Support for the use of Mohs Micrographic Surgery for Skin Cancer

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Support for the use of Mohs Micrographic Surgery for Skin Cancer

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CONTENTS

Chapter 1

Introduction

INTRODUCTION

Skin cancer results from an abnormal growth of skin cells. Our skin is made up of three layers, each consisting of many different cell types. The outermost layer of the skin is the epidermis, which consists predominantly of keratinocytes and in between a few melanocytes. Trough carcinogenesis, keratinocytes can become a basal cell carcinoma (BCC) or a cutaneous squamous cell carcinoma (cSCC), while melanocytes can become a melanoma. The majority of skin cancers are BCC, cSCC or melanoma, while only 2% comprise other cell types (e.g. soft tissue tumours, appendageal tumours, neural tumours).[1] In contrast to melanoma, the mortality of BCC, cSCC and the majority of rare skin tumours is low because they rarely metastasize.[2-5] But if untreated, BCC, cSCC and rare skin tumours do destruct local tissue, which could lead to major functional and cosmetic morbidity. Functional and cosmetic morbidity is specifically related to the head and neck area where the majority of skin tumours occur due to carcinogenesis by ultraviolet (UV) radiation in sunlight.[6] Therefore, for BCC, cSCC and rare skin tumours, surgical treatment is aimed on histologically proven local tumour clearance. This thesis focuses on the quality of surgical treatment for BCC, cSCC and rare skin cancers, whereby melanoma is beyond the scope of this thesis.

EPIDEMIOLOGY

Skin cancer is the most common type of cancer in the Caucasian population and its incidence is rising.[7] BCC is the most common skin cancer, representing 71% of all skin cancers.[1] BCC accounts for 40,000 cases in the Netherlands each year and its incidence increases five percent each year.[8] In the Netherlands, at least one in five to six Caucasians will develop a BCC before the age of 85 years.[9] Patients with a BCC have a 17-fold increased risk of a subsequent BCC compared with the general population.[10]

CSCC is the second most common skin cancer after BCC, representing 16% of all skin cancers.[1] CSCC account for more than 15,000 cases in the Netherlands each year and its incidence increases two percent each year.[1,11] In the Netherlands, at least one in 15 Caucasians will develop a cSCC before the age of 85 years.[1,11]

Other skin cancer types are rare and together represent 2% of all skin cancers.[1] In the Netherlands, the incidence per year of rare skin tumours is highest among soft tissue tumours ($n \approx 87$), followed by appendageal tumours ($n \approx 79$), and neural tumours ($n \approx 45$).[1] More than three quarters of the soft tissue tumours of the skin are dermatofibrosarcoma protuberans (DFSP, 77%).[1] About a third of the appendageal tumours are sweat gland

carcinomas (33%), and a quarter are sebaceous glands carcinomas (24%). Almost all neural tumours were Merkel cell carcinomas (MCC, 99%).[1] In contrast to soft tissue tumours, the incidence of appendageal and neural tumours increases by 3% annually, probably because these tumours are UV-related, just like BCC and cSCC, while soft tissue tumours are not.[1]

Of all skin tumours, the mortality rate of BCC is the lowest (0.55%) because BCC rarely metastasizes.[2] The mortality rate of cSCC is higher with 2%, because it metastasises in 4% of the cases.[3,4] The mortality rate among rare skin tumours varies widely between the different tumour types. The mortality rate of DFSP is the lowest with 1%, while the mortality rate of MCC by ten years after diagnosis is around 50% for patients with localised disease, 56% for patients with regional nodal disease and 84% for patients with distant metastasis.[5,12]

The majority of skin tumours are UV-related.[6] Other risk factors resulting in skin cancer include older age, male sex, fair skin, a history of skin cancer, and immunosuppression.[6] Besides the morbidity of skin cancer for the individual patient, the high and increasing incidence of skin cancer leads to expending costs for society. To decrease the morbidity of skin cancer and to assure that money on skin cancer care is spent wisely, it is crucial to improve skin cancer treatment strategies.[6] Therefore, the objective of the studies presented in this thesis was to determine the quality of surgical treatment for BCC, cSCC and rare skin tumours.

BASAL CELL CARCINOMA

A BCC is a solitary slowly growing de novo epidermal tumour. It could take up to 10 years before a BCC becomes clinically visible and symptomatic. Symptoms are usually mild for small BCCs and comprise a non-healing ulcer, pain, and irritation. The clinically visible tumour is always smaller than the true histological size. The clinical presentation of BCC can be divided into three main subtypes, i.e. *nodular*, *superficial*, and *morpheaform*. *Nodular BCC* is the most common subtype and represents 60% of all BCC cases. Nodular BCCs typically present on the face as solitary, sharply defined, flesh coloured, pearly nodules with telangiectasia and raised borders, and a commonly ulcerated centre. Histologically, nodular BCC represents lobules of basophilic cells with well-defined contours with typical palisading of the peripheral row of cells and retraction from surrounding stroma with invasion into the reticular dermis or deeper.[13]

After nodular BCC, *superficial BCC* is the most common subtype and represents 30% of all BCC cases. Superficial BCCs typically present on the trunk as solitary, well-defined, light red, shiny and scaly plaques. Histologically, superficial BCC represents relatively small nests of basophilic cells which tend to have a broad base of attachment to the epidermis and hair follicle epithelium with well-defined contours with palisading of the peripheral row of cells and stromal retraction.[13]

A minority (10%) of all BCC cases are *morpheaform*. Morpheaform BCCs typically present as ill-defined fibrosing white maculae. Histologically, morpheaform BCCs represent small, thin and elongated islands of basophilic cells with usually less than five cells in line with ill-defined contours and absence of peripheral palisading and stromal retraction, with invasion into the reticular dermis and frequently deeper.[13]

Beside the nodular, superficial and morpheaform BCC subtypes, there are many other histological growth patterns described (e.g. infiltrative, micronodular), and approximately one third of all BCCs comprise mixed subtypes.[13]

BCC subtypes differ in outcome and prognosis, and can be categorized on the basis of most aggressive growth pattern as follows: morpheaform > infiltrative > micronodular > nodular > superficial.[13] Additional risk factors for a worse outcome are perineural invasion, lymphovascular invasion, deep tumour invasion (beyond the subcutaneous fat), localization in the H-zone (corresponding to the embryonic fusion plates which includes the following areas: peri-oculair, peri-oral, peri-nasal, peri-auricular, and temporal), large tumour size (> 10 mm for BCC in the H-zone, and > 15 mm for facial nodular BCC outside the H-zone), previously incompletely excised or recurrent BCCs, and clinically poorly demarcated BCCs.[14,15] For BCC, the TNM classification (tumour, node, metastasis) and American Joint Committee on Cancer (AJCC) stage system is rarely used, because of the low incidence of nodal and distant metastasis for BCC. This thesis focuses on BCC without metastasis, because metastatic BCC needs systemic treatment strategies while the studies presented in this thesis focus on the local clearance of BCC by surgical treatment.

CUTANEOUS SQUAMOUS CELL CARCINOMA

In contrast to BCC, cSCC is a rapidly growing epidermal tumour which originates de novo or from precursor lesions (e.g. actinic keratosis, Bowens disease). Within weeks to months, a cSCC can become clinically visible and give rise to a painful non-healing ulcer. Similar to BCC, cSCC is typically solitary, but some patients present with more than one cSCC in an anatomical field. If multiple cSCCs present in a field, they could all be

primary cSCCs caused by field cancerization, or, although rare, they could be in transit metastases of one primary cSCC (< 0.5%).[16-19] It is important to histologically differentiate between primary cSCC and in transit metastasis, because the latter tends to have a significantly worse prognosis.[16-19]

CSCC is usually located on the sun-exposed skin (i.e. head and neck area, back of hands, forearms and lower legs) and it clinically presents as a moderately defined, red, scaly, indurated nodule or plaque, with or without a verrucous surface or ulceration. The surrounding tissue is often inflamed and the clinically visible tumour borders are smaller than the true histological borders of the cSCC.

