If Mohs surgery is the 'gold standard for non-melanoma skin cancer treatment', why doesn't everyone have it?

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Introduction

On the face of a rising skin tumour incidence, Mohs micrographic surgery (MMS) has been touted by some as a one-size-fits-all solution. Since its development in the 1930s by Frederic Mohs, MMS has grown to be accepted as the gold standard for most non-melanoma skin cancers (NMSCs), which constitute the bulk of the skin tumour caseload. This is because MMS, using a stage-by-stage removal guided by intra-operative mapping of horizontal sections, allows maximal sparing of normal tissue while ensuring high cure rates.

Inevitably, this raises the question: if MMS is indeed the gold standard for NMSCs, why doesn't everyone have it? To begin to answer this question, we must agree on what constitutes a 'gold standard'. This is typically defined as the best diagnostic test or treatment available under reasonable conditions. However, this concept revolves solely around the efficacy of an intervention, and as such is too narrow to understand which treatments are delivered to patients in a real-world situation. In fact, complex factors other than what is deemed the 'gold standard' determine whether a patient receives a treatment or not. These can be broadly categorised into:

1. Clinical effectiveness
2. Cost-effectiveness
3. Service availability
4. Patient acceptability

Clinical effectiveness of Mohs surgery

For a treatment to be even considered, evidence has to demonstrate its efficacy. National guidelines provide insight into how clinical evidence is translated into indications. NICE and multiprofessional guidelines support MMS for high-risk basal cell (BCC) and squamous cell (SCC) carcinomas located at the face, and recurrent or aggressive NMSCs [1-3] (Table 1). However, since the NHS is a public healthcare system, NICE guidelines take into account factors other that clinical effectiveness, including cost-effectiveness using QALYs and contributions from patients and professionals[4].

Table 1. Summary of UK guidelines for the appropriate use of MMS

High-risk basal cell carcinoma				
Histological subtype	Morphoeic	Infiltrating	Micronodular	Basosquamous
Histological features	Perineural invasion	Invasion below dermis		
Sites	Ears, nose paranasal folds	Lips	Periocular	Scalp and temples
Other factors	Size >2 cm	Immuno-suppression	Genetic disorders (e.g. Gorlin's syndrome)	Previously treated lesion
High-risk squamous cell carcinoma				
Histological features	Perineural invasion	Poor differentiation	Depth >4mm	Extension to subcutaneous tissue
Sites	Ears	Lips	Non sun-exposed sties	Areas of previous injury
Other factors	Size >2 cm	Immuno-suppression	Previously treated lesion	

Adapted from the British Association of Dermatologists[24]

Perhaps a reflection of a different healthcare set-up, American MMS guidelines take lesser consideration of cost, and are phrased as clinical 'appropriate use' criteria. This set of guidelines includes 270 different scenarios, graded as 'appropriate', 'uncertain', and 'inappropriate' based on evidence reviews, clinical experience, and expert judgment[5] (Table 2).

Table 2. Summary of American guidelines for the appropriate use of MMS

Basal cell carcinoma			
Recurrent BCC	Aggressive	Nodular	Superficial in area H or M
Primary aggressive BCC	Area H or M	Size >0.5 cm	
Primary superficial BCC	Area H	Area M if >0.5 cm	
Primary nodular BCC	Area H or M	Area L if >2 cm	
Squamous cell carcinoma			
Recurrent SCC	All areas unless actinic keratosis, Bowenoid, or SCC in situ		
Primary aggressive SCC	All areas		
Primary non-aggressive SCC	Area H or M	Area L if >2 cm	
Primary verrucous SCC	Area H or M	Area L if >1 cm	
Other skin tumours			
Lentigo maligna and melanoma in situ	Area H or M	Area L if locally recurrent	
Adenocystic carcinoma	All areas		
Adnexal carcinoma	All areas		
Dermatofibrosarcoma protuberans	All areas		
Mucinous and sebaceous carcinoma	All areas		

