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Randomized Controlled Trials and High Intensity Spine Surgery

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The randomized controlled trial (RCT) has been considered the gold-standard in scientific experimentation since it was first introduced in 18th century studies regarding treatment for scurvy.¹ More recently, and specific to the spine surgical field, investigations such as the Spine Patient Outcomes Research Trial (SPORT)² and the Spinal Laminectomy versus Instrumented Pedicle Screw (SLIP)³ trial have immeasurably contributed to the understanding of spinal disease and advancements in spine surgical care. At the same time, the RCT has been lionized given its scientific prominence and the high visibility of successful RCTs conducted in spine surgery and other areas of medicine. As a result, it is not unusual to see retrospective studies suggesting that RCTs are needed to further evaluate the impact of specific interventions or improve understanding in certain clinical contexts. Some of these, such as RCTs studying the effect of symptom duration on outcomes in lumbar radiculopathy⁴, are more likely to be conducted and completed than investigations that are fraught with ethical and logistical dilemmas like the use of magnetic resonance imaging in cervical spine evaluation after trauma⁵, or chemoprophylaxis for venous thrombo-embolic disease following spine surgery⁶.

Most of the RCTs that have been completed in the field of spinal medicine involve elective spine surgical interventions, such as discectomy for herniated lumbar discs², or decompression and instrumented fusion for spondylolisthesis and spinal stenosis³, or the treatment of spinal fractures in neurologically intact patients⁷. While there are certainly risks and benefits to any intervention, and a complication profile exists for all spine surgical procedures to some degree, the stakes tend to be lower for the most part when considering the types of spine surgery involved in most RCTs. For example, in the SPORT study involving discectomy, there were no perioperative deaths² and in the RCT of Wood et al regarding thoracolumbar burst fracture management, 2/53 patients died within two-years of study enrollment⁷.

In contrast, the risks of morbidity and mortality are typically much higher, and the stakes of any intervention considerably greater, in the context of high-intensity spinal disorders. High-intensity spinal conditions are those that carry high acuity, with potential for precipitous

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physiological and functional decline and, consequently, long-term ramifications for physical function, independence and survival.⁸ Examples of high-intensity spinal disorders include traumatic spinal cord injury associated with fracture or dislocation, epidural abscess and spinal metastatic disease. The treatment of these conditions is expensive and often requires experienced, multidisciplinary teams, with relatively low degrees of clinical equipoise and high levels of preference-based care.^{9,10,11,12,13}

While some RCTs have been completed in these arenas in the past, such as the oft-cited work of Patchell et al in 2005¹⁴, the fact of the matter remains that both surgical and non-operative treatments have advanced considerably since that time, including improvements in minimally invasive procedures, interbody constructs, radiation techniques and the use of immunotherapy¹³. The landscape of the spine surgical field, as well as that of oncology, radiation oncology, pain management and physiatry cannot be considered comparable to that of 1992, when Patchell's study was initiated, or even 2002 when the investigation was concluded.

We now know that in certain situations early surgical intervention can improve physical function and longevity in the setting of spinal metastatic disease^{11,13}, spinal cord injury¹⁵ and epidural infection¹⁶. Due to the availability of the internet and enhanced healthcare literacy (both with respect to peer-reviewed and anecdotal/spurious literature), patients and families are able to access scientific work nearly as readily as physicians. As a result, in the information age, there is less objectivity and more preference-driven care in these contexts than there may have been nearly 30 years ago. In fact, in recent qualitative work conducted among patients receiving treatment for spinal metastatic disease, strong preferences were expressed by these individuals for either operative or non-operative intervention.¹² Furthermore, the magnitude of the diagnosis and the prospect for irrevocable impact on functional status and survival led many patients to defer to their clinicians' judgment or the decision of a multidisciplinary team, regarding the treatment course that best suited their needs.¹² These realities would invariably raise ethical concerns regarding the conduct of RCTs among such vulnerable populations and difficulty recruiting a sample of sufficient size to allow for meaningful comparisons of outcomes.^{15,17} This could also lead to large degrees of non-adherence to the randomized treatment among patients who did consent, which presents a particular challenge in interpreting the outcomes of an RCT.¹⁷ As non-adherence approaches 50% in any treatment arm, especially in the context of operative versus non-operative management, the results of an RCT analyzed using the appropriate intent-to-treat protocols have limited implications for direct patient care.¹⁷

