoadjuvant Therapy

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Increasingly, through recent clinical trials, neoadjuvant therapy has demonstrated important advantages in the management of patients with advanced resectable melanoma. Perhaps most significant is the incredibly powerful prognostic biomarker information that the pathologic response of the resected treated tissue can provide. Several issues and controversies continue to surround the utilization of neoadjuvant therapy in melanoma, including the duration of therapy, the extensiveness of surgical resection pending clinical and pathologic response, and decisions on the type and duration of adjuvant therapy. Some of these issues have been the primary subject of work by the International Neoadjuvant Melanoma Consortium, which has sought to standardize methodology in neoadjuvant clinical trials for melanoma.[1] Even so, many questions remain, including the extent to which, if any, neoadjuvant therapy confers therapeutic benefit over adjuvant therapy.

In a manuscript entitled "Surgeon Assessment of the Technical Impact of Neoadjuvant Systemic Therapy on Operable Stage III Melanoma," Hieken et al. investigate an important topic regarding neoadjuvant therapy that is discussed anecdotally among surgeons but rarely studied in a systematic way.[2] Importantly, in a survey study of surgeons operating on 25 high-risk stage III patients who underwent 12 weeks of combinatorial neoadjuvant therapy with vemurafenib, cobimetinib, and atezolizumab, or cobimetinib and atezolizumab, as part of the NeoACTIVATE trial (NCT03554083), they found that the surgeon's perception of technical difficulty of the case comparing pre- (baseline) and postneoadjuvant treatment decreased more often (25% of cases) than it increased (17% of cases). While there are several limitations to this study, namely a relatively small cohort size, heterogeneity of treatments, variable surgeon experience, and bulkiness of tumor lymphadenopathy, this study begins to provide important data to an area where quantifiable data are largely lacking. Because of the lack of a control group not undergoing neoadjuvant therapy, perception of surgical difficulty relies on prior recollection of historical high-risk stage III cases based on imaging findings, which may introduce further study bias and not perfectly correlate with intraoperative findings. Nonetheless, this investigation provides further reassurance that neoadjuvant therapy appears safe and highlights the increasing importance of careful documentation of intraoperative findings (with respect to unexpected challenges, e.g., dense or infiltrative fibrotic reaction, tumor necrosis resulting in more friable tumors, etc.), as well as postoperative complications following neoadjuvant approaches.

Targeted therapy with BRAF/MEK inhibitors and immune checkpoint inhibitors has revolutionized the care of patients with metastatic melanoma and found their way to routine use in the adjuvant setting. A number of clinical trials have now shed light on the potential utility of neoadjuvant approaches for patients with resectable melanoma. "Downstaging" or rendering tumors easier to resect (a classic reason for neoadjuvant therapy for other tumor types) is perhaps less important a consideration in most cases of stage III or oligometastatic stage IV melanoma. Importantly, tumor progression is uncommon with neoadjuvant approaches, especially with a short course of therapy that appears to be sufficient, particularly with PD-1 checkpoint blockade in eliciting a pathologic (and prognostic) response. As a result, initial concerns that a neoadjuvant treatment sequence would result in a "missed

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opportunity" for curative surgery due to isolated regional progression has not generally been observed across published trials.

Prognostication appears to be surfacing as one of the most important reasons for neoadjuvant therapy.

In a pooled analysis of neoadjuvant trial patients, of 131 patients receiving immunotherapy, 2-year relapse-free survival was 96% among patients who had a pathologic complete response (CR), near pathologic CR, or partial response, and notably lower (79%) in 51 patients undergoing neoadjuvant targeted therapy with even a pathological CR.[3] These exciting results, particularly with respect to neoadjuvant immunotherapy regimens, highlight the durability in treatment response following a short course of preoperative therapy, but also open up new avenues for clinical investigation. Importantly, pathologic response may serve as an important (and early) surrogate endpoint for evaluating the efficacy of new drug therapies, particularly immunotherapeutics.

Currently ongoing are several neoadjuvant melanoma trials that are also looking at whether pathologic response data can be used to guide further treatment strategies, namely the type and duration of adjuvant therapy. However, an additional question, with particular relevance to the surgical community, is whether pathologic response can also be used to influence the extensiveness of surgery. The ongoing PRADO extension of the OPACIN-neo trial (NCT02977052) is one such study where the pathologic response of an index node determines whether patients undergo limited removal of an index node versus full therapeutic lymph node dissection. As answers to these questions start to emerge in the near future, the rate at which therapeutic lymph dissections are performed for clinical nodal disease may decrease, a trend already seen for the management of micrometastatic disease following the Multicenter Selective Lymphadenectomy (MSLT)-2 and the German Dermatologic Cooperative Oncology (DeCOG) trials. The current study by Hieken et al. becomes even more relevant as it assures that neoadjuvant strategies will not negatively impact the safety of surgeries, especially as the number of extensive lymphadenectomies continues to decline.

As the melanoma treatment landscape continues to evolve rapidly with new therapeutics (including novel immune checkpoint inhibitors) and combination therapies, it will become increasingly important to identify better predictive biomarkers for therapy response that can help guide selection of patients for specific neoadjuvant treatment regimens. Neoadjuvant therapy will only likely continue to expand in its usage, and studies such as this should be welcomed to better understand its impact on surgery and to define its optimal role and utility for patients with melanoma.

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