Area H: mask areas of face. Area M: cheeks, forehead, scalp, neck, jawline, pretibial surface. Area L: trunk and extremities. Adapted from Ad Hoc Task Force *et al.*[5]

Despite guidelines being a useful starting point, adherence to MMS guidelines is rarely perfect[6, 7]. Furthermore, in contrast to clinical research, they do not use clinical effectiveness as their sole criteria. Most studies have been conducted on the use of MMS for BCCs and SCCs, with the evidence remaining scant for rarer tumours. Although a Cochrane review revealed a lack of systematic evidence for MMS in BCCs[8], randomised controlled trials (RCTs) support the efficacy of MMS versus surgical excision, with MMS resulting in decreased 5-year[9, 10] and 10-year[11] recurrence rates for high-risk or recurrent BCCs. Patients undergoing MMS had a cumulative 10-year recurrence rate of 3.9%, compared to 13.5% in the excision group[11]. However, other studies have reported equivalent results to MMS using staged vertical non-Mohs excision for high-risk BCCs[12, 13]. Moreover, the superiority of MMS is less clear for low-risk or primary BCCs[9].

Systematic evidence for MMS use in SCCs is also scarce, with systematic reviews finding no suitable RCTs[14]. Lower-quality evidence from observational cohort studies have found low 5-year recurrence rates for primary (2.6%) and recurrent SCC (5.9%)[15]. The evidence is compelling for the superiority of MMS for recurrent BCCs and SCCs in high-risk areas, but further studies are required to gauge its appropriateness in primary NMSCs and other subtypes.

MMS is not the solution for all NMSCs. For low-risk tumours, alternative options including topical chemotherapy, curettage and cautery, radiotherapy, cryosurgery, and surgical excision (Table 3 and 4), can offer equivalent outcomes with fewer risks[14, 16]. On the opposite side of the spectrum, in very advanced tumours, surgical morbidity may be unacceptably high, and these may be best treated with radiotherapy or vismodegib. Finally, clinical effectiveness does not depend solely on the disease, but also on patient

characteristics such as fitness for surgery. In elderly frail patients, alternative topical therapies may be more suitable for low-risk superficial tumours.

Table 3. Treatment alternatives for primary BCC

	Indications	Contraindications
Photodynamic therapy	Superficial, large and low-risk	Infiltrative or high-risk, recurrent
Topical imiquimod	Superficial and low-risk	Infiltrative or high-risk, recurrent
Curettage and cautery	Superficial or nodular and low-risk	Infiltrative, large or high-risk
Radiotherapy	Superficial or nodular, large, or unfit for surgery	Infiltrative
Cryosurgery	Superficial or nodular, large or small, low-risk or high-risk	Infiltrative
Surgical excision	Most resectable tumours	Unfit for surgery
Vismodegib	Metastastic or unfit for radiotherapy and surgery	Low-risk, pregnancy

Adapted from Telfer *et al.*[2]

Table 4. Treatment alternatives for primary SCC

	Indications	Contraindications
Curettage and cautery	Small, well-defined, low-risk	Infiltrative or high-risk
Radiotherapy	Unfit for surgery	Ill-defined margins
Cryosurgery	Small, well-defined, low-risk	Infiltrative, high-risk or recurrent
Surgical excision	Most resectable tumours	Unfit for surgery

Adapted from Motley *et al.*[3]

Cost-effectiveness of Mohs surgery

In an increasingly constrained NHS, demonstrating cost-effectiveness is key for the approval of a treatment. However, whether MMS offers better value for money than alternative therapies remains controversial[8, 17]. One of the first studies comparing MMS with surgical excision found that MMS was more expensive than surgical excision with permanent sections, but cheaper than excision with frozen sections[18]. A similar analysis showed that MMS incurs higher total treatment costs when compared to topical treatments, curettage and cautery, and surgical excision[19]. In the context of healthcare rationing, this could be interpreted as evidence to opt for cheaper treatments in cases where they have proven to be non-inferior to MMS, such as low-risk superficial BCCs.

