



## The Surgeons' Role When Systemic Therapies Fail in Metastatic Melanoma: The Salvage Metastasectomy

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The past decade has seen a tremendous improvement in the advent of newer, much more effective, and less toxic systemic therapies for melanoma including immunotherapies such as CTLA-4, and anti-PD-1 inhibitors as well as targeted therapies (BRAF and MEK inhibition). How many times have we heard that phrase? There are numerous published articles and podium talks where we start out with the same statement or a close version of it. But what do we do when these new, powerful, and effective therapies fail? The current article in this issue of *Annals of Surgical Oncology* by Li, Ch'ng, and colleagues attempts to answer this therapeutic challenge in a patient with metastatic melanoma.<sup>1</sup> There have been numerous articles published on the surgeons' instrumental role in the management of patients with advanced melanoma, how resection of progressive and isolated disease has led to improved survival in select patients, and how a multidisciplinary team approach combining systemic therapies (systemic, adjuvant, or neoadjuvant) with surgery has many advantages in terms of prolonging survival.<sup>2–6</sup> Nelson et al. looked at patients with stage IV melanoma and characterized them by treatment era (prior to 2007 and 2007–2015). In their paper, they discuss a matched-pair analysis of outcomes in surgical and nonsurgical patients receiving modern-day systemic therapies for metastatic melanoma. Among over 2000 patients analyzed, just under half underwent surgical

treatment, with the only independent selection factor associated with surgical metastectomy in the current era (2007–2015) being age of the patient. Surgery followed by modern therapy in 47 matched pairs was associated with higher melanoma-specific survival (MSS), with single-organ involvement ( $p = 0.02$ ), first-line surgery ( $p = 0.04$ ), and use of modern-day systemic therapies ( $p < 0.001$ ) independently associated with improved MSS on multivariate analysis when compared with older-era patients with stage IV disease.<sup>5</sup> This clearly shows that the multidisciplinary approach of combining systemic therapies with upfront surgery for stage IV disease in selected patients leads to better outcomes. In that same issue of *Annals of Surgical Oncology*, Song and colleagues also discussed a retrospective analysis looking at patients with clinical stage III melanoma and came to a similar conclusion looking at over 3700 patients; those treated in the modern era for their clinically evident metastatic stage III melanoma followed by modern-day adjuvant therapy did better in terms of overall survival (OS).<sup>6</sup> These two papers clearly show that, in selected patients, surgery followed by modern-day systemic therapies can lead to improved survival.<sup>5,6</sup> But what do we do when we treat patients with upfront systemic immuno- or targeted therapies, and they fail or progress? It is apparent that we will be presented with these types of patients more commonly, as systemic therapies are obviously not 100% effective. Bello et al. previously described favorable survival outcomes after metastasectomy for isolated progressive disease in patients with prior checkpoint blockade.<sup>7</sup> The current article's authors, Li, Ch'ng, and colleagues, further attempt to characterize the outcomes of 190 patients who failed systemic therapy for extracranial metastatic disease (2009–2020) and then went on to have salvage surgery/

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metastasectomy. These patients received at least 4 weeks of systemic immuno- or targeted therapy before determining progression. Among all 190 patients included in the analysis, the 5-year OS from the time of metastectomy was 52%, 3-year progression free survival (PFS) was 21%, and 5-year local recurrence-free survival was 61%. These numbers heavily favored those resected to no evidence of disease (NED) (5-year OS 69%, 3-year PFS 23%) and those who had their unresponsive or progressive disease resected and were left with only nonprogressive residual disease (5-year OS 62%, 3-year PFS 24%) versus those with where all unresponsive disease could not be resected and we're left with residual progressive disease (5-year OS 8%, 3-year PFS 10%). Fewer lines of preoperative therapy, the use of immunotherapy preoperatively, and resection to NED improved OS.<sup>1</sup>

A few items are noteworthy to point out. The authors excluded patients with brain metastases owing to their poor prognosis, and it is not clear what the denominator of this "progressive disease" group is. We are looking at 190 patients who progressed after systemic therapies who then went on to surgery to have their isolated progressive disease, but there are likely many more patients who progressed and were not surgical candidates or never made it to surgery after disease progression, side effects from therapies, refused surgery, or just having an overall poor prognosis due to disease burden that precluded any surgical intervention. With that being said, Li, Ch'ng, and colleagues clearly have shown a benefit to operating on *select* patients who fail systemic therapies. The patients who benefited from the salvage metastasectomy were those where all progressive disease was removed. This held true in patients where nonprogressive or stable disease was left behind at the time of the salvage metastasectomy. The authors also mention that a multidisciplinary discussion is paramount in the planning of treatment for these patients and selecting the right patients for salvage metastasectomy. It is fairly certain that we will be encountering these patients who fail systemic therapies for metastatic melanoma more often, especially if predictions, as published in *Estimated Projection of US Cancer Incidence and Death to 2040* by Rahib et al., hold true that the incidence of invasive melanoma will more than double between the years 2020 and 2040, going from 101,000 to 219,000 cases in the

USA per year.<sup>8</sup> We will certainly be relying on the surgeon to prolong survival and salvage these select patients with resectable progressive metastatic melanoma after failure modern day systemic therapy.

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