Histologically, cSCCs are composed of aggregates of atypical epithelial cells invading the dermis, with variable mitotic activity, keratin pearl formation and premature cornification, surrounded by an inflammatory infiltrate with lymphocytes and plasma cells.[20] There are many different histological variants of cSCC described, whereby lower risk variants are *verrucous cSCC* and *clear cell cSCC*, and higher risk variants are *acantholytic cSCC*, *spindle cell cSCC*, and *adenosquamous cSCC*.[20]

Overall, cSCCs are classified by their degree of tumour differentiation ranging from well to poor. *Well differentiated* cSCCs (less aggressive) are composed of less than 25% undifferentiated cells, it is easily to determine the keratinocyte lineage, and mitosis is rarely seen.[20] Histologically well differentiated cSCCs sometimes present clinically as a keratoacanthoma, a tumour which typically exhibits rapid initial growth, manifesting as a crateriform nodule with a central keratotic core that resolves with a scar.[21] *Poorly differentiated* cSCC (more aggressive) are composed of >75% undifferentiated cells, a keratinocyte lineage is difficult to determine, and mitosis is common.[20]

In addition to differentiation grade, other prognostic factors are perineural invasion, lymphovascular invasion, deep tumour invasion (> 6 mm or beyond the subcutaneous fat), tumour size > 20 mm in diameter, previously incompletely excised or recurrent cSCC, clinically poorly demarcated , localization on the mucosal lip, immunosuppression, and cSCC arising in a scar (e.g. from a leg ulcer or skin burn).[22]

In contrast to BCC, it is essential to use the TNM classification and staging for cSCC, because of the potential of cSCC to metastasize. The AJCC staging system is most frequently used. The AJCC-8 was introduced in 2018 whereby cSCCs are classified as follows: T1 when < 20 mm in diameter; T2 when 20-39 mm in diameter; T3 when ≥ 40 mm in diameter or with minor bone erosion or perineural invasion (for nerves located deeper than the dermis or with a diameter ≥ 0.1 mm) or deep invasion (beyond the

subcutaneous fat or > 6 mm measured from the stratum granulosum of adjacent normal epidermis to the base of the tumour); T4a when invading cortical bone or marrow; and T4b when invading skull base or skull base foramen.[23] As an alternative to the AJCC system, the Brigham and Women's Hospital Tumour (BWH) classification system aims to better differentiate cSCC with poor outcome by subdividing AJCC T2 tumours into T2a and T2b, whereby T2a includes cSCC with one high risk feature (i.e. tumour size ≥ 20 mm, invasion beyond the subcutaneous fat, perineural invasion of nerves ≥ 0.1 mm in calibre, and poor differentiation), and T2b includes cSCC with two or three high risk features, and T3 includes cSCC with all four high risk features or bone invasion.[24] None of the staging systems include patient related high risk features (e.g. immunosuppression, male, higher age, history of burns) and previous incomplete removal or recurrence of cSCC. To determine whether the AJCC-8 system differentiates cSCC with poor outcome sufficiently, validation in cohorts is needed.

If extended cSCC invasion is clinically suspected, pre-operative imaging is used to assess deep tumour invasion and perineural invasion with MRI or bone invasion with CT. In the Dutch cSCC guideline it is recommended to pre-operatively palpate the lymph nodes close to the tumour and on indication perform nodal ultrasound with optional cytological examination.[22] If distant metastasis is clinically suspected, a PET-CT scan should be used. This thesis focuses on cSCC without nodal and distant metastasis, because metastatic cSCC needs a systemic treatment strategy while the studies presented in this thesis focus on the local clearance of cSCC by surgical treatment.

DERMATOFIBROSARCOMA PROTUBERANS

Rare skin tumours include a wide variety of tumours, each characterised by different clinical and histological features. DFSP is the most common rare skin tumour with a European standardized incidence rate of 0.39 per 100,000 person-years (2001-2005).[1] The clinical and histological features of DFSP will be introduced here, because this thesis focuses on the quality of surgical treatment of DFSP.

DFSP is an indolent and slowly growing soft tissue tumour which originates from a translocation of chromosome 17 and 22 resulting in tumour cell proliferation of fibrohistiocytic lineage.[25] The epidemiology of DFSP differs from BCC and cSCC, predominantly because DFSP is non UV-related. Incidence of DFSP among men and women is equal.[26,27] DFSP occurs most commonly in young and middle-aged adults, but DFSP cases in children and elderly are described as well.[26,27] DFSP is most commonly located on the trunk (50%), proximal extremities (20-30%) or head and neck (10-15%).[26-29]

Clinically, DFSP presents as an asymptomatic, slowly growing, skin coloured, indurated plaque with subsequent nodule that is frequently present for many years before diagnosis.[25] The clinically visible tumour is always way smaller than the true histological borders of the DFSP due to the subcutaneous tumour spread underneath clinically normal appearing skin.

In consistency with the clinical presentation, usually DFSP histologically spares the epidermis and papillary dermis while tumour cells diffusely infiltrate the reticular dermis, subcutaneous fat, and sometimes muscle and rarely bone.[25] Tumour cells are remarkably uniform with small oval spindled nuclei and a pale cytoplasm which are arranged in a storiform pattern with entrapment of the fat, resulting in a honeycomb pattern. Metastasis of DFSP is rare (<0.5%) and seems to occur more frequently in recurrent DFSP that has undergone fibrosarcomatous transformation.[25] This thesis focuses on the local clearance of DFSP, which is a challenge because of the difficulty to demarcate the tumour clinically, due to the invasion into subcutaneous tissue.

SURGICAL TREATMENT OF SKIN TUMOURS

The goal of treatment of skin tumours is local control to prevent morbidity, recurrence, metastasis and disease specific death. Local control of the tumour could be achieved by surgical treatment with histopathological confirmation of clear margins. The studies presented in this thesis determine the quality of different aspects of standard excision (SE) and Mohs micrographic surgery (MMS), whereby all non-histologically controlled treatment options are beyond the scope of this thesis (i.e. curettage and electrocoagulation, cryosurgery, topical agents, and radiotherapy). In the Dutch BCC and cSCC guideline it is recommended to take a punch biopsy to histologically diagnose the tumour type and subtype to determine the optimal treatment strategy, i.e. SE or MMS.[14,22]

STANDARD EXCISION

With SE, the skin tumour is excised in a fusiform shape with a standardized surgical margin of normal-appearing tissue around the tumour. The concept of a standardized excision margin is based upon the assumption that the clinically visible margin of the tumour bears a predictable relationship to the true extent of the tumour, which ensures that excision of a margin of clinically normal-appearing tissue around the tumour will encompass any microscopic tumour extension. After SE of the tumour, the defect is reconstructed, while the specimen is post-operatively assessed by a pathologist with stan-

dard vertical bread loaf technique and haematoxylin and eosin staining. Incompletely excised tumours need re-excision to prevent recurrence, as recurrent tumours are at higher risk of significant functional and cosmetic morbidity, metastasis and disease specific death. To prevent incomplete excisions and recurrences, in guidelines for BCC and cSCC, the recommended surgical margin is wider for high risk tumours. High risk clinical and histopathological features are pre-operatively identified.

The strength of SE is that the procedure takes usually less than 30 minutes, which makes it less exhausting for the patient and less time-consuming for the medical staff and scheduling of the operating theatre. Furthermore, for patients SE is broadly accessible because many physicians (e.g. dermatologist, surgeon, plastic surgeon, ear-nose-throat (ENT) specialist, ophthalmologist, general practitioner) perform SE.