These studies, however, were cost-comparison rather than cost-effectiveness analyses, and did not incorporate clinical outcomes. Several cost-effectiveness studies argue that MMS is superior cost-wise because it diminishes the need for additional procedures and re-excision of recurrences[20, 21], while others have found that the cost of MMS is higher regardless of histologic subtype and tumour location[22]. It should be noted that most analyses have been conducted in the US, where there is a distinct privatised insurance-based healthcare system. Overall, it seems plausible from a cost-effectiveness perspective that the initial treatment cost of MMS may be justified in cases with a high risk of complications or recurrence.

Therefore, we can envision a two-tier system where for low-risk NMSCs, the total costs of MMS do not outweigh the potential benefits, whereas for high-risk NMSCs, these costs are outweighed by a reduced need for delayed closure, duration of follow-up appointments, and further re-excisions.

Service availability

Although MMS has expanded since NICE recommended one MMS service per skin cancer network in 2006[1], only 29 UK centres currently have a MMS service[23]. Furthermore, not all centres offer MMS for all indications, with only 55% of centres offering it for SCCs, and 21% for other lesions including lentigo maligna and dermatofibrosarcoma protuberans[23].

Establishing a MMS unit requires staff, training, facilities and clinical governance procedures. National guidelines recommend a minimum of two Mohs surgeons, along with surgical assistants and histotechnicians[24]. MMS trainees are expected to undertake a fellowship of at least 12 months, and this training needs to be maintained with a regular caseload of a minimum of two weekly programmed activities. Furthermore, once a service is established, annual audit is required, with targets including recurrence rate, discordance, functional and aesthetic outcomes[25].

All these factors constitute a rate-limiting step for patient access, regardless of clinical or cost considerations. The expansion of services would ameliorate this problem, but may prove difficult due to decreasing government funding. A parallel effort to improve access would consist of standardising the indications for MMS for all services, given the variability shown by national surveys. This could also minimise possible surgeon biases regarding the age and race of patients[26], which may influence who is offered MMS.

Patient acceptability

In the current model of patient-centred care, the decision of whether to receive a treatment ultimately comes down to the patient. Although the reasons why a patient may refuse treatment are personal and multi-factorial, standard objective and patient-reported outcomes are used in research: waiting time, length of procedure, rate of complications, functional and aesthetic outcomes.

Due to the limited number of MMS services, waiting times are longer than for standard surgical procedures, with most patients waiting 4-12 weeks. Similarly, MMS are often not available locally, with 15% of patients travelling >100 miles for the procedure[27]. The length of the procedure is also longer than standard excision, with the average procedure taking 3 hours to complete, and complex cases taking an entire day. All these factors could discourage informed patients from having MMS.

MMS has a proven safety record and patient tolerability, with minor complications being uncommon (0.72%), and major complications extremely rare (0.02%)[28, 29]. As such, post-operative factors are unlikely to be a reason why patients refuse MMS. Although there have been studies investigating post-operative pain and analgesia, no studies have compared pain outcomes against other treatment options. Head-to-head comparisons of functional outcomes could be conducted in the future with validated quality-of-life instruments for patients with NMSCs[30].

Conclusion

For every treatment, including MMS, the number of patients that end up receiving it arises from a trade-off between what doctors offer and what patients want. What doctors offer partly relies on guidelines based largely on clinical and cost-effectiveness. The notion that MMS is the gold standard for all NMSCs is perhaps too broad, with evidence suggesting that MMS is only conclusively superior for high-risk BCCs or SCCs. Thus, for low-risk tumours, alternative economical therapies may prove beneficial for NHS healthcare rationing. Further research is needed to fine-tune clinical guidelines, especially RCTs on the efficacy of MMS for SCC and rarer tumours, and UK cost-effectiveness analyses comparing MMS with alternative management options. On the other hand, what patients want depends on the availability of services and on satisfactory patient-reported outcomes. Increasing access to MMS, with measures including service expansion, standardisation, and bias reduction, could allow a higher number of patients who are already suitable clinically and cost-wise to receive MMS.

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