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Authors

Powell, Kerrington
Marquart, John
Olivier, Timothée
et al.

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Commentary

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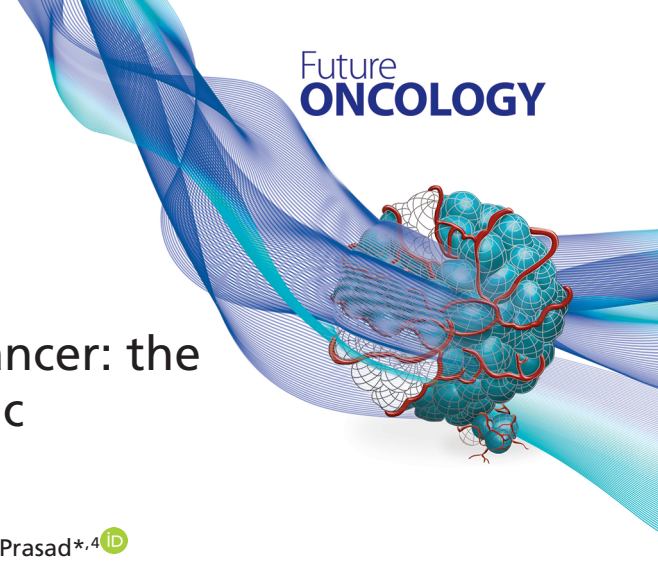

The role of surgery in metastatic cancer: the case for a pragmatic tumor-agnostic randomized trial

Kerrington Powell[1], John Marquart[2], Timothée Olivier[3,4] & Vinay Prasad*[,4]

[1]School of Medicine, Texas A&M Health Science Center, Bryan, TX 77807, USA

[2]Department of Surgery, Medical College of Wisconsin, 999 North 92nd Street, Suite CCC 320, Milwaukee, WI 53226, USA

[3]Department of Oncology, Geneva University Hospital, 4 Gabrielle-Perret-Gentil Street, 1205, Geneva, Switzerland

[4]Department of Epidemiology & Biostatistics, University of California San Francisco, 550 16th St, 2nd Fl, San Francisco, CA 94158, USA

*Author for correspondence: vinayak.prasad@ucsf.edu

"In this paper, we propose a framework for conducting randomized controlled trials (RCTs) that assess the effectiveness of metastasectomy irrespective of histology or anatomy, focusing instead on factors such as growth rate kinetics to determine the therapeutic efficacy of surgical intervention. This strategy may help identify target patients who will benefit regardless of the specific tumors they harbor."

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In current oncology practice, most patients with metastatic disease are managed with systemic treatments that target all sites of illness. Surgery is rarely employed in the care of a metastatic patient, though when it occurs it is often critical. Currently, patients with metastatic cancer are eligible for one of three types of surgery: the primary tumor may be removed or debulked for local (breast cancer) or systemic benefit (kidney cancer); metastatic lesions may be removed (i.e., metastasectomy) to result in cure (colorectal cancer) or prolonged survival; or a combination of both chemotherapy and surgery may be performed, such as with intraperitoneal hyperthermic chemoperfusion. These procedures are often driven by tumor histology, location, number of metastases, comorbid conditions, palliative intent and the unique history of surgery over the last 200 years. In this paper, we propose a framework for conducting randomized controlled trials (RCTs) that assess the effectiveness of metastasectomy irrespective of histology or anatomy, focusing instead on factors such as growth rate kinetics to determine the therapeutic efficacy of surgical intervention. This strategy may help identify target patients who will benefit regardless of the specific tumors they harbor.

Despite a paucity of RCTs supporting its use, metastasectomy continues for specific tumors and patients in high-volume centers [1]. In an ideal world, surgical intervention for a metastatic cancer patient would consider the following analogy. First, imagine a speedometer. The left side of the speedometer, where speeds are slow, is meant to indicate that some cancers can be characterized as turtles (in reference to the popular barnyard analogy regarding tumor progression) [2]; that is, they represent indolent disease with a favorable prognosis. The aggressive fast-growing maladies that are likely to metastasize uncontrollably and become lethal – the birds – are on the other side of the speedometer, where speeds are fast. In the center is a gray zone, where metastasectomy may provide survival gains: here is where the rabbits may be 'caught'. This zone likely contains disease of low volume (i.e., surgical extirpation will make substantial inroads) with a slow growth rate (i.e., recurrence does not rapidly occur in the postoperative period) and with limited sites. It is within the gray zone that we recommend conducting studies based on a coefficient of biology rather than tumor histology.

To some extent, retrospective efforts have been made to identify patients who present with this so-called 'sweet spot' of growth kinetics (i.e., those likely to obtain a survival benefit from metastasectomy). Due in part to the failure of previous RCTs involving metastasectomy to accrue patients [3], researchers are now attempting to identify

prognostic biomarkers – among other clinical factors – in order to gain insight into metastatic tumor biology, and as a result of that insight, to adjust surgical management procedures to improve patient outcomes [4]. The concept is analogous to how researchers utilize growth-rate kinetics to guide the development of chemotherapeutic agents; monitoring a tumor's growth parameters may also be advantageous for surgical treatment management. However, due to reliance on uncontrolled data, we have no way of determining whether these invasive procedures provide a net benefit over less invasive modalities; and perhaps equally as important, these prognostic biomarkers remain unvalidated and subject to bias.

