The Evolving Role of Surgery in Advanced Melanoma

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The recent rapid development of targeted drugs and immunotherapies for melanoma has left many unanswered questions about the role of surgery in advanced melanoma. Traditionally, patients with advanced melanoma were treated first with aggressive surgery. Now, however, the pace of recent developments means that clinical trial data on the role—if any—and timing of surgery in advanced melanoma are lacking.

Take, for instance, *BRAF*-mutated melanoma, which occurs in approximately 50% of melanomas. In the past, we'd operate on these patients; now we treat them with BRAF inhibitors and/or one of the new immunotherapies, and the role of surgery for these patients has not yet been defined. In fact, except in cases in which a patient is bleeding, needs pain alleviation, or has a tumor that is eroding through the skin, surgery for metastatic disease is rare.

Does this mean that surgery has no place in the future treatment of advanced melanoma? The answer is not clear. Among the questions yet to be answered: How much time should we allow for treatment to "work" with the various new therapies? Should a neoadjuvant approach be taken, in which patients are treated with targeted therapy before or during surgery? Will targeted or immunotherapy work better after surgery to clear some of the disease? If a patient has a complete response while on therapy, do we need to operate to clear residual disease? The clinical trials have not yet caught up to these issues, so right now the answers are still the choice of the medical oncologist and surgeon.

Currently, many patients prefer not to have surgery, because treatment with one of the new therapies means potentially less morbidity, less time lost from work, and no surgical wound. However, the majority of patients aren't cured by the new treatments. Some patients may remain on drug therapy for years, trying successive drugs for their melanoma. The problem with this approach is that in the process of trying different therapies, the melanoma may grow or spread. By the time a patient has run out of drug options, he or she may have numerous tumors and no longer be a candidate for surgery. It's not clear if surgery at some point in the process of trying drug therapy would help prevent the spread or growth of the disease, but there is much room for uncertainty. As an example, trials of anti-PD-1 antibody therapy have demonstrated a lower success rate in patients with more tumor volume. This begs the question of whether surgery to remove some of the tumors would improve the success rate of the anti-PD-1 antibody in these patients.

New therapies are also changing the role of surgery for in-transit melanoma. Clinical trials are exploring intralesional injection of the experimental agents talimogene laherparepvec (T-VEC) and PV-10 (from Provectus). Use of BRAF inhibition, anti-CTLA-4 therapy, or immune checkpoint blockade with a PD-L1 inhibitor are also under consideration. These strategies may impact the role of surgery in management of in-transit disease. However, as with management strategies for other forms of advanced melanoma, clinical trials are needed to better define if and how surgery can be used to optimize outcomes.

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