Clinical benefit of treatment for metastatic renal cell cancer at high volume facilities

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Advancements in molecular biology and the ability to prime the immune system to target cancer cells have opened new frontiers in anti-cancer therapy, particularly in the metastatic setting. A combination of nivolumab-plus-ipilimumab, when used for patients with advanced melanoma, has demonstrated significantly longer overall survival (OS) than either agent used alone, with a 3-year OS rate of 58% observed in these patients (1). Use of pembrolizumab has been demonstrated to have significant anti-tumor activity in patients with programmed death ligand 1 (PD-L1) expressing, pre-treated, extensive stage small cell lung cancer (2), which has previously been accepted to be a uniformly fatal disease with no good treatment options. Additionally, the combination of nivolumab-plus-ipilimumab, when used for patients with advanced clear cell renal cancer, has demonstrated significantly longer OS than use of single-agent sunitinib (3). While the use of these newer immunotherapeutic agents has been shown to demonstrate improvement in outcomes for metastatic cancer, the utilization of these agents by practitioners within the US has not fully been explored. Importantly, there is concern that given the novelty of these agents, they may be underutilized in the community setting, and that higher volume centers (HVC), due perhaps to greater access to clinical trials or greater familiarity with the newer agents, may be using these agents at a greater rate than practitioners at lower volume centers (LVC). If this were true, it may be possible that treatment for patients with metastatic cancer at HVC would be associated with superior OS than patients treated at LVCs.

The correlation between improved clinical outcome and volume of the treatment facility has been well established for multiple sites of cancer in the non-metastatic setting. Studies have demonstrated that for high risk oncologic surgical procedures, patients that receive treatment at HVC have superior outcomes to patients treated at LVCs. In particular, this has been demonstrated for patients undergoing surgery for pancreatic cancer (pancreaticoduodenectomy), adrenal cancer (adrenalectomy), rectal cancer (total mesorectal excision), colon cancer (colectomy), or lung cancer (lobectomy) (4-8). In fact, due to the improved outcome following high-risk surgical procedures at HVCs, investigators have suggested that in the absence of information regarding the quality of care delivered at hospitals, Medicare patients undergoing these specialized cardiovascular or cancer surgeries could reduce the risk of death by opting to receive their treatment at a HVC (9).

There is also data to suggest that the volume of the radiation oncology facility delivering radiation therapy can have an impact on clinical outcomes. A greater OS for patients receiving radiation therapy at a HVC has been demonstrated for patients undergoing definitive chemoradiation for cervical cancer, lung cancer, or anal cancer (10-12), and also for patients undergoing postoperative radiation therapy for glioblastoma or medulloblastoma (13,14). These findings associating

improved outcomes with high-volume surgical centers and radiation centers suggests that increased volume may serve as a surrogate for improved quality, and that this improved quality translates into meaningful clinical benefits for patients.

The aforementioned data that demonstrated improved outcomes for patients treated at HVCs were limited to patients receiving treatment for localized, non-metastatic disease. The question of whether treatment at a HVC translates to superior outcomes for patients with metastatic cancer has not been explored to the extent that it has for patients with non-metastatic cancer. The study by Joshi *et al.* (15) attempts to fill this void by studying the impact of treatment facility volume on patients receiving treatment for metastatic renal cell cancer (mRCC). This study was unique in that it was limited solely to patients with metastatic cancer. The authors used the National Cancer Data Base (NCDB) to extract treatment records for patients with mRCC, stratified patients by treatment facility volume, and compared OS outcomes for patients when stratified by the volume of the treatment facility. In order to account for differences in treatment and to better evaluate quality of treatment delivered, the patients were broken up into smaller groups by treatment, including patients receiving active treatment, patients receiving systemic therapy, and patients receiving systemic therapy with known status of liver and lung metastases. Furthermore, the analysis was repeated with patients receiving local surgery. The results demonstrated that treatment facility volume was correlated with clinical outcome across each cohort. One-year OS amongst all patients was 36% for facilities treating 2 patients/years, while 1-year OS was 46% for patients treated 20 patients/year. Furthermore, a statistically significant improvement in OS was observed when limiting the study to patients undergoing surgery.

The results of the aforementioned study are meaningful and novel in that they clearly demonstrate a difference in outcome for patients with metastatic cancer when stratified by the volume of the treatment facility. This suggests that it is possible that quality of treatment can have a significant impact on longevity even for patients with the most poor prognosis, those with metastatic cancer. However, while the study does show significant improvement in OS for patients receiving treatment at HVCs, the reasons underlying this observed difference in outcome are unclear. It may be possible that there is a superior quality of treatment delivered at the HVCs, and that this superior treatment quality is what is driving the difference in OS. As the authors of the study point out, possible advantages of receipt of treatment at a HVC may include greater surgical expertise, greater access to clinical trials, increased familiarity by with new developments in therapy such as targeted therapy and immunotherapy, and more experienced staff that is better able to respond to toxicities of treatment. This is all speculation, of course, as the study is not able to fully answer the fully elucidate the reasons underlying the observed OS difference. Importantly, while the authors do stratify patients by the volume of the facility, they are unable to stratify by the experience of the physicians providing the treatment. That is to say, it is entirely possible that a HVC may have an inexperienced physician, and vice-versa. Also, some of the differences may be due to a selection bias. For example, patients with greater socioeconomic resources and lower disease burden may be more likely to travel to seek care at a HVC (16), and these patients may have had a superior clinical outcome regardless of treatment facility. Importantly, the authors were unable to account for metastatic disease burden, as this is not coded for by the NCDB. Finally, the authors of the study did not compare differences in the treatment delivered at the various institutions. For example, while the investigators did stratify by surgery and by systemic therapy, there was no attempt to stratify by type of surgery. It has been demonstrated that partial nephrectomy offers equivalent cancer control and potentially better long-term survival when compared to radical nephrectomy (17), and a delineation of the type of surgical treatment offered at HVC *vs.* LVC may have helped to explain the reason for the difference in OS. Additionally, the study did not report utilization of immunotherapy. Immunotherapy has been demonstrated to result in superior OS outcomes for patients with advanced RCC (3), and one possible explanation for the superior OS observed in HVCs may be greater use of effective immunotherapy. While this is coded for in the NCDB, an analysis of its use was not present in the investigation, which may also have helped to elucidate the reasons behind the observed difference in OS.

The results of this study are important in that they suggest differences in treatment quality can have a meaningful impact on OS for patients with mRCC. The reasons for the observed difference in OS are unclear, likely multifactorial, and unable to be fully explained in the paper by Joshi *et al.* (15). Nevertheless, these results highlight the importance of delivering high quality treatment, and that the quality of treatment delivered can potentially improve OS for patients with mRCC. Further exploration is required to determine the reasons for these observed OS differences

so that greater standardization of treatment can be achieved with the goal that all patients are able to receive the highest quality of care.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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