By conducting RCTs based on biological coefficients, the underlying premise becomes a window of tumor growth kinetics in which metastasectomy is either advantageous or not. Despite the observational nature of the study, Lee *et al.* reported a positive correlation between a tumor doubling time (TDT) ≥61 days and 5-year post-metastasectomy survival in the setting of pulmonary metastasectomy [5]. The purpose of the study was to determine whether TDT has prognostic significance for resection eligibility and survival in metastatic melanoma patients with pulmonary lesions following metastasectomy. Owing to possible confounding factors, this remains uncertain, but the study succeeded in paving the way for prospective validation. Clinical intuition dictates that patients with longer TDTs will have a better prognosis regardless of the treatment modality they receive, or lack thereof, owing to their fundamentally more indolent biology. In fact, professional consensus statements on the treatment of pulmonary lesions in patients with metastatic melanoma identify TDT as a predictor of overall survival [6]. Related to TDT, international guidelines mention a long disease-free interval as associated with favorable outcome after ablation of metastases (e.g., in renal cell carcinoma), or allowing patient selection for metastasectomy in soft-tissue sarcoma [7,8]. What is unknown is whether prolonged TDT indicates which patients benefit the most from metastasectomy or if certain individuals are destined to live longer regardless of whether they have the procedure [9]. Because these prognostic indicators were developed from observational studies on a limited number of highly selected cancer patients who were not compared with a control group, their reliability as an effective predictive value is limited.

To strengthen the evidence base for one indication for metastasectomy, an important RCT was attempted: the PulMiCC trial [10]. This study sought to randomize metastatic colorectal cancer patients with lung metastases to undergo metastasectomy or not. However, the trial was stopped early owing to deteriorating patient recruitment. We speculate that one barrier to this trial was that it only selected patients with metastatic colorectal cancer and imposed additional and more stringent inclusion criteria, such as the location of metastases. Despite its shortcomings, this trial served as an invaluable lesson and prompts the following question about future trials: is it feasible to reimagine the experiment in a tumor-agnostic context?

One strategy is to conduct a large pan-tumor RCT. This trial could incorporate all metastasectomies that a surgeon wishes to perform over a 5-year period into a registry-based RCT in which patients are randomly assigned to surgical intervention or not. Our primary inclusion criterion is that a surgeon deems resection feasible, practical and reasonable. By conducting such a large trial, sufficient power will be acquired to determine whether there are differences in patient outcomes according to tumor type, growth rate kinetics, or other subgroup prognostic factors (i.e., tests for interaction).

This complements the approach of Stein *et al.*, who pooled data from five National Cancer Institute prostate cancer trials to investigate the relationship between growth rate constants and survival outcomes and proposed that growth constants could be validated as a potential surrogate end point for therapeutic efficacy in the future [11]. Although the trials they studied were randomized, their retrospective analysis is not immune to selection and other biases, and the authors propose that RCTs be conducted for validation [11]. An important advantage of our trial design is that, in contrast to other retrospective studies that are prone to confounding variables (most notably concerns of confounding by indication), this trial design minimizes them.

To conduct our proposed randomized study, a single-payer healthcare system, such as that found in the UK, could elect to pay for metastasectomy only as part of the randomized trial protocol. Alternatively the Centers for Medicare & Medicaid Services could fund such a study, just as it is covering the Alzheimer's disease drug aducanumab only for Medicare patients who enroll in clinical trials [12]. Additionally, to solve accrual difficulties, a pragmatic trial design based on a catch-all strategy would be implemented [13]. Certain opponents may raise objections to this approach, citing limitations in the heterogeneity of trial participants, such as the number and location of metastases and the need for precise and predefined conditions. However, by using an all-comers approach rather than more stringent inclusion criteria like those used in the PulMiCC trial [3], adequate accrual may be achieved while simultaneously enrolling a patient population typical of the real world, yielding a more accurate appraisal of metastasectomy's

effectiveness. An advantage of such rapid accrual is that any modification in systemic treatment strategies during the accrual period will be less likely to affect the results' applicability.

One recent example of such a study that utilizes our design is the RECOVERY trial, which employed a pragmatic design to examine different therapies for patients hospitalized with COVID-19 [14]. Readers may be worried about the constraints of such a design, such as the inability to identify a core efficacy subgroup, but commentators point out that these concerns are circumvented, and even capitalized on, by using prespecified subgroup analysis [15,16]. The same principles may be applied to our proposed trial design by measuring patients' tumor growth rate constants prior to enrollment by either using serial radiological data or any other growth kinetic coefficient deemed appropriate [17]. Even if the trial results are negative, it is still possible to identify predefined subgroups that benefit, while also including components of prospective biomarker validation. This is important because while the trial may not result in an overall benefit, some subgroups may demonstrate a clear advantage with metastasectomy, allowing the potential for strategic extrapolation. As part of the analysis, we would be able to establish the appropriate patient populations to target.

