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The next generation in surgical research for patients with spinal metastases

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Since the landmark randomized trial of Patchell and colleagues was published in 2005¹, enthusiasm for surgical intervention as a treatment for patients with spinal metastases has increased substantially^{2–5}. This, combined with parallel improvements in adjuvant therapies, enhanced perioperative safety, efficiency and surgical techniques have culminated in the fact that spine surgical procedures are now considered viable treatment options for individuals who little more than a decade ago would not have been deemed candidates for anything beyond palliative care, let alone a major operative event.^{4,5} As acceptance for spine surgery as a standard (and sometimes preferred) approach for the treatment of spinal metastatic disease has grown among the orthopaedic spine, neurosurgical and oncology communities, so have the number of papers touting the advantages and value of these interventions.^{2–10} Within the last five years a variety of research reports have appeared in print maintaining advantages of surgical intervention alone, or in combination with chemotherapy and/or radiation, for patients with spinal metastases as a whole, those with metastases resulting in epidural compression and individuals with metastases from lung cancer and breast cancer, among others.^{2–10} Research has confirmed the importance of surgical volume and experience as drivers of perioperative outcomes in the setting of spinal metastases⁵ and there are now a variety of competing scoring systems, many of which are intended to inform surgical decision making, patient expectations and the risk of adverse events following surgery.^{4,7} The question remains, however, as to the best means of applying these myriad research studies, data points and prognostic schemes to clinical practice and patient care. Moreover, physicians and surgeons who devote sizable portions of their practice to the treatment of patients with spinal metastases will ask what should the next generation of research look like in order to help advance the field.

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Although there are invariably differences between practices across the US and globally, at present there are several typical scenarios that result in a recommendation for surgical intervention for patients with spinal metastases: 1) Precipitous neurological decline resulting from spinal canal compromise, instability, or other impingement of neural structures; 2) Intractable pain in patients with structural compromise who have otherwise failed non-operative management, or for whom non-operative treatment is not considered appropriate; 3) Spinal metastases from primary tumors felt to be radio-resistant, not amenable to chemotherapy, or where non-operative management is unlikely to achieve the desired effect (e.g. structural instability with high risk of neurological compromise, solitary metastasis); 4) Determination that surgical intervention is likely to preserve or enhance functional independence to a greater extent than non-operative care.

At the same time, it is generally understood that there is a great deal of clinical heterogeneity within the population of patients who present with spinal metastases and the benefits of surgery are not only variable but may also be stochastic to some degree. A patient with a solitary metastatic nidus from breast cancer, for example, would not be anticipated to have a similar outcome following surgery as an individual with diffuse lung metastases involving multiple organs and regions of the spine. In addition, a patient whose symptoms include neurological impairment or imminent paraplegia is more likely to derive immediate benefit from a surgical intervention when compared to an individual solely with axial pain, while simultaneously having elevated risks of perioperative complications and early mortality.^{4,6,7,8}

Many recent studies support the notion that surgical intervention does a better job of preserving ambulatory capacity and functional independence and that these clinical characteristics are both directly tied to, if not mediators of, long term survival.^{1,2,6,7,8} These facets were initially touched on in the work of Patchell et al¹ and elaborated further in terms of describing the influence of pre-operative performance score in the prospective multicenter effort published by Choi and colleagues². A multicenter retrospective effort published by our own group found that patients who were independent ambulators at the time of surgery had close to a 10-fold advantage in the odds of survival at 30-days following surgery and a three-fold advantage at 90-days after the procedure.³ This led us to include pre-operative ambulatory capacity as one of the prognostic factors included in the New England Spinal Metastasis Score (NESMS), a predictive algorithm intended to inform the risk of peri-operative morbidity as well as long term survival following surgery.⁴