If we recognize the inherent challenges in conducting an RCT capable of informing patient care in high-intensity spinal disorders, it is also appropriate to ask: what would represent the most feasible approach to developing high-quality evidence? While relatively large, prospective studies have been completed in both the areas of spinal cord injury¹⁵ and spinal metastatic disease^{9,10}, these remain prone to confounding by selection and indication bias at a minimum. At the same time, these investigations do demonstrate the potential for assembling large-scale cohorts of patients with high-intensity spinal disorders, across multiple centers, short of the need for randomization. There are reasonable, stepwise, approaches that can be conducted in these contexts that would also allow for research that

approximates the equipoise built in to randomized trials¹⁸, while simultaneously enabling optimal patient care that honors the preferences of patients and their families.

Such an approach would rely on a multi-disciplinary team of operative and non-operative investigators, supplemented by an advisory council where deemed necessary. The multi-disciplinary team would establish a pre-determined set of inclusion and exclusion criteria, agreed to by both operative and non-operative researchers and clinical contributors, that would mirror what would be considered the entry criteria for the randomized trial that the prospective observational study intends to emulate. In phase two, an independent board of researchers and clinicians, including the advisory council as appropriate, should review the eligibility of all cases enrolled by study sites and ensure that entry criteria and necessary clinical equipoise are met. Given the time-sensitive nature of high-intensity surgery, one recognizes that patients may already be receiving, or have completed, treatment by the time their case is reviewed by the adjudicating board. If a case is not deemed eligible for the study due to issues with the inclusion criteria, that patient could still be followed in a separate arm of the investigation. Their outcomes would not be included, however, in the analyses that intend to emulate the RCT. In the third phase, an appropriate statistical strategy that can address residual confounding from selection, or preference-based, confounding would be performed. This could consist of appropriately powered and performed propensity score matching techniques^{18,19} (where the propensity score is constructed around the likelihood of surgery) or other approaches such as logistic regression with an unstructured correlation matrix estimated by generalized estimating equations.

In conclusion, technical advances in healthcare and the current environment serve to render prior RCTs in the field of high-intensity spinal surgery obsolete at the same time they materially impair the capacity for similar level-I research to be conducted in the future. While the possibility of an RCT in the areas of spinal cord injury, epidural infections or spinal metastases is not impossible, outside of certain trials in niche aspects of these disorders level-I evidence is not likely to be forthcoming in the near term. Given the high-stakes nature of these conditions for patients, I think this is understandable and should be honored. At the same time, this reality should not prevent us as a field from developing the best-available evidence possible through thoughtful and well considered approaches to the conduct of prospective, observational investigations. While certainly not the only plausible manner through which a study that approximates a randomized trial can be performed, the steps I outline here would at a minimum facilitate high-quality research that balances the need to develop evidence capable of equitably informing patient care against the inherent risks that randomization may pose to patients and study integrity in the setting of high-intensity spine surgery.

