

General discussion

GENERAL DISCUSSION

The studies presented in this thesis support the conclusion that Mohs micrographic surgery (MMS) is an excellent treatment for basal cell carcinoma (BCC), squamous cell carcinoma (cSCC) and rare skin tumours due to the low rate of recurrences. In the Netherlands, the use of MMS for BCC increased steeply over the past few decades, while MMS is sparsely used for cSCCs and rare skin tumours. At the same time there is a lack of quality control systems.¹⁻⁴ The present level of evidence of MMS for BCC, cSCC and rare skin tumours will be discussed and recommendations will be made to improve the quality of MMS and skin cancer care in the Netherlands.

MMS FOR BCC: PRESENT LEVEL OF EVIDENCE

During the past decades, surgical care has developed from extensive to minimally invasive surgery which greatly improved patients quality and length of life.⁵ In contrast to drug development, which proceeds through well characterised and regulated stages, surgical progress has been a process of trial and error for decades.⁵ Then, the IDEAL paradigm was introduced in 2009, in order to derive surgical innovation and evaluation from evidence-based principles rather than by trial and error.⁵⁻⁷ This paradigm defines a five stage framework, similar to drug development stages.⁵ Ideally, along with each subsequent stage, the level of evidence evolves (Table 1).⁷

Table 1. Present IDEAL stage and level of evidence of MMS for skin tumours.⁷

IDEAL stage	Level of evidence	Number of patients treated with MMS	BCC	cSCC	DFSP
I. Innovation	E. Laboratory tests	Very few	Yes	Yes	Yes
II. Development	D. Expert opinion	Few	Yes	Yes	Yes
III. Exploration	C. Case reports	Many	Yes	Yes	Yes
IV. Assessment	B. non-RCT	Majority	Yes	Ongoing	No
	A-II RCT	All eligible	Yes	No	No
	A-I SR of RCT	All eligible	No	No	No
V. Long term monitoring	Registries and audits	All eligible	No	No	No

BCC, basal cell carcinoma; cSCC, cutaneous squamous cell carcinoma; DFSP, dermatofibrosarcoma protuberans; MMS, Mohs micrographic surgery; RCT, randomised clinical trial; SR, systematic review.

For aggressive facial BCC, the superiority of MMS above surgical excision (SE) is proven in randomised clinical trial (RCT) with long term follow-up (IDEAL stage IV, level of evidence A-II) which shows lower rates of recurrences after MMS (4%) than after SE (14%).⁸ Subsequently, MMS for the treatment of facial aggressive BCC was implemented in current

national and international guidelines.⁹⁻¹¹ Ever since, an increasing number of dermatologists were trained to perform MMS and an increasing number of patients were treated with MMS.^{1,4} Meanwhile, post marketing surveillance studies were performed to assess and improve safety, cost-effectiveness and the quality of BCC surgery (IDEAL stage V).

The quality of BCC care was assessed in **part I** of this thesis. For all surgical interventions and visually based diagnosis, it is known that the success largely depends on the quality of the individual physician.⁶ The quality of the individual physician largely depends on the received training and number of procedures performed.⁶ The study presented in **chapter 2** is a good example of this principle. This retrospective cross-sectional study of pathology records showed that primary BCCs were more often completely excised by a dermatologist (93%), than by a plastic surgeon (83%) or a general practitioner (GP, 70%) probably because the latter are less extensively trained and experienced in BCC care.¹² To improve the quality of BCC care, there is a strong need for an integrated care pathway, including adequate training for GPs.¹²

During the implementation of MMS in Dutch health care services, it was questioned if quality of diagnosis of MMS slides by MMS surgeons was sufficient and equal to pathologists. It was uncertain if the quality of MMS training and numbers of MMS procedures needed for MMS credential were sufficient to result in MMS surgeons who were well skilled to perform their own intra-operative histological diagnosis. **Chapter 3** showed that the level of agreement on the diagnosis of BCC presence from 50 MMS slides was substantial among six raters (three MMS surgeons and three pathologists), even while difficult to diagnose slides were oversampled.¹³ **Chapter 4** showed that the pathologist detected incompletely excised BCC in 2% of the MMS slides.¹⁴ These two studies and the known low rate of BCC recurrences after MMS, support the conclusion that in general MMS surgeons are very well able to diagnose BCC on MMS slides.^{8,13,14}

RECOMMENDATIONS TO IMPROVE THE QUALITY OF MMS

Recommendation 1: Control of the quality of diagnosis of MMS slides

As mentioned earlier, the quality of diagnosis of MMS slides depends largely on the individual MMS surgeon, and even for the very best MMS surgeon applies that to err is human. Therefore, to detect incompletely excised BCC on MMS slides, we recommend to organize a postoperative additional review of all MMS slides. At the Erasmus University Medical Center, the MMS slides are additionally reviewed the following day by another MMS surgeon as a quality check, which is less costly than a quality check by a pathologist.