The most important limitation of SE is the lack of full microscopic margin control. With the standard vertical bread loaf technique <1% of the true surgical margins are reviewed and incompletely excised tumour cells might be missed (Figure 1). Furthermore, the standardized excision margin might encompass large portions of healthy tissue. This might unnecessary damage functional and cosmetic outcome.

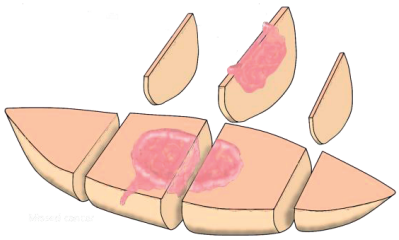

Figure 1. Standard excision with bread loaf sectioning method and missed incompletely excised tumour cells.

According to the Dutch BCC guideline, SE with a surgical margin of three mm is the first choice of treatment for low risk BCC, and SE with a surgical margin of five mm for non-facial high risk BCC (Table 1).[14] According to the Dutch cSCC guideline, SE with a surgical margin of five mm is the first choice of treatment for low risk cSCC, and SE with a surgical margin of ten mm for high risk cSCC (Table 1).[22] The recommended excision margins in the Dutch cSCC guideline are wider than the recommended margins in the British and American guidelines (i.e. four mm for low risk cSCC and six mm for high risk cSCC).[30,31] For rare skin tumours, there is a lack of guidelines and the width of the surgical margin is not standardized and varies widely from half to several centimetres.[32,33]

Table 1. Advised surgical margins for basal cell carcinoma and squamous cell carcinoma according to the Dutch guidelines.

	3 mm excision margin for low risk BCC	5 mm excision margin for high risk BCC
Histology	Nodular Superficial	Morpheaform Micronodular Infiltrative
Location	Trunk	H-zone[a]
Clinical diameter	< 20 mm	≥ 2 mm
Surgical history	Primary BCC	Recurrent BCC
	5 mm excision margin for low risk cSCC, i.e. T1[b]	10 mm excision margin for high risk cSCC, i.e. ≥ T2[b]
Clinical diameter	< 20 mm	≥ 20 mm
Invasion depth	Dermis ≤ 6 mm[c]	Beyond the subcutaneous fat > 6 mm[c]
Perineural invasion	Absent	Present in nerves > 0.1 mm in diameter Present in nerves lying deeper than the dermis
Bone invasion	Absent	Present (minor erosion or invasion[d])

BCC, basal cell carcinoma; cSCC, cutaneous squamous cell carcinoma; mm, millimetre.
[a] H-zone includes the following areas: peri-oculair, peri-oral, peri-nasal, peri-auricular, and temporal.
[b] According to the AJCC-8 classification system.
[c] Tumour invasion is measured from the stratum granulosum of adjacent normal epidermis to the base of the tumour.
[d] For cSCC with bone invasion (T4) post-operative radiotherapy is recommended.

MOHS MICROGRAPHIC SURGERY

In 1970, MMS was introduced as an alternative to SE. Dr. Frederic Edward Mohs, who was a general surgeon, developed a surgical technique in 1936 that now bears his name.[34] Mohs used an in vivo fixation technique with 20% zinc chloride paste formulation to remove the skin cancer layer-by-layer to examine the entire tumour margin.[34] Although Mohs effectively removed the skin cancer, the in vivo fixation was extremely painful for the patient and the entire procedure took a few days. The procedure was speed-up by the use of fresh frozen tissue in 1953.[34] An American dermatologist, dr. Theodore A. Tromovitch modified the technique in 1970 by the introduction of ex vivo fixation to the procedure, which is still used now.[34]

With MMS the skin tumour is excised with a minimal surgical margin after which the specimen is colour coded. The specimen is directly compressed, frozen and sliced horizontally by a trained MMS technician in a lab. This process may take approximately one hour while the patient is waiting in a comfortable waiting room. The entire excision margins

are microscopically examined on the fresh frozen slides by a MMS trained dermatologist (Figure 2). Residual tumour is mapped on a digital photo and then subsequently excised (Figure 3). The procedure is repeated until complete tumour clearance is achieved after which the defect is subsequently reconstructed.

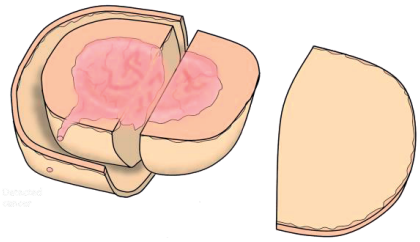

Figure 2. Sectioning method of Mohs micrographic surgery with detected incompletely excised tumour cells.

The major strength of MMS is the microscopic control of the entire excision margin intraoperatively. MMS is superior to SE for facial aggressive or recurrent BCC, because of the low rate of incompletely excised and recurrent BCC combined with maximum preservation of healthy tissue.[35-41] For facial cSCC, the evidence of the superiority of MMS to SE is less extending but it is shown that after MMS the rate of incompletely excised and recurrent cSCC is very low.[42-46]

There are several limitations to MMS, e.g. the waiting time. For each MMS stage applies, the larger the specimen is the longer it takes to make and read the fresh frozen slides. Furthermore, the more MMS stages are needed to clear the tumour, the longer the entire MMS procedure takes. A MMS procedure can last up to one day, which is exhausting especially for the elderly patient. If the tumour size is > 10 cm in diameter or if the MMS procedure is to exhausting for a patient, it might be preferable to excise the tumour with 'slow MMS', i.e. an excision with extended reconstruction and three-dimensional histology by hematoxylin and eosin stained slides of formalin-fixed paraffin-embedded tissue (e.g. Breuninger surgery). Another limitation of MMS is that a specifically trained MMS technician and dermatologist are needed, and a lab including a cryostat. Therefore, the accessibility of MMS is less than for SE, although in the Netherlands the number of dermatologic centres offering MMS is rising and waiting times and traveling distances are relatively short.

When compared head to head, MMS is more costly than SE, i.e. €1720 for MMS versus €430 for SE with simple closure and €785 for SE with advanced closure.[47] But when the cost-effectiveness of SE and MMS is compared including the risk of a re-excision with SE, the costs of MMS where shown to equal those of SE for all primary BCC > 5 mm in diameter in the H-zone and for BCC > 20 mm in diameter in the face.[41] MMS is a cost-

