Exploring opposing arguments in the call for randomized controlled trials to demonstrate benefit of Mohs micrographic surgery for cutaneous melanoma

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Abstract

Importance: The call for robust randomized clinical trials (RCTs) comparing Mohs micrographic surgery (MMS) with wide local excision for treatment of melanoma has stymied the development of guidelines for MMS despite growing evidence of benefit. This commentary explores the controversy by detailing opposing arguments, reviewing the relevant evidence supporting the use of MMS for early-stage melanoma, and discussing the role that RCTs may play in development of national guidelines for surgical treatment options for melanoma. Randomized clinical trials are considered the gold standard of clinical research, but there are no such trials currently to support MMS for melanoma. However, there is a growing literature base of retrospective and prospective cohorts and meta-analyses consistently demonstrating the efficacy and cost-effectiveness of MMS for melanoma. The dearth of clear consensus guidelines has contributed to confusion by referring specialties, controversy across specialties managing melanoma, and inequality in access. Recognizing that this is an ongoing area of discussion within dermatologic surgery, we explore opposing arguments with regard to the demand for RCT data to support dermatologic surgery practices.

Keywords: clinical trial, cutaneous melanoma, Mohs micrographic surgery, opposing arguments

Introduction

The call for evidence-based clinical guidelines for surgical management is increasing as the utilization of Mohs micrographic surgery (MMS) for melanoma more than doubled from 3.5% in 2004 to 7.6% in 2019 [1]. The 2022 National Comprehensive Cancer Network (NCCN) guidelines were pivotal in that they suggested that MMS may be considered for in situ disease but recommend against using MMS for invasive melanoma when standard margins are possible. Instead, guidelines propose MMS be utilized selectively for minimally invasive (T1a) melanomas in anatomically constrained areas [2].

Recognizing that this is an ongoing area of discussion within dermatologic surgery, we explore opposing arguments regarding the demand for randomized controlled trial (RCT) data to support dermatologic surgery practices. Growing evidence from retrospective and prospective studies and meta-analyses has demonstrated commensurate to improved modest survival, local recurrence, and cost benefits for MMS over wide local excision (WLE), [3-8]. Moreover, MMS offers potential benefits, including a tissue-sparing approach, patient piece of mind with same-day complete margin assessment, and reproducible interpretation of frozen histopathology slides with the evolution of immunohistochemistry techniques. Despite this evidence of its benefits, one barrier to expanding guidelines for MMS is the lack of RCTs comparing

MMS to WLE. This raises the question: what value would an RCT assessing MMS for melanoma provide?

Observational studies for Mohs micrographic surgery

Observational studies make up the bulk of supportive evidence for the use of MMS for melanoma. From the first large cohort published by Dr. Frederic Mohs in 1977 [9], there have been over 70 such articles describing modern MMS and staged excision techniques, comprising more than 17,000 patients, at least 12 non-randomized comparative studies, and more recently large multicenter cohort studies that have expanded the literature pool [8,10]. However, these methodologies are also prone to bias and confounding owing to a lack of randomization and investigator control that cannot be fully eliminated even with careful study design and statistical analysis [11,12]. One study analyzing the current evidence base for MMS and staged excision for melanoma found serious or critical bias in 47 of 48 observational studies, typically related to poorly defined outcomes such as local recurrence [13].

Pros and cons of randomized controlled trials

Currently, there is no RCT comparing MMS for melanoma to other surgical approaches. As observational studies have variance in reporting standards, many argue an RCT would be required to definitively demonstrate the efficacy of this therapeutic approach [14]. Randomized controlled trials are regarded as the gold standard for clinical research, with methodological strengths including explicit inclusion and exclusion criteria, precise interventions, premeditated endpoints, and inherent bias control [15]. Moreover, RCTs are adaptable to help answer specific research questions, including assessing whether MMS is better (superiority) than, or as good as (non-inferiority) WLE.

However, RCTs have many drawbacks. Patients are assigned randomly to each of the intervention arms in RCTs, bypassing the typical shared decision-making process of selecting appropriate treatment. Some have argued that to use WLE in lieu of MMS for early-stage melanoma of special sites would not be the standard of care, whereas others believe an RCT is required to make this determination. This is a hotly debated topic, though ethicists consider the local standard of care an important factor when designing an appropriate study control arm [16]. Cost is certainly an important factor to consider in designing an RCT for MMS, since long-term follow up is both expensive and required to assess outcomes of interest such as local recurrence and survival. The recruitment period may also be prolonged by the inability to recruit patients of interest, such as patients with special site melanomas such as the groin or acral lentiginous melanomas which are less frequently observed.

The equipoise principle

Clinical equipoise describes the genuine uncertainty within the expert medical community about the preferred treatment for a condition [17]. Mohs micrographic surgery for melanoma has been used widely for at least three decades and there has yet to be substantial evidence that this surgical technique results in worse outcomes for these patients. In fact, most familiar with the MMS literature know that it provides satisfactory cosmetic, functional, and oncologic outcomes for this population. Thus, some argue that to embark on a demonstrative RCT study for an already proven therapy would be detrimental to patients randomized to the control arm given the expected futility and the expectation that MMS may provide a tissue-sparing approach to patients [17,18].