Furthermore, it is important to control and improve the minimum level of quality that each MMS surgeon should gain for MMS credential. As the quality of an individual MMS surgeon primarily largely depends on the received training and number of MMS procedures performed, it should be assessed if the current credential criteria for MMS are sufficient, i.e. 100 MMS procedures under supervision to gain MMS credential and 300 MMS procedures in five years per MMS surgeon to maintain MMS credential.¹⁵ Volume based criteria for surgical credential are based on the observation that the more procedures one performs, the better one gets.¹⁶ The cut off (i.e. minimal number of procedures needed) to assure a minimum level of quality is often debatable. For MMS, the cut off was studied by Murphy et al. who showed that 1,500 MMS procedures were required before one fellow (board certified in dermatology for three years) reduced his misinterpretations to a minimum acceptable level of fewer than one per 100.¹⁷ Although this study involved only one individual, the result of this study suggests that the volume-based criteria used by the Dutch Society of Dermatology and Venereology (NVDV) and the European Society for Micrographic Surgery (ESMS) to gain MMS credential may be too low (i.e. 100 MMS procedures under supervision).¹⁵

Also, the histological skills of MMS surgeons should be formally tested prior to MMS credential (e.g. written exam to histologically diagnose 100 MMS procedures) and post credential to monitor and level the quality of each MMS surgeon over time (e.g. external control of the histological diagnosis of 50 randomly selected MMS procedures each five years). The histological skills of the MMS surgeon should be tested because misinterpretation of MMS slides is an important predictor for recurrence of tumour.

In addition to misinterpretation of MMS slides, pitfalls for incomplete tumour excision are acceptance of poor-quality slides and incorrect initiation of later MMS stages.¹⁸⁻²¹ In the United States and Australia, five randomly selected MMS slides are assessed intermittently to determine the quality regarding staining and thickness of slide, completeness of the specimen and orientation. To prevent incomplete tumour excision, it is recommended to use a standardized MMS file with the integration of digital photographs instead of freehand drawings.²² This will not only increase the precision of the MMS procedure but this will also help to reconstruct what went wrong when a tumour recurred after a MMS.

Recommendation 2: To conduct a nationwide MMS registry

Although the use of MMS for BCC increases, there is a lack of long term monitoring (IDEAL stage V) and quality control systems. To monitor, benchmark and improve the outcome measures of MMS and skin cancer care in general, there is a strong need for standardized multidisciplinary disease and treatment specific quality registries. Information

from these registries could be used for quality assessment and improvement by clinical auditing and research. For clinical auditing, the main goal of the MMS registry would be to monitor appropriate use of MMS to assure cost-effectiveness, to prevent overuse, and to evaluate the clinical quality of individual MMS surgeons. Regarding research, insight into effectiveness of an intervention in daily clinical practice can be of great value, in addition to efficacy data obtained from RCT.^{23,24} While an RCT is a suboptimal model of the real world whereby only a subgroup of the true patient population is included (i.e., positive selection bias), quality care registries deliver outcome measures of daily practice in a more heterogeneous sample of patients and providers.

Multiple national [e.g. Dutch Institute for Clinical Auditing (DICA)] and international quality of care registries exist for several cancers such as metastatic melanoma [e.g. Dutch Melanoma Treatment Registry (DMTR)], breast cancer and lung cancer, but none for non-metastatic skin cancer.^{3,25} Although the impact of a BCC is often small on an individual patient, making it a less likely candidate for registries, the global burden of disease is very large due to its high incidence, and therefore BCC and treatment specific registries are appropriate.²⁶