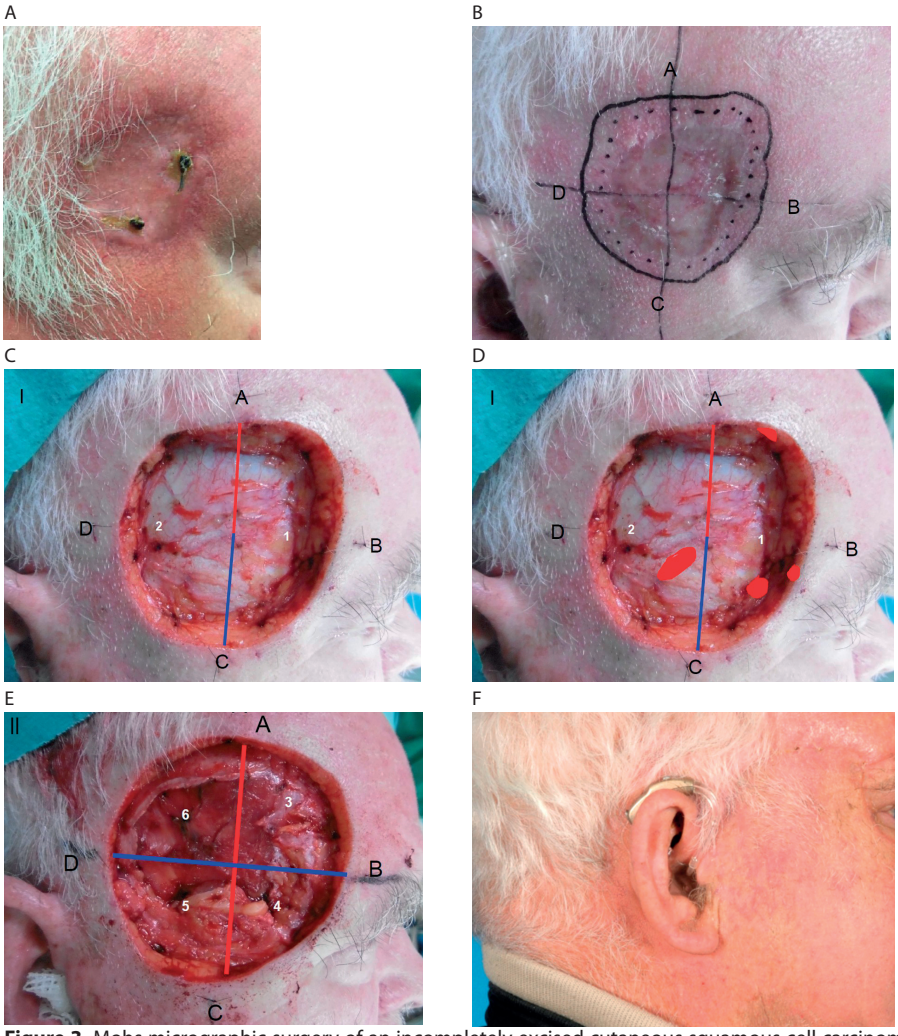

Figure 3. Mohs micrographic surgery of an incompletely excised cutaneous squamous cell carcinoma. A. Pre-operative clinical appearance. B. Demarcation of the first stage. C. Defect after excision of the first stage. D. Demarcation of the tumour cells corresponding to the fresh frozen slides. E. Final defect. F. One month postoperatively.

effective treatment as long as it is performed by skilled physicians and used in properly selected patients with high risk skin tumours.[6]

According to the Dutch BCC guideline, MMS is appropriate for facial high risk BCC (Table 2).[14] According to the recent update of the Dutch cSCC guideline, MMS is appropriate for facial cSCC (T1 and T2) when it is aimed to preserve the healthy tissue and thereby to decrease the functional or aesthetic comorbidity (Table 2).[22] In the previous version of the Dutch cSCC guideline from 2010, MMS was only mentioned as an alternative to SE if

SE would lead to extensive functional or aesthetic comorbidity.[48] For rare skin tumours, there is a lack of guidelines and the indication criteria for MMS are unspecified.[32,33] In contrast to the more narrow indication criteria for MMS in the Netherlands, the American appropriate use criteria indicate that MMS is appropriate for approximately 80% of BCC and cSCC.[49] Appropriate use of MMS in the treatment strategies of skin cancer is crucial , first to increase quality of skin cancer care, and second to prevent over-use of MMS which would lead to an increase in costs.[6]

Table 2. Criteria for Mohs micrographic surgery for basal cell carcinoma and squamous cell carcinoma according to the Dutch guidelines.

Indication criteria for MMS for BCC
Primary BCC in de H-zone > 10 mm in diameter
Primary BCC on the eye lids, or ala nasi, or nose tip > 5 mm in diameter
Primary nodular BCC on the face, but outside de H-zone[a] > 15 mm in diameter
Primary morpheaform, infiltrative or micronodular BCC on the face, outside de H-zone[a] > 10 mm in diameter
Incompletely excised or recurrent BCC on the face
Indication criteria for MMS for cSCC
T1[b] and T2[b] facial cSCC, when it is aimed to preserve the healthy tissue

BCC, basal cell carcinoma; cSCC, cutaneous squamous cell carcinoma; mm, millimetre; MMS, Mohs micrographic surgery.

[a] H-zone includes the following areas: peri-oculair, peri-oral, peri-nasal, peri-auricular, and temporal.

[b] According to the AJCC-8 classification system.

AIMS OF THIS THESIS

In this thesis different aspects of quality of SE and MMS were researched, in order to better position MMS in skin cancer treatment strategies.

Part I The most obvious quality check of SE of BCC is complete excision confirmed by a pathology report. For SE of BCC, health insurance companies and governments promote a shift of care from medical specialists to GPs while it is unknown whether the quality of care among GPs is sufficient. Therefore, differences were determined for the rate of completely excised primary BCC by GPs, compared to dermatologists and plastic surgeons in a large pathology based sample (**chapter 2**).

Although for high risk BCC the superiority of MMS above SE is already proven, the quality of histological diagnosis of MMS slides is poorly studied while the success of MMS largely depends on the correct interpretation of slides. Therefore, the reliability of MMS slides diagnosis was determined (**chapter 3**) and it was determined whether an additional review of slides by a pathologist in addition to the MMS surgeon would improve the quality of MMS (**chapter 4**).

Part II concerns the quality of surgical treatment of cSCC. In contrast to BCC, the evidence for the use of MMS for cSCC is less robust and it is still debated if MMS is preferable to SE. Therefore, the recurrence rate of cSCC of the head and neck after MMS versus SE was determined retrospectively in a secondary and tertiary care hospital in the Netherlands between 2003 and 2012 (**chapter 5**). Furthermore, to investigate whether the quality of SE of cSCC is sufficient, or whether a shift of cSCC care to MMS is needed, the rate of incompletely excised cSCC was determined prospectively across six dermatology centres between 2015 and 2017 (**chapter 6**).

Part III concerns the quality of surgical treatment of rare skin tumours. For rare skin tumours, the quality of SE is poorly studied as well as the added value of MMS. To investigate whether MMS is an appropriate treatment for rare skin tumours, the long term recurrence rate of rare skin tumours after MMS was determined retrospectively for all rare skin tumours treated with MMS in Erasmus Medical Center Cancer Institute, Rotterdam, The Netherlands between 2008 and 2012 (**chapter 7**). Furthermore, in order to investigate whether the quality of SE for DFSP is sufficient, or whether a shift of DFSP care to MMS is needed, the rates of re-excisions and recurrences of DFSP were determined retrospectively in a nationwide cohort study between 1989 and 2016 (**chapter 8**).

Finally, strategies to assure and improve the quality of skin cancer surgery are discussed (**chapter 9**). Ideally, the clinical evidence of this thesis should help patients and clinicians to position MMS better in their skin cancer treatment strategies.

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Part I

Basal cell carcinoma

Chapter 2

Differences in rate of complete excision of basal cell carcinoma by dermatologists, plastic surgeons and general practitioners: a large cross-sectional study

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ABSTRACT

Background: Due to the increasing incidence of basal cell carcinoma (BCC) and rising health care costs, health care insurance companies seek ways to shift skin surgery for BCC from secondary to primary care.

Objectives: To study the differences in complete excision of BCC by general practitioners (GPs), dermatologists, and plastic surgeons.

Methods: A retrospective cross-sectional study of pathology records of 2,986 standard excisions of primary BCCs performed by a GP, dermatologist, or plastic surgeon in the Southwest area of the Netherlands between 2008 and 2014. To compare the risk of an incomplete BCC excision between the specialties, the odds ratio (OR) was used adjusted for patient age, sex, tumour site, size, and histological subtype.

Results: BCCs were completely excised by GPs in 70% of the excisions, which was lower than the 93% by dermatologists and 83% by plastic surgeons ($p < 0.001$). Compared to the dermatologist, BCCs which were excised by a GP were six times higher at risk of an incomplete excision (adjusted OR 6, 95% CI 5-8) and two times higher at risk when excised by a plastic surgeon (adjusted OR 2, 95% CI 2-3).