Staunch RCT supporters may claim that all interventions need to be validated by this study design. Although there are extremely few black-and-white interventions with clear evidence of efficacy, it is contentious whether the accumulated literature supporting MMS is sufficient to mollify uncertainty regarding its role in the treatment of melanoma and whether clinical equipoise remains. Although there is substantial RCT-derived evidence supporting WLE as the gold-standard treatment for melanoma, the retrospective and prospective cohort studies demonstrating positive outcomes for patients with melanoma treated with MMS has engendered fervent support and implementation of this technique amongst those practicing MMS for melanoma. Some in favor of MMS for melanoma may feel this technique has experienced what is often

referred to as the Buxton law of surgical RCTs, in that the rapid adoption of this surgical technique makes a comparative trial difficult with the question of equipoise and interest in participation—"it's always too early until, unfortunately, it's suddenly too late" [19].

Why is the focus on melanoma?

Perhaps most perplexing is the polarizing demand for RCT data supporting MMS for melanoma when such data is lacking for other common MMS indications. There are no randomized trials comparing MMS with WLE for cutaneous squamous cell carcinoma and yet it is widely supported given a plethora of retrospective studies demonstrating effectiveness [20-23]. Similarly, recent NCCN guidelines based on retrospective comparative and non-comparative studies recommend MMS or other forms of *peripheral and deep en face margin assessment* for the treatment of dermatofibrosarcoma protuberans, and if unavailable, then WLE should be considered [24-33]. The higher potential for metastasis and disease-specific mortality likely fuels the controversy surrounding MMS for melanoma, but one must ask what is considered sufficient evidence to employ therapeutic modalities across the spectrum of dermatologic neoplasms.

In part, critics share concern that without taking wide margins for melanoma, non-contiguous disease including in-transit micro-metastases may exist beyond the excised MMS margins and potentially lead to higher rates of local recurrence, metastasis, and disease-specific death [34]. However, in-transit metastases are in fact very rare in WLE specimens and the available data shows at least equivalent oncologic outcomes [34-36].

Evidence supporting wide local excision

In contrast to MMS, WLE resection margins have been extensively studied and current recommendations are based on multiple multicenter randomized clinical trials including sample sizes ranging from 300 to nearly 1,000 participants that examined local recurrence rates with various surgical margins [37-43]. The need for large sample sizes to assess margin adequacy in part reflects the technological limitation of WLE, namely partial margin assessment. Wide margins are taken to increase the probability that the entire tumor is removed, whereas only a subset of the entire sample is histologically visualized, leading to potential underestimation of residual disease at margins. This has necessitated multiple large studies comparing initially arbitrary resection margins to fine tune the narrowest acceptable excision margins without negatively impacting patient outcomes. In contrast, MMS ensures complete circumferential and deep margin assessment to ensure complete tumor extirpation without sacrificing surrounding tissue, which is particularly important in special sites without large tissue reservoirs. Of note, some have made the argument that the tissue-sparing effect of MMS has not been demonstrated; however, an understanding of the MMS technique by definition entails tissue sparing as additional tissue resections are taken only in focal areas where there is histologically-proven tumor. Therefore, tumors that necessitate larger MMS defects result from subclinically-larger tumors and this does not suggest that MMS does not spare healthy tissue.

Recipe for a successful randomized controlled trials for melanoma

For an RCT evaluating MMS for melanoma to succeed, several criteria must be met. First, it must be sufficiently powered to assess outcomes of interest. Many RCTs aim to demonstrate that the intervention of interest is superior to reference treatment, requiring a very large sample size for sufficient power. Demonstrating that MMS for melanoma is not unacceptably worse than WLE with regard to local recurrence or disease-specific survival via a non-inferiority design would require fewer patients and also help to delineate its role in special sites where tissue sparing would provide clinical benefit.

The population studied must also be adequately generalizable. Disparities in health information are perpetuated when certain patient populations are excluded from clinical research. It has been well documented [44] that the proportion of dermatology clinical trials with sufficient ethnic and racial diversity has been lagging despite mandates from the Food and Drug Administration [45] and National Institutes of Health [46]. Including patients

with skin of color and melanoma subtypes that are more common in these patients such as acral lentiginous melanoma will help to maximize the generalizability of the study results.

Similarly, the widely varied practice patterns of MMS for melanoma must be addressed, including clinical margin assessment, first MMS layer margin size, tissue processing including the utilization of immunohistochemistry, and margin assessment techniques [47]. The key outcomes of interest, including the rates of local recurrence, in-transit metastasis, disease-specific survival, and overall survival must be clearly defined and tracked with sufficient follow-up. Follow-up of at least 5 years is warranted to allow for comparison of long-term patient outcomes between treatment modalities; many previous surgical RCTs for melanoma tracked patients from at least 5-years to more than 10-years [41-43]. One of the key deliverables of a well-designed RCT in this realm would be a clear public health message regarding which patients and tumors would be best treated with MMS.