Like for all cancer care quality registries, an MMS registry should include quality indicators for clinical outcome, patient reported outcome measures (e.g. functional and cosmetic morbidity and disease specific quality of life) and information for casemix adjustment (i.e. baseline patient characteristics, tumour characteristics, and procedure related characteristics).^{16,27,28} For MMS, clinical outcome measures of interest differ from the existing quality registries. Quality registries of most surgical cancer treatments are often initially based on complications and survival, while for MMS major complications grade III/IV and even minor complications (e.g. bacterial wound infections, postoperative bleeding and suture reaction) are rare, and for BCC and cSCC the rate of disease-specific death is very low.²⁹⁻³³ Therefore, for MMS the most important clinical outcome measure is recurrence as this is a strong predictor for local functional and cosmetic morbidity, as well as for metastasis and disease-specific death.³⁴⁻³⁷ The recurrence rate is only valuable as outcome of quality of MMS on the long term because skin tumour recurrences may develop even after five years postoperatively.^{8,38} The major issue in preventing a skin tumour recurrence is preventing an incomplete excision. Therefore, in addition to the regular surgical outcome measures for cancer care (i.e. rate of complications, recurrences, metastasis and disease-specific death) it is most useful to measure the rate of misinterpreted MMS slides.

A nationwide standardized MMS registry is not yet established, probably largely due to privacy legislation, causing difficulties in sharing patient data across different hospi-

tals.³⁹ In addition, a general limitation to quality registries is the administrative burden associated with data collection by the busy clinicians.³⁹ One of the solutions to reduce administrative burden is (partly) automated data extraction from existing data sources such as electronic patient records, structured reports of diagnostics (e.g. Netherlands Cancer Registry), treatment (e.g. Vektis, Opendis data), and pathology (e.g. Dutch nationwide network and registry of histopathology and cytopathology).³⁹ Integration with a larger platform, like DICA, could be an advantage in this, if close cooperation is sought between the registry platform, the data processor and hospital-IT-providers.³⁹ To develop and implement a nationwide MMS registry, the NVDV would need to initiate the formation of a project team including clinicians, project managers, IT experts, and most importantly patients.²⁸ To prevent health care insurances to take over the lead of MMS auditing, it is preferable that the NVDV empowers and prioritizes MMS auditing.

Ultimately, a nationwide MMS dataset might evolve to a disease-specific based international multidisciplinary registry which would allow for the comparison of treatments (e.g. MMS versus SE, radiotherapy, and possible future systemic drug) within and between geographical locations (i.e. practice variation). Disease-specific quality registries will help to inform patients and clinicians about the efficacy of different treatment options, which will help to make individually based treatment plans. Furthermore, disease-specific quality registries will help to increase insight in to the cost-effectiveness of different treatment options which will help to constrain or even reduce the costs of skin cancer care.²⁸

Recommendation 3: To monitor the appropriate use of MMS to assure cost-effectiveness

The cost of skin cancer care is in many countries within the top five most costly cancers.⁴⁰ The costs of skin cancer care increased by 50% between 2007 and 2016, largely due to the increase of incidence of skin cancer.² In the United States, a relatively large part of treatment cost comprises MMS (over two billion dollar) due to a tenfold increase use of MMS in the past 20 years.² In the Netherlands, the total costs of MMS per year increased with 267% from 6000.000 euro's in 2012 up to 16.000.000 in 2017 due to a twofold increase of use of MMS (3.394 in 2012 up to 9.048 in 2017).^{1,4} The costs per MMS procedure remained around 1.720 euro's between 2012 and 2017.^{1,4}

The positioning and appropriate use of MMS in the treatment strategies of skin cancer is crucial, because it may push the increment in costs related to skin cancer care.²⁶ MMS is a cost-effective treatment as long as it is performed by skilled physicians and used in properly selected patients with high risk skin tumours.²⁶ From at least a cost perspective, indication of MMS should be monitored in quality registries to prevent over-usage, as

seen in the United States.²⁶ Additionally, future research is needed to further determine indication criteria for MMS to assure its cost-effectiveness.

In addition, MMS costs could be decreased by reducing the time a MMS procedure takes. Real-time intra-operative *in vivo* imaging (e.g. optical coherence tomography, multispectral optoacoustic tomography, Raman spectroscopy) of the tumour borders (both side and deep margins) holds promise to speed-up the MMS procedure, because visualisation of the subclinical tumour extension could reduce the number of MMS stages.⁴¹⁻⁴³ Barriers to adaptation include the high cost and training that is needed to effectively use the devices.⁴² Ultimately, a cost-effective and easy to applicate imaging technique should display a result binary (i.e. tumour or no tumour based on objective measures), avoiding the subjective interpretation of an image and therefore the risk of misinterpretation. Although promising studies are presented, none of these devices are widely used in daily practice yet because further innovations have to be made first.