Conclusion: BCCs were more often completely excised by dermatologists than by GPs and plastic surgeons. Dermatologists probably perform better because of their extensive training and high experience in BCC care. To minimize incomplete BCC excision, GPs should receive specific training before the shift of BCC care from secondary to primary care is justifiable.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cancer in the Netherlands. According to the Netherlands Cancer Registry, the BCC incidence rate is about 40,000 per year with an increase of 5% each year.[1] In the Netherlands, patients initially visit a general practitioner (GP) for their skin lesions. The GP decide whether to treat the patient themselves or to refer to a specialist. Although Dutch GPs are not specifically trained in skin tumour care (unlike counterparts in the UK and Australia), they do excise 27% of the benign skin tumours they encounter and 31% of the skin tumours they suspect to be malignant.[2,3] If GPs refer a patient with a skin tumour, this is most often to a dermatologist or plastic surgeon, and less often to an ophthalmologist, general surgeon or ear-nose-and-throat specialist. In the Netherlands, until June 2017, a specific BCC guideline for GPs was lacking, while specialists could refer to their multidisciplinary conducted Dutch BCC guideline since 2002. Adherence to guidelines, however, might vary within and between specialists, which may result in different treatment choices and quality of care. According to the Dutch BCC guideline, the first choice of treatment for BCC is a standard excision, with a clinical tumour free excision margin of 3 mm for nonaggressive BCC subtypes (i.e., nodular and superficial) < 2 cm and a 5 mm margin for larger BCCs or BCCs with an aggressive histological subtype (i.e., infiltrative or micronodular).[4] Incompletely excised BCCs need re-excision to prevent recurrence, as recurrent BCCs can be more aggressive and therefore more difficult to treat, leading to impaired functional and cosmetic outcome for patients and higher costs for society.

Health insurance companies and governments worldwide promote a shift of minor skin surgery from secondary to primary care in order to reduce health care costs.[5-7] Accordingly, the Dutch Collaborating Centre of the WHO promotes a shift of BCC care, even though it is unknown whether the quality of BCC care among GPs is sufficient compared to medical specialists. The quality of BCC care among GPs and medical specialists needs to be carefully assessed, as quality of care should not be compromised in order to reduce costs. One of the indicators for the quality of BCC care is the rate of completely excised BCCs. This retrospective cross-sectional study of pathology records compared the rate of completely excised BCCs between GPs, dermatologists, and plastic surgeons in the Netherlands.

METHODS

For this retrospective cross-sectional study we analysed all pathology records of standard excisions of primary BCCs performed by a GP, dermatologist or plastic surgeon in the Southwest area of the Netherlands between 2008 and 2014 (Figure 1). Pathology

records were extracted from PATHAN. PATHAN is a regional pathology laboratory that serves GPs and secondary care hospitals in the Southwest area of the Netherlands. To identify all records of excisions of primary BCCs in PATHAN, an algorithm was used with a filter on the diagnosis according to the Systematized Nomenclature of Medicine (SNOMED) classification which is implemented in the Dutch Pathology Database system (PALGA). Pathology records were included from the 31st of December 2014 and consecutively backwards until enough cases per specialty were included. The length of inclusion period differed per specialty, due to the different excision frequencies per year per specialty. The different lengths of inclusion period per specialty were accepted because the Dutch BCC guidelines did not change during the entire study period. Pathology records were excluded if they concerned surgical techniques other than standard excision (e.g. shave excision or Mohs micrographic surgery) or if the data of interest were missing (see the studied variables below). The following variables were extracted from the pathology records: physician (i.e. GP, dermatologist or plastic surgeon), histological conclusion on tumour free margins (complete or incomplete BCC excision), tumour site (i.e. head and neck, trunk or limbs), histological subtype [i.e. nodular, superficial, infiltrative (including micronodular), nonaggressive mixed subtypes (i.e. mixed nodular and superficial subtypes) or aggressive mixed subtypes (i.e. nodular and or superficial mixed with infiltrative subtypes)] and specimen size (i.e. ≤ or > 2.5 cm in shortest dimension). Specimen size was used as a proxy of tumour size because the tumour size was missing in the majority of records. To correct for the assumed surgical excision margin and tumour shrinkage, specimen size was categorized in ≤ or > 2.5 cm in shortest dimension as a proxy of small (≤ 2 cm) and large (> 2 cm) BCCs.[4]

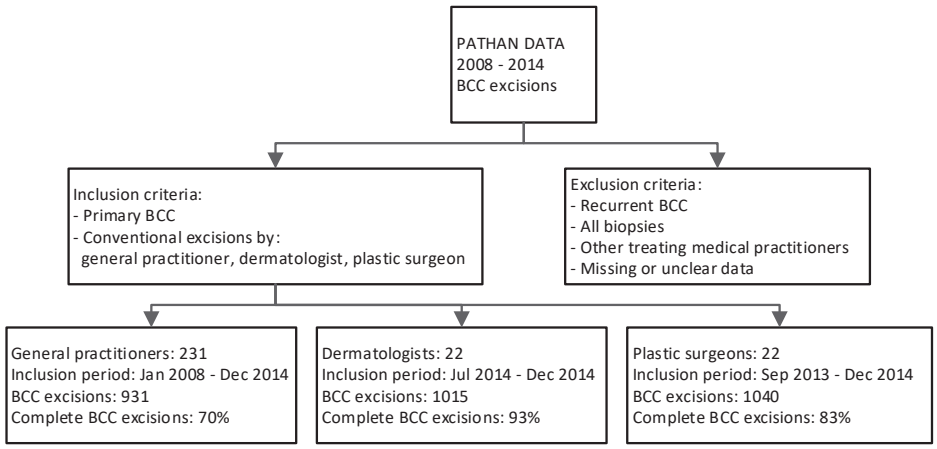

Figure 1. Flowchart of material and methods.
BCC, basal cell carcinoma; PATHAN, regional pathology laboratory that serves general practitioners and secondary care hospitals in the Southwest area of the Netherlands.

Study outcomes

The primary outcome of this study was the proportion and the likelihood of complete excisions by GPs, dermatologists and plastic surgeons. The secondary outcomes were the proportion of complete excisions per specialty, per site and per histological subtype.

Histological assessment

All specimens were assessed postoperatively by pathologists for tumour free margins using the bread loaf technique after histochemical staining with haematoxylin and eosin. Because of the retrospective design of this study, pathologists were not blinded for the operating physician.

Statistical analysis

The power calculation showed that 974 BCC excisions per specialty were needed to assess whether there was a difference between GPs, dermatologists and plastic surgeons in proportions of complete BCC excisions. Oneway ANOVA, Pearson Chi-Square test and Fisher's exact test were used to determine if there were differences between the specialties in patient and tumour characteristics. The significance level was 0.0125 (Bonferroni correction for multiple testing, power 80%). Comparison of the risk of an incomplete BCC excision between GPs, dermatologist and plastic surgeons was assessed with univariable and multivariable logistic regression models adjusted for patients' age, sex, tumour site, tumour size and histological subtype.

The sample size was calculated with the statistical program R version 3.1.1. (http://Rproject.org) and the statistical analyses were performed with SPSS for Windows version 21 (SPSS, Chicago, IL, USA). The study was conducted and reported according to the STROBE guidelines for cross-sectional studies. The Medical Ethical Committee of the Erasmus University Medical Center Rotterdam approved the study protocol (reference number NL52923.078.15).

RESULTS

In total 2,986 pathology records of BCC excisions were included. The patients' median age was 69 years (SD 13 years), and 52% were men. Of the 2,986 BCCs, 931 were excised by a GP (n = 231) in a period of six years, 1,015 by a dermatologist (n = 22) in a period of six months, and 1,040 by a plastic surgeon (n = 22) in a period of 15 months (Table 1).