Nebulous health messaging contributes to inequality

Pending RCT data, patients and front-line physicians do not have a clear, unified message regarding the best treatment strategy. This may create referral pattern biases. If clinicians are unaware that MMS may provide clinical benefit for patients with melanoma, they will not be able to refer these patients. As such, those without health literacy or access to self-research treatment options for their melanoma may be less likely to receive MMS for their treatment, potentially perpetuating inequity in access to MMS primarily for disadvantaged communities. Patients may thus be referred later for their care, resulting in larger tumor sizes and postoperative defects [48]. Even if RCT data were to demonstrate superiority of MMS for melanoma, would a unified message of efficacy be accepted by payors and healthcare providers alike?

Challenges to conducting a Mohs micrographic surgery randomized controlled trial for melanoma

One of the chief barriers to performing an RCT evaluating MMS for melanoma is funding. The dermatology-specific funding pool is relatively small and the difference in outcomes for surgically-managed melanomas may be too narrow a scope within the larger house of medical funding that typically prioritize disease-specific survival outcomes. In particular, federal funding for surgical RCTs has been declining in recent years, whereas many non-surgical RCTs are funded by pharmaceutical companies to support the sale of new medications [49]. Surgical trials must also accrue large enough sample sizes with sufficient follow-up to uncover long-term outcomes, but with rarer tumors such as melanoma with low rates of local recurrence for early-stage disease, this can increase the required study length and thus overall costs. In a review of 88,943 RCTs, surgical RCTs were more likely to be discontinued than non-surgical studies, most often secondary to poor recruitment [50].

Another barrier to a well-designed trial is the variability in how MMS for melanoma is performed. Standardizing a relatively complex procedure like MMS for the sake of a trial is difficult given the wide range of how the procedure is currently performed, but can be done with consensus on surgical techniques included in an RCT. Practice pattern differences between participating institutions in immunohistochemistry protocols, size of first margins taken, and even patient selection can lead to vast differences in patient outcomes and would need to be standardized between institutions to make meaningful conclusions [47]. By the nature of dermatologic surgery, it would be impossible to have blinded participants and study investigators who perform MMS versus WLE; this can lead to selection bias if participants choose whether to receive the intervention after randomization.

The effects of the results of a randomized controlled trial

Performing an RCT to evaluate the efficacy of MMS for melanoma is an investment, and one must consider how the results could change surgical practice. Interestingly, a Cochrane review did not identify significant differences in outcomes obtained from RCTs or observational studies, regardless of study design heterogeneity [51,52]. Therefore, it is quite possible that an RCT would recapitulate the

benefits of MMS for melanoma that have been observed thus far in the literature, including reduced local recurrence and commensurate to modestly improved survival as compared to WLE even when taking narrower margins [4,5,53,54]. Though this would be reassuring to see, how would we weigh RCT data that does not show a benefit for MMS despite the plethora of available evidence to the contrary?

If the promising results of observational data supporting the use of MMS for melanoma are recapitulated in an RCT, MMS for melanoma will still take time to be widely implemented in the United States. It is an investment in both money and margin assessment turnaround time for practices to implement intraoperative immunohistochemistry for melanoma even if it is associated with improved outcomes, particularly for superficially-invasive tumors [55,56]. This can add to the already overwhelming backload of dermatologic surgery cases for non-melanoma skin cancers, particularly given the finite number of surgeons currently practicing MMS for melanoma. We will require strong collaboration within the dermatology community and within the broader house of medicine to tactfully broaden access to the finite resource of MMS surgeons equipped to treat cutaneous melanomas; an RCT could reinforce the value of such an investment in our healthcare system.

Lack of consensus

The American College of Mohs Surgeons currently does not have a consensus statement regarding the role of RCTs to confirm the efficacy of MMS for melanoma. Without a coordinated effort and agreement amongst leaders in the field, it will be incredibly difficult to prioritize resources to conduct this large, costly, time-consuming research. A Delphi study would likely prove useful to promote discussion of the pros and cons of performing RCTs assessing the efficacy of MMS for melanoma and to identify a consensus position among the College. Although the Delphi process can also be resource-intensive, we believe it is critical to encourage a dialogue amongst leading experts regarding the current and future evidence-base supporting current MMS practices.

Conclusion

The preponderance of observational evidence currently suggests that MMS is efficacious for both melanoma in situ and superficially invasive disease. Nevertheless, there remains ambiguity regarding the precise role of MMS for melanoma in the absence of RCT data corroborating its efficacy. As with most contentious topics in medicine, the goal of the discourse surrounding RCTs for MMS for melanoma is to provide the best possible evidence-based treatment for our patients. Were an RCT to demonstrate equivalence or superiority of MMS as compared to WLE in the treatment of early-stage melanoma, clearer consensus guidelines could provide much needed clarity to patients and their physicians regarding the best treatment option for their melanoma. Dermatologic surgeons need to be included in the treatment guidelines at the NCCN.

Regardless of the study design, we must rely on rigorous research to guide best surgical practices, and such evidence for MMS is already mounting.

Potential conflicts of interest

The authors declare no conflicts of interest.

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