MMS FOR CSCC: PRESENT LEVEL OF EVIDENCE

Equal to BCC, the potential advantages of MMS over SE for cSCC are high rate of complete excisions, low recurrence rates and the saving of healthy tissue. However, there are several differences between BCC and cSCC, causing concerns when treating cSCC with MMS. First, the evidence for the use of MMS for BCC is more robust (level of evidence A-II) than for cSCC (level of evidence C-B). This is probably because the incidence of BCC is over twofold higher than for cSCC. Hereby, when compared to cSCC, the need to perform studies was higher for BCC and it was easier to include patients in prospectively designed studies. Secondly, while BCCs grow slowly, metastasize hardly ever and mortality is extremely low, cSCCs grow more aggressively resulting in slightly higher rates of morbidity, metastasis and mortality.^{29,32,33} Thirdly, cSCCs grow more often perineural and intravasal than BCCs do. Perineural and intravasal tumour growth are predictors for both intransit and distant metastasis.^{29,32,33} Although some argue that MMS is less appropriate than SE for cSCC because of its aggressive growth pattern, this argument could well be reversed, i.e. to prevent metastasis and mortality of cSCC it is important to locally excise the complete cSCC with largest certainty possible, i.e. with MMS instead of SE. Furthermore, because the recommended excision margins are wider for cSCC than for BCC, MMS is even more valuable for cSCC in terms of tissue saving and thereby preservation of functional and cosmetic outcome.

For cSCC, the superiority of MMS above SE is shown in many observational studies which are mainly single centre, non-comparative, and retrospectively designed (IDEAL

stage III, level of evidence C and B).⁴⁴ Lansbury et al. conducted a systematic review of observational studies which showed that after MMS (ten studies) the pooled estimate of recurrence was 3.0% (95% CI, 2.2-3.9), which was non-significantly lower than the 5.4% (95% CI 2.5-9.1) after SE (12 studies). Conclusions must be drawn carefully because most of the included studies were of limited methodological quality and prone to bias, with variable patient mixes in terms of prognostic factors, overall disease severity, and duration of follow-up.⁴⁴ Due to selection bias, the difference between MMS and SE was probably underestimated because cSCC treated by MMS are likely to be at higher risk of poor outcome than cSCC treated by SE.

Further evidence for the higher efficacy of MMS above SE for cSCC of the head and neck was provided in **part II** of this thesis. First, the retrospective cohort study in **chapter 5** (IDEAL stage III, level of evidence C) showed that the rate of incompletely excised cSCC after SE was high (18%), which shows the need for improvement of the efficacy of the surgical treatment of cSCC.³⁸ Secondly, chapter 5 showed that the recurrence rate after MMS was lower than after SE (3% vs 8%) during a median follow-up of five years (IQR 3-7). When adjusted for tumour size and deep tumour invasion, cSCCs treated with MMS were found to be at a three times lower risk of recurrence than SE (adjusted HR 0.31, 95% CI 0.12-0.66).³⁸

To further improve the level of evidence of surgical treatment for cSCC, a prospective multicentre observational study was performed to determine the rate of incompletely excised cSCC (**chapter 6**) and to compare MMS with SE regarding rates of recurrence, metastasis, and disease specific deaths after follow-up of at least five years, which is still ongoing (IDEAL stage IV, level of evidence B-II). The rate of incompletely excised cSCC was only 4% in the cohort that was dominated by low risk facial and non-facial cSCCs. This outcome suggests that the used excision margin of 5 mm for low risk cSCC is sufficient and that dermatologists are very well able to clinically demarcate cSCC. The additional systemic review showed that the pooled average rate of incompletely excised cSCC was 12% (95% CI 10-16, range 0-39%), however the majority of included studies were retrospectively designed, used heterogenic inclusion criteria, and the majority of excisions were performed by non-dermatologic specialists. Conclusions on the quality of SE for cSCC must be made carefully due to the heterogenic results presented in the literature. Furthermore, the follow-up of this study has to clarify to what extend the efficacy of SE compares to MMS in terms of recurrence rate, metastasis and disease specific death.