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References

1. Dunn PM. James Lind (1716–94) of Edinburgh and the treatment of scurvy”. Arch. Dis. Child Neonatal Fetal Ed. 1997;76: F64–65.
2. Weinstein JN, Tosteson TD, Lurie JD, Tosteson AN, Hanscom B, Skinner JS, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. JAMA. 2006 22;296(20):2441–50.
3. Ghogawala Z, Dziura J, Butler WE, Dai F, Terrin N, Magge SN, et al. Laminectomy plus Fusion versus Laminectomy Alone for Lumbar Spondylolisthesis. N Engl J Med. 2016;374(15):1424–34. [PubMed: 27074067]
4. Bailey CS, Rasoulinejad P, Taylor D, Sequeira K, Miller T, Watson J, et al. Surgery versus Conservative Care for Persistent Sciatica Lasting 4 to 12 Months. N Engl J Med. 2020;382(12):1093–1102. [PubMed: 32187469]
5. Schoenfeld AJ, Tobert DG, Le HV, Leonard DA, Yau AL, Rajan P, et al. Utility of adding magnetic resonance imaging to computed tomography alone in the evaluation of cervical spine injury: a propensity matched analysis. Spine (Phila Pa 1976) 2018;43:179–84. [PubMed: 28632646]
6. McLynn RP, Diaz-Collado PJ, Ottesen TD, Ondeck NT, Cui JJ, Bovonratwet P, et al. Risk factors and pharmacologic prophylaxis for venous thromboembolism in elective spine surgery. Spine J. 2018 ;18(6):970–978. [PubMed: 29056565]
7. Wood K, Buttermann G, Mehdod A, Garvey T, Jhanjee R, Sechriest V. Operative compared with nonoperative treatment of a thoracolumbar burst fracture without neurological deficit. A prospective, randomized study. J Bone Joint Surg Am 2003;85: 773–781. [PubMed: 12728024]
8. Schoenfeld AJ. Balancing Risks and Benefits in High-Intensity Surgery for Spinal Tumors. Spine (Phila Pa 1976). 2019 Dec 10. doi: 10.1097/BRS.0000000000003362. [Epub ahead of print].
9. Choi D, Ricciardi F, Arts M, Buchowski JM, Bunger C, Chung CK, et al. Prediction accuracy of common prognostic scoring systems for metastatic spine disease: Results of a prospective international multicentre study of 1469 patients. Spine 2018;43: 1678–1684. [PubMed: 30422958]
10. Schoenfeld AJ, Blucher JA, Barton LB, Schwab JH, Balboni TA, Chi JH, et al. Design of the prospective observational study of spinal metastasis treatment (POST). Spine J. 2019 Nov 8 pii: S1529–9430(19)31068-X. doi: 10.1016/j.spinee.2019.10.021. [Epub ahead of print].
11. Schoenfeld AJ, Losina E, Ferrone ML, Schwab JH, Chi JH, Blucher JA, et al. Ambulatory status after surgical and non-surgical treatment for spinal metastasis. Cancer 2019; 125: 2631–2637. [PubMed: 30985913]
12. Lape EC, Katz JN, Blucher JA, Chen AT, Silva GS, Schwab JH, et al. Patient experiences in decision-making in the treatment of spinal metastases: A qualitative study. Spine J 2019 Dec 30. pii: S1529–9430(19)31156–8. doi: 10.1016/j.spinee.2019.12.018. [Epub ahead of print].
13. Shankar GM, Van Beaver LA, Choi BD, Hadzipasic M, Sivaganesan A, Karhade AV, et al. Survival after surgery for renal cell carcinoma metastatic to the spine: Impact of modern systemic therapies on outcomes. Neurosurgery 2020 (Accepted for publication 3/30/20).
14. Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: A randomised trial. Lancet 2005;366: 643–648. [PubMed: 16112300]
15. Fehlings MG, Vaccaro A, Wilson JR, Singh A, W Cadotte D, Harrop JS, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PLoS One. 2012;7(2):e32037. [PubMed: 22384132]
16. Kim SD, Melikian R, Ju KL, Zurakowski D, Wood KB, Bono CM, et al. Independent predictors of failure of nonoperative management of spinal epidural abscesses. Spine J 2014;14: 1673–1679. [PubMed: 24373683]
17. Anderson PA, McCormick PC, Angevine PD. Randomized controlled trials of the treatment of lumbar disk herniation: 1983–2007. J Am Acad Orthop Surg. 2008;16(10):566–73. [PubMed: 18832600]
18. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758–64. [PubMed: 26994063]

19. Ho DE, Imai K, King G, Stuart EA. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Political Analysis* 2007;15: 199–236.

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