One of the critical disconnects that persists at present, however, is how to apply the evidence presented above to the highly variegated clinical presentation, treatment goals and anticipated longevity for patients with spinal metastatic disease. We understand the influence of pre-operative function, nutritional parameters and tumor characteristics on complication risk and intermediate survival^{2-4,6-9}, but many studies seem to ignore the very tangible risks of surgical intervention itself. Patchell et al reported median survival for patients treated surgically in the range of 4 months¹, with Choi et al reporting 50% survival at one year after surgery². However, our retrospective multicenter study found the mortality rate to be close to 10% at 30-days and 30% at 3-months.³ Similar findings were encountered in an effort that relied on data from the National Surgical Quality Improvement Program.⁴ To this, we should

add that the complication rate for these procedures has been found to approximate 50% in certain instances, especially among individuals with truncated survival.³ The risk of surgery also includes an often unrecognized but unavoidable peri-operative reduction in independence in patients who already have a limited life-expectancy as well as the fact that iatrogenic or nosocomial events around the surgical procedure may irrevocably alter neurologic function and even hasten mortality in certain circumstances. These realities are less of a concern in a patient presenting with progressive neurologic decline or frank paralysis, where surgical decompression and stabilization may represent the only treatment option with some hope for functional recovery. The outlook is vastly different, however, for an individual who is neurologically intact and functionally independent yet for whom surgery is still being entertained.

Given the retrospective nature of much of the evidence base, the role of selection, indication and expertise bias in influencing reported outcomes is difficult to quantify, let alone tease out in order to present an anticipated independent effect of surgery. It remains possible that in many of these reports, the sunny outlook for surgery derives from the fact that only individuals who can tolerate the procedure, and are most likely to benefit from such an intervention (e.g. the most functional patients who also have the greatest life expectancy), ultimately receive a surgery. Patients who are too ill or debilitated, have additional co-morbidities, or are otherwise deemed unsuitable for a procedure are not considered in efforts focused solely on receipt of surgical interventions. As surgery is an irreversible life event, the counterfactual remains that in some respects patients deemed eligible for a procedure may have similarly benefitted from non-operative care without having to assume the attendant peri-operative risks. Furthermore, the fact that most of the available literature derives from limited patient samples treated at single centers by individual surgeons or a select group of providers means that the findings are not necessarily translatable to other practices elsewhere in the United States or other parts of the world.

To summarize, then, the current limitations in the body of literature supporting surgical intervention for patients with spinal metastases: There is an impaired capacity to make individualized recommendations for patients based on their primary tumor characteristics, pre-operative functional levels and symptoms; It is difficult to understand the influence of selection, indication and expertise bias on the results of most retrospective research; Limitations in sample size and the reality of single center derivation for most studies means that the capacity for generalization to other clinical contexts remains open to question. Investigations that directly confront these challenges should likely represent the next generation in surgical research for patients with spinal metastases.

Recognizing that randomized prospective trials will probably not be supported on this topic in the future, the field must rely on prospective observational studies that ideally would be multidisciplinary and multicenter in scope. Individual research efforts should be hypothesis driven and focused to a specific type of patient with spinal metastases whenever possible, including careful attention to primary tumor characteristics, symptoms at presentation and functional status when tailoring inclusion criteria a-priori. Enrollment should include both operative and non-operatively treated patients, as well as those who receive expectant or palliative care for whatever reason, so that natural history can be observed in a more

balanced way and post-hoc comparisons subsequently engendered. In a sufficiently homogeneous population, causal inference statistical techniques such as inverse probability weighting or propensity matching can be employed to simulate the clinical equipoise typically associated with randomized studies.

In these scenarios the prospective nature and a-priori elaboration of primary outcome(s) and study-specific measures can serve to minimize the potential for selection, indication and information bias. Selection and indication biases may also be mitigated through the inclusion of surgical as well as non-operative patients and the use of causal inference approaches in the analysis. Multicenter design and a reliance on multidisciplinary research teams will further aid in the translational capacity and generalizability of study findings.

Undoubtedly, spine surgical research over the last 10–20 years has advanced our understanding regarding the potential benefits of these procedures and the value they can impart to patients with spinal metastases. The next generation of spine surgical research in this arena must be devoted to generating evidence-based recommendations for patients who present with specific clinical patterns, and symptomatic spectrums of disease, while simultaneously minimizing the potential for selection, indication and other associated biases to confound generalization and the translational capacity of study results to everyday patient care. It is our hope that the recommendations imparted above can serve to galvanize this next step forward and help to generate the best available evidence to both inform surgical decision making and advance comprehensive care for patients with this challenging spinal disorder.

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