Although an RCT (IDEAL stage IV, level of evidence A-II) has never been performed to prove the superiority of MMS above SE for cSCC, in the United States MMS is widely used

to treat cSCC. In the Netherlands, the use of MMS for cSCC is less widely adapted than for BCC. This is probably because the evidence of the efficacy and effectiveness of the use of MMS for cSCCs is less comprehensive than for BCC. In addition, only since the 2018 update of the Dutch cSCC guideline, MMS is mentioned as appropriate for facial cSCC (T1 and T2) if SE would lead to extensive functional or aesthetic comorbidity.⁴⁵

The question is if it is still ethical to conduct an RCT to compare MMS versus SE for cSCC (IDEAL stage IV) or that the current evidence of the superior efficacy of MMS is clear and substantial and that equipoise is lost.⁶ Moreover, all though an RCT is valued as the best possible study design to establish safety and efficacy of an intervention, RCT for surgical interventions are associated with several methodological and practical concerns which are nonissues for drug development.⁶ An important concern for an RCT for MMS versus SE for cSCC is the feasibility of the numbers needed to include because surgical and oncology trials found a low level of willingness of patients' to participate because of a stated dislike for randomisation, and a desire to make their own decisions about the selection of the intervention especially when the preferred intervention is already widely available, as it is for MMS.⁶ Another important concern is the generalisability of an RCT on MMS versus SE for cSCC because, as for all surgical interventions and visually based diagnosis (i.e. diagnosis of MMS slides), the success of MMS depends on the MMS surgeon, the MMS team, and pre-operative and post-operative management.⁶

As an alternative to RCT, long term studies on the quality of cSCC care are needed. To further determine the efficacy of MMS versus SE, disease specific nationwide registries are needed to gain big and long term data. The collection of big data provides some protection against selection bias because statistical adjustment could be used to overcome potential confounding effects.⁷

MMS FOR RARE SKIN TUMOURS: PRESENT LEVEL OF EVIDENCE

For rare skin tumours such as DFSP, Merkel cell carcinoma, atypical fibroxanthoma and microcystic adnexal carcinoma, the superiority of MMS above SE is mainly based on expert opinions and small retrospective case series (IDEAL stage II, level of evidence D) and only a minority of rare skin tumours are treated with MMS.

The quality of surgical treatment of rare skin tumours was assessed in **part III** of this thesis. **Chapter 7** showed the efficacy of MMS for rare skin tumours because only 2% (2 atypical fibroxanthomas) recurred after a median follow-up of 3.7 years (SD 1.4) while all other included tumours were cured, i.e. dermatofibrosarcoma protuberans (n = 27),

atypical fibroxanthoma (n = 20), Merkel cell carcinoma (n = 8), microcystic adnexal carcinoma (n = 9), sebaceous carcinoma (n = 6), extramammary Paget's disease (n = 2) and other (n = 6).⁴⁶

The need for improvement of the efficacy of the surgical treatment of DFSP was shown in **chapter 8**. The large nationwide cohort study showed that half of all DFSP were incompletely excised (847/1,644) and 29% (192/622) of all re-excisions were incomplete. The cumulative incidence of a recurrence was 7% (95% CI 6-8) during a median follow-up of 11 years (IQR 6-17). While after MMS (n = 34), there were no recurrences during a median follow-up of four years (IQR 3-6). These results support the current European guidelines that recommend to treat DFSP with MMS instead of excision.⁴⁷

It is impractical to conduct RCT for rare diseases. Therefore, to further innovate and evaluate the care for rare skin tumours, there is a need for long term studies and disease specific international registries. Furthermore, to improve the quality of care, it is recommended to treat rare skin tumours in a limited number of centres where multidisciplinary experts on skin cancer work together to plan the optimal treatment strategy. The specialists who work in such skin cancer specialty centres must network internationally, whereby international quality registries must be initiated for quality assurance and improvement by research. Such international network and research groups are especially important for rare diseases

In conclusion, this thesis argues that MMS is an excellent treatment option for BCC, cSCC and rare skin tumours. The studies presented in this thesis have increased the level of evidence of the efficacy of MMS for skin tumours. To monitor, benchmark and improve the quality and cost-effectiveness of skin cancer care by auditing and research, future initiatives would best focus on the development of multidisciplinary disease and treatment specific automated nationwide registries.

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