Overall, BCCs were completely excised in 82% (2,462/2,986) (Table 1). BCCs were completely excised by GPs in 70% (649/931), which was lower than the 93% (946/1,015) by

Table 1. A comparison of patient characteristics and number of complete basal cell carcinoma excisions between specialties, with subdivisions per site and histopathological subtype.

	GP n (%)	DE n (%)	PS n (%)	GP, DE, PS n (%)	GP, DE, PS P-value	GP vs DE P-value	PS vs DE P-value
Excisions, n	931	1015	1040	2986			
Physicians, n	231	22	22	275			
Patients							
Age yr (mean SD)	67 (13)	70 (12)	69 (14)	69 (13)	<0.001		
Men	468 (50)	608 (60)	469 (45)	1545 (52)	<0.001	<0.001	<0.001
Complete excisions	649 (70)	946 (93)	867 (83)	2462 (82)	<0.001	<0.001	<0.001
Per site							
Head/neck	173 (56)	414 (89)	638 (80)	1225 (78)	<0.001	<0.001	<0.001
Trunk	299 (78)	356 (97)	126 (93)	781 (88)	<0.001	<0.001	.062
Limbs	177 (74)	176 (96)	103 (95)	458 (86)	<0.001	<0.001	.501
Per subtype							
Nodular	305 (73)	441 (96)	386 (89)	1132 (86)	<0.001	<0.001	<0.001
Superficial	129 (81)	212 (94)	102 (92)	443 (90)	<0.001	<0.001	.417
Infiltrative	33 (45)	49 (88)	79 (69)	161 (66)	<0.001	<0.001	.008
Mixed nonaggr[a]	58 (67)	90 (90)	58 (74)	206 (78)	.001	<0.001	.006
Mixed aggr[b]	124 (64)	154 (89)	242 (80)	520 (78)	<0.001	<0.001	.015
Per site/per subtype							
Head/neck							
Nodular	112 (65)	238 (93)	323 (87)	673 (84)	<0.001	<0.001	.022
Superficial	3 (50)	31 (89)	28 (80)	62 (82)	.075		
Infiltrative	9 (24)	28 (82)	65 (65)	102 (59)	<0.001	<0.001	.058
Mixed nonaggr[a]	6 (38)	32 (87)	35 (69)	73 (70)	.002	<0.001	.052
Mixed aggr[b]	43 (56)	85 (83)	187 (78)	315 (75)	<0.001	<0.001	.334
Trunk							
Nodular	143 (82)	143 (99)	34 (97)	320 (90)	<0.001	<0.001	.275
Superficial	62 (83)	134 (97)	44 (98)	240 (93)	<0.001	<0.001	.809
Infiltrative	19 (79)	15 (94)	8 (100)	42 (87)	.198		
Mixed nonaggr[a]	27 (68)	31 (86)	14 (88)	72 (78)	.089		
Mixed aggr[b]	48 (69)	33 (100)	26 (84)	107 (80)	.001	<0.001	.016
Limbs							
Nodular	50 (69)	60 (98)	29 (97)	139 (85)	<0.001	<0.001	.604
Superficial	64 (82)	47 (90)	30 (97)	141 (88)	.083		
Infiltrative	5 (46)	6 (100)	6 (86)	17 (71)	.036		
Mixed nonaggr[a]	25 (83)	27 (100)	9 (82)	61 (90)	.076		
Mixed aggr[b]	33 (70)	36 (97)	29 (97)	98 (86)	<0.001	.001	.880

Percentage were rounded.

aggr, aggressive; DE, dermatologist; GP, general practitioner; n, number; nonaggr, nonaggressive; PS, plastic surgeon; SD, standard deviation; yr, years.

[a] Mixed nonaggressive basal cell carcinoma were superficial with nodular (n = 264).

[b] Mixed aggressive basal cell carcinoma were: superficial with infiltrative(n = 48), superficial with nodular and infiltrative (n = 67), nodular with infiltrative (n = 544), and infiltrative with micronodular (n = 9).

Table 2. Risk of incomplete basal cell carcinoma excision between specialties, adjusted for tumour and patient characteristics.

	Univariable OR (95% CI) for incomplete BCC excision	P-value	Multivariable OR (95% CI) for incomplete BCC excision	P-value
Patients				
Men	1.00			
Women	1.1 (0.9-1.4)	.207	1.0 (0.8-1.2)	.768
Age (for a difference of 1 yr)	1.0 (1.0-1.0)	.074	1.0 (1.0-1.0)	.069
Physicians				
Dermatologist	1.00			
General Practitioner	6.0 (4.5-7.9)	<.0001	6.2 (4.6-8.4)	<.0001
Plastic surgeon	2.7 (2.0-3.7)	<.0001	2.0 (1.5-2.7)	<.0001
BCC characteristics				
Trunk	1.00	<.0001	2.7 (2.0-3.6)	<.0001
Head/neck	2.1 (1.7-2.7)	.248	1.1 (0.8-1.5)	.605
Limbs	1.2 (0.9-1.7)	<.0001	0.4 (0.3-0.5)	<.0001
Size ≤ 2.5 cm	1.00	0.055	1.3 (0.9-1.9)	.146
Size > 2.5 cm	0.3 (0.2-0.4)	<.0001	3.4 (2.4-4.7)	<.0001
Nodular	1.00	<.001	2.6 (1.8-3.7)	<.0001
Superficial	0.7 (0.5-1.0)	<.0001	2.0 (1.6-2.6)	<.0001
Infiltrative	3.2 (2.4-4.3)			
Mixed nonaggressive[a]	1.7 (1.3-2.4)			
Mixed aggressive[b]	1.8 (1.4-2.2)			

Percentages were rounded.

BCC, basal cell carcinoma; CI, confidence interval; OR, odds ratio; yr, year.

[a] Mixed nonaggressive basal cell carcinoma were superficial with nodular (n = 264).

[b] Mixed aggressive basal cell carcinoma were: superficial with infiltrative(n = 48), superficial with nodular and infiltrative (n = 67), nodular with infiltrative (n = 544), and infiltrative with micronodular (n = 9).

dermatologists and 83% (867/1,040) by plastic surgeons ($p < 0.001$). Compared to the dermatologist, BCCs which were excised by a GP were six times higher at risk of an incomplete excision (adjusted OR 6, 95% CI 5-8) and two times higher at risk when excised by a plastic surgeon (adjusted OR 2, 95% CI 2-3) ($p < 0.0001$) (Table 2). The risk of an incomplete excision was higher for small BCCs (adjusted OR 0.4, 95% CI 0.3-0.5, $p < 0.0001$). The risk of an incomplete BCC excision was not increased by patients' age or sex.

BCCs of the head and neck

BCCs of the head and neck were completely excised in 78% of the excisions, which was lower than the 88% of completely excised BCCs of the trunk and 86% of the limbs (Table 1). The risk of an incomplete excision was higher for BCCs of the head and neck

than for BCCs of the trunk and limbs (adjusted OR 3, 95% CI 2-4) ($p < 0.0001$) (Table 2). BCCs of the head and neck were completely excised by GPs in 56% of the excisions, which was lower than the 89% for dermatologists and 80% for plastic surgeons (Table 1). For the complete excision of a BCC of the head and neck, dermatologists performed better than GPs and plastic surgeons ($p < 0.001$). When BCCs of the head and neck were subdivided per histological subtype, GPs still showed the lowest proportion of complete excisions when compared to the dermatologists ($p < 0.001$ for each subtype), while differences between dermatologists and plastic surgeons were not significant ($p > 0.0125$).

BCCs with an infiltrative or mixed histological subtype

Infiltrative BCCs were completely excised in 66% of the excisions, which was lower than the 86% of nodular, 90% of superficial, 78% of mixed nonaggressive, and 78% of mixed aggressive BCCs ($p < 0.001$) (Table 1). The risk of an incomplete excision was higher for BCCs with the following histological subtypes: infiltrative (adjusted OR 3, 95% CI 2-5), mixed nonaggressive (adjusted OR 3, 95% CI 2-4) and mixed aggressive (adjusted OR 2, 95% CI 2-3) ($p < 0.0001$). Infiltrative BCCs were completely excised by GPs in 45% of the excisions, which was lower than the 88% for dermatologists, and 69% for plastic surgeons. For the complete excision of an infiltrative BCC, dermatologists performed better than GPs and plastic surgeons ($p < 0.0125$). For both mixed nonaggressive and mixed aggressive subtypes, GPs had the lowest proportions of completely excised BCCs when compared to dermatologists and plastic surgeons. For the complete excision of mixed nonaggressive and mixed aggressive subtypes, dermatologists performed better than GPs ($p < 0.001$).

DISCUSSION

This retrospective cross-sectional study of 2,986 pathology records from a Dutch regional laboratory, showed that primary BCCs were more often completely excised by a dermatologist (93%) than by a GP (70%) or plastic surgeon (83%). Compared to the dermatologist, BCCs which were excised by a GP were six times higher at risk of an incomplete excision (adjusted OR 6, 95% CI 5-8) and two times higher at risk when excised by a plastic surgeon (adjusted OR 2, 95% CI 2-3) ($p < 0.0001$).

Previous studies found similar proportions of complete BCC excisions; however, these studies lack a sample size calculation, subgroup analyses per tumour site and histological subtype and logistic regressions.[8-11] Dermatologists probably excise BCC more often complete than GPs and plastic surgeons because dermatologists are specifically trained in BCC care during their five years of specialization and dermatologists are more expe-

rienced in BCC care due to the high case load in their daily practice. This might result in better clinical skills among dermatologists in recognizing skin lesions as suspected for BCC, and in demarcating the tumour preoperatively. Both skills contribute to the success of a complete BCC excision.

The risk of an incomplete excision was found higher for BCCs of the head and neck than for BCCs of the trunk and limbs (adjusted OR 3, 95% CI 2-4) ($p < 0.0001$), irrespectively of the specialist who performed the excision. First, this could be explained because BCCs of the H-zone are known to grow more aggressively. Second, physicians might narrow their excision margins for BCCs of the head and neck to preserve functional and cosmetic outcome.

The risk of an incomplete excision was found to be higher for BCCs with an infiltrative or mixed histological subtype than for nodular or superficial BCCs. Smeets et al. showed that excisions with a clinical tumour free margin of 3 mm for primary facial BCCs with an infiltrative histological subtype were more often incomplete (25%) than other subtypes (12%, $p < 0.05$).[12] These findings suggest that preoperative histological subtype determination might be useful to indicate when wider clinical tumour free excision margins are needed. Although in one out of six BCCs the most aggressive growth pattern is missed by the preoperative biopsy (i.e., sampling error), a biopsy was shown to be more sensitive and more specific than the clinical diagnosis on the histological subtype.[13,14] Remarkably, the risk of an incomplete excision was found higher for small BCCs (i.e. ≤ 2 cm). The clinical demarcation of a small BCC might be more difficult due to scar formation after a preoperative biopsy.

Strengths of this study are: the comparative design, the large sample size, analysis per tumour site and histological subtype. This study was limited to a retrospective design which implicated selection bias between the specialties. Therefore, risk of an incomplete BCC excision between the specialties was adjusted for BCC site, specimen size, histological subtype, patients' age and sex. But due to missing data, BCC localization in the H-zone and exact clinical tumour size could not be specified. Also, it was unknown whether the BCC diagnosis was confirmed histologically prior to the excision and which excision margins were used. The real proportion of completely excised BCCs was overestimated in all groups due to missing tumour on the histological margins by applying the bread loaf technique.

In conclusion, this study shows that primary BCCs were more often completely excised by dermatologists than by GPs and plastic surgeons. Among GPs, complete excisions were specifically low for BCCs of the head and neck and BCCs with an infiltrative subtype.

Dermatologists probably perform better because of their extensive training and high experience in BCC care. Before a shift of BCC care from secondary to primary care, there is a strong need for an integrated care pathway, including adequate training for GPs.

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Chapter 3

Reliability of diagnosis from Mohs slides: interpersonal and intrapersonal agreement on basal cell carcinoma presence and histological subtype

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ABSTRACT

Background: The success of Mohs micrographic surgery (MMS) depends partly on the correct diagnosis of slides.

Objectives: To determine reliability of diagnosis from MMS slides.

Methods: This was a prospective study evaluating the reliability of diagnosis from MMS slides of basal cell carcinoma (BCC) presence, BCC location on the slide and BCC subtype among six raters who independently assessed 50 MMS slides twice with a two-month interval. Slides were randomly selected whereby difficult to diagnose slides were oversampled. For each slide, a reference diagnosis was established by an expert panel. Cohen's kappa (K) was calculated to determine levels of agreement interpersonally (rater vs. reference diagnosis) and intrapersonally (rater at T1 vs. T2). Multivariable logistic regression was used to determine independent risk factors for slides with interpersonal discordant diagnosis. The variables studied were BCC presence, whether a slide was scored as easy or difficult to diagnose, review duration of the 50 slides, profession and years of experience in diagnosis from MMS slides.

Results: Interpersonal and intrapersonal agreement were substantial on BCC presence (K = 0.66 and 0.68) and moderate on BCC subtype (K = 0.45 and 0.55). Slides that were scored as difficult to diagnose were an independent risk factor for interpersonal discordant diagnosis on BCC presence (OR 3.5, 95% CI 1.8-6.8).

Conclusions: Reliability of diagnosis from MMS slides was substantial on BCC presence and moderate on BCC subtype. For slides that are scored difficult to diagnose, a second opinion is recommended to prevent misinterpretation and thereby recurrence of skin cancer.

INTRODUCTION

Mohs micrographic surgery (MMS) is a preferred treatment for aggressive or recurrent facial basal cell carcinoma (BCC), due to the low recurrence rate and preservation of healthy tissue.[1,2] With MMS all surgical margins are microscopically viewed intraoperatively, whereas with conventional excision only a small percentage of the margins are viewed at all, and only postoperatively.

To warrant the additional costs of MMS compared to conventional excision, optimization of the procedure is pivotal. Because clinical recurrences after MMS often become apparent after five to ten years, a critical appraisal of the procedure is needed before MMS is more widely introduced in Europe. Although the success of MMS depends mainly on the correct diagnosis of slides, the reliability of diagnosis from MMS slides is poorly documented.[3,4] A better insight into the reliability of diagnosis from MMS slides might decrease slide misinterpretation. A decrease in slide misinterpretation prevents excision of healthy tissue and results in fewer skin cancer recurrences and, which are both the most important characteristics of MMS.

This is a reliability study on diagnosis from MMS slides. We determined interpersonal and intrapersonal levels of agreement on BCC presence, BCC location on the slide and BCC subtype. Furthermore, to explore possible approaches to improve the reliability of diagnosis from MMS slides, we identified risk factors for slides with interpersonal discordant diagnosis on BCC presence.

METHODS

This prospective reliability study determined interpersonal and intrapersonal levels of agreement on the diagnosis of 50 MMS slides among six raters and an expert panel.

Selection of slides

Slides were obtained from the MMS registry of the Erasmus University Medical Center, Rotterdam, the Netherlands. Frozen MMS slides were stained with haematoxylin and eosin; the distance between each section was 100 µm and the sections were 8 µm thick. Slides of bad quality were excluded.

In total, we selected 300 MMS slides derived from 50 different MMS procedures, all indicated for BCC: six slides per MMS procedure, subsequently cut from one tissue block. In some cases, BCC was present in the deepest cut, while BCC was absent in the outermost

slide. Therefore, one of the six slides was non-randomly selected, marked and used for the final diagnosis (n = 50). Raters were allowed to review all six slides, although they were instructed to diagnose the indicated slide only. All 300 slides were anonymized and coded with a specific study number. Comparable to our daily practice, half of the slides were tumour-free and half of the slides contained BCC. Slides with BCC contained variable BCC subtypes.

Slides were non-randomly selected by the researchers with oversampling of difficult to diagnose slides. We wanted to focus on the histological pitfalls in MMS such as small BCC strands that are easily missed, benign structures mimicking BCC and dense inflammation.[5] We expected that approximately half of all selected slides were difficult to diagnose due to histological pitfalls, which differs from our daily MMS practice where we score approximately five percent of the slides as difficult to diagnose. We chose to oversample difficult slides to determine the minimum level of agreement on diagnosis from MMS slides.

Selection of raters

Six raters (three MMS surgeons and three pathologists) were selected from three different centres: Erasmus University Medical Center Rotterdam (raters A, D), Isala Hospital Zwolle (raters B, E) and Maastricht University Medical Center (raters C, F). Raters had four to fifteen years of experience in diagnosis from MMS slides.

Rating process

Raters were instructed to review all 300 slides independently, twice, with two month intervals. Raters reviewed the slides without any clinical information (e.g. BCC location, BCC subtype, preoperative treatment). They were blinded to their own previous interpretation and to each other's interpretations. Before the second review, the slides were shuffled and recoded to prevent identification. Diagnoses were recorded on standardized study forms including: BCC presence (yes or no); BCC subtype with or without perineural invasion (i.e. superficial, nodular, micronodular, morpheaform or any combination); and exact BCC location. Raters marked the exact BCC location with a waterproof pencil on the slide. One of the researchers copied the marks to translucent paper and then removed the marks from the slides. Furthermore, raters scored the slides easy or difficult to diagnose, the time it took to review all slides, their years of experience in diagnosis from MMS slides, their profession and whether they worked in an academic or non-academic setting. At last, to verify if we indeed oversampled difficult to diagnose slides, raters were asked what percentage of difficult slides they find in their daily MMC practice.

Expert panel consensus-derived reference diagnosis

In the absence of a gold standard, an expert panel consensus-derived reference diagnosis was established for each slide. The expert panel consisted of one MMS surgeon and one pathologist, both with over 15 years of experience in diagnosis from MMS slides. Similar to the rating process, both experts reviewed all 300 slides independently, twice, with 2-month intervals. They were blinded to their own previous interpretation and to each other's interpretation. To establish the reference diagnosis, slides with experts' interpersonal or intrapersonal discordant diagnosis were resolved with consensus discussion. At this consensus discussion, experts were blinded to their own and each other's previous interpretations. If the experts did not reach consensus on BCC presence, deeper paraffin slides of the corresponding tissue blocks were made to reach a consensus diagnosis for all slides. The reference diagnosis included BCC presence (yes or no); BCC subtype with or without perineural invasion (i.e. superficial, nodular, micronodular, morpheaform or any combination); and BCC location on the slide.

Outcome 1: Interpersonal and intrapersonal agreement

Interpersonal agreement was determined between each rater vs. the reference diagnosis. Intrapersonal agreement was determined within each rater at T1 vs. T2. To evaluate the reliability of the reference diagnosis, we also determined the interpersonal and intrapersonal agreement of the two experts. Agreement concerned BCC presence, BCC subtype and BCC location on the slide. To indicate if BCC location was equally marked on a slide, the translucent papers of corresponding slides were stacked.

Outcome 2: Risk factors for slides with interpersonal discordant diagnosis

We determined independent risk factors for slides with discordant diagnosis between raters and the reference diagnosis at T1. Discordancy was based on BCC presence (yes or no), plus equal BCC location on the slide. The variables studied were: BCC presence [1. absent; 2. nonaggressive (i.e. superficial or nodular); 3. aggressive (i.e. micronodular, morpheaform, perineural invasion)]; whether raters scored slides as either easy or difficult to diagnose; the time it took each rater to review all slides; raters' years of experience in diagnosis from MMS slides; and profession (MMS surgeon or pathologist).

Statistics

For BCC presence and subtype, Cohen's kappa coefficients (K) were calculated to determine interpersonal and intrapersonal levels of agreement. Additionally, the t-test with Bonferroni correction was used to calculate whether the levels of agreement differed significantly between the raters. Overall mean K values were computed inside the programme. As described by Malpica et al., levels of agreement were interpreted as slight (K = 0-0.2), fair (K = 0.2-0.4), moderate (K = 0.4-0.6), substantial (K = 0.6-0.8) or almost

perfect (K = 0.8-1.0).[6] Regarding the sample size, to detect a K value of at least 0.6, we needed 50 cases and six raters for a power of 0.9 with alpha = 0.05. K could not be used for the agreement on BCC location. For BCC location we calculated percentages of equally marked BCC out of the total number of slides with concordant BCC presence. Univariable and multivariable logistic regression models were used to determine risk factors for slides with interpersonal discordant diagnosis on BCC presence. All statistical analyses were conducted in the Bayesian framework. Statistical analyses were performed using software package R version3.1.1 and JARG version 3.4.0. Guidelines for reporting reliability and agreement studies were used to report this study.[7]

RESULTS

In total, 800 slide assessments were analysed: six raters and two panel experts diagnosed 50 slides twice.

Reference diagnosis

The experts' diagnosis from MMS slides on BCC presence differed interpersonally at T1 or T2 in 23% (23/100). For expert 1, diagnosis on BCC presence differed intrapersonally in 8% (4/50). For expert 2, diagnosis on BCC presence differed intrapersonally 10% (5/50). At the consensus meeting, the experts did not reach consensus on BCC presence 10% (5/50). Of these five cases, deeper paraffin slides of the corresponding tissue blocks were made. With these deeper slides, the experts reached consensus in all cases. The reference diagnoses of the 50 MMS slides were 'tumour-free' in 26 slides and 'BCC present' in 24 slides. The reference diagnoses on BCC subtypes are summarized in Table 1.

Table 1. Reference diagnosis of the 50 Mohs micrographic surgery slides.

Variable	Cases n = 50 (%)
Tumour free	26 (52)
BCC present[a]	24 (48)
Superficial	1 (2)
Nodular	8 (16)
Morpheaform	10 (20)
Micronodular	3 (6)
Perineural invasion	2 (4)

Percentage were rounded.
BCC, basal cell carcinoma; n, number.
[a] In the case of mixed BCC subtypes, the most aggressive subtype was recorded, i.e. superficial < nodular < micronodular < morpheaform < perineural invasion.

Description of diagnosis from MMS slides at T1

At the first rating session (T1), raters needed 80-140 minutes to diagnose the 50 MMS slides (Table 2). Altogether, the six raters scored 21% (64/300) diagnoses as difficult. In their daily MMS practice, the experts and raters score approximately 6% of cases difficult to diagnose (range 2-10%), which confirms that difficult to diagnose slides were oversampled in this study. Raters diagnosed 'BCC presence' equally to the reference diagnosis in 17-24 slides out of 24 (mean 85%, range 67-100%). Raters diagnosed 'tumour-free' equally to the reference diagnosis in 14-26 slides out of 26 (mean 82%, range 58-100%).

Table 2. Description of the six raters and their diagnosis from Mohs micrographic surgery slides at T1.

Rater	Profession	Academic or Nonacademic	Experience in diagnosis from MMS slides (years)	Duration to diagnose 50 MMS slides (minutes)	Difficult to diagnose MMS slides out of 50 