With an adequately powered catch-all trial, we will be able to answer the following questions. First, does metastasectomy improve survival? And second, does it vary according to the clinical scenario; for example, does the histology of the initial tumor matter? Is the rate of growth significant? Do the number of metastatic sites and their location matter? We speculate that metastasectomy may be beneficial for young individuals whose tumors have moderate growth rates and few metastatic sites, but not for elderly people with rapid growth rates and numerous sites. However, what if none of these scenarios are true? What if both groups benefit – or, worse, if neither group benefits? The only way to develop a gold-standard method for addressing these issues is through randomization.

There may be immediate concerns about the number of patients required to appropriately power a study to address these questions. Between the years 2000 and 2011, an estimated 192,221 metastasectomies (16,018 per year, on average) were performed for colorectal, lung and breast cancers and melanoma, with a significant upward trend in the frequency of these procedures [1]. In a comparable pragmatic registry-based RCT, the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial showed 61% accrual rate for all patients who would have otherwise undergone a procedure during the nearly 3-year enrollment period [18]. Assuming more conservative values – with 50% accrual rate and 15,000 procedures per annum, and a control arm median survival of more than 3 years (based on the PulMiCC trial) – a trial enrolling 15,000 patients over a 2-year period would have a statistical power higher than 99.9% to detect a hazard ratio of 0.80 ($\alpha = 0.05$; eMethods in Supplementary Materials). One could argue that such high numbers of patients are impossible to accrue. However, with a power of 80%, the same trial would need to accrue only 2000 patients over 2 years to detect the same 0.80 hazard ratio difference. In other words, given a high accrual rate, the trial would have sufficient power for interaction analysis in prespecified subgroups, as the RECOVERY trial has been constructed [15].

Perhaps most importantly, barriers must be addressed while organizing such a study. Equipoise is one such issue. While it is vital to acknowledge the difficulty and complexity of establishing studies comprising surgical interventions, particularly those involving patients with metastatic disease, the absence or difficulty of obtaining randomized data cannot result in fatalism as an excuse for not attempting to procure it. We recognize that conducting RCTs in the surgical setting is challenging due to the inability to standardize procedures, the difficulty of implementing adequate blinding and, maybe most difficult of all, adequately conveying equipoise [19]. In contrast, when interventions are adopted and incorporated into existing practice without conducting randomized trials, equipoise often becomes poisoned. One such example is seen by the rationale for metastasectomy's use in the management of advanced sarcomas, which proponents contend should not even be debated, let alone put to trial [20,21]. This is an illustration of how, even with a lack of randomized evidence, surgical ablation of lung metastases from sarcomas has gained broad acceptance to the point that contesting it may be prohibitive. This acceptance may be related to the poor results associated with systemic therapies, but maybe more significantly, to the lengthy wait for rigorous studies to be conducted [20]. Importantly, if our proposed trial is successful – as we expect it will be in at least some subgroups – surgeons can enthusiastically offer the procedure and increase uptake of a life-extending intervention. It is almost certain that current surgical referral patterns will be deemed suboptimal, as many patients are not considered for metastasectomy.

We believe that there is equipoise to conduct our proposed trial, and that previous RCTs in metastatic cancer patients demonstrate the need to maintain humility when dealing with observational data. Consider that resection of the primary tumor in women with metastatic breast cancer was previously thought to provide a survival advantage, as shown by nearly a dozen retrospective studies in a meta-analysis [22]. However, after an RCT was conducted to

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test this hypothesis, the data shifted, revealing that the intervention did not confer a survival advantage and that the retrospective analyses were influenced by the examples of bias discussed throughout this manuscript [23]. Although this is a different procedure, the insights garnered from this trial are pertinent to metastasectomy's present and future use in the care of metastatic cancer patients. Surgical intervention must be in the interest of the patient; in addition to the medical risks, these extensive procedures include psychological, social and financial toxicities, all of which may have a substantial impact on a patient's quality of life [20]. As a result, it is critical to establish a standard of evidence for these procedures and to identify patient groups that benefit from them in order to prevent ineffective therapy and harm for others.

In conclusion, the paucity of data supporting metastasectomy, along with an abundance of unvalidated prognostic biomarkers, presents an opportunity to conduct a pragmatic, nationally sponsored, open-label study for metastatic cancer patients. By using prespecified subgroups, appropriate candidates for metastasectomy may be identified based on tumor type, growth dynamics, the number of metastatic sites and their locations, or any other prognostic characteristic preferred by investigators. Patients who do not benefit from this intervention will avoid potential harm, while the evidence base for metastasectomy will strengthen and guide future research. Importantly, patients who do benefit are currently unknown in the current system, and thus surgery may only be infrequently offered to them. Identifying and defining these patients has potential to increase the number of life-extending procedures performed annually.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0840

Author contributions

V Prasad conceptualized the study design; K Powell and J Marquart reviewed literature; T Olivier performed statistical analysis; V Prasad, T Olivier and J Marquart reviewed and confirmed abstracted data; K Powell wrote the first draft of the manuscript; and all authors reviewed and revised subsequent and finalized drafts of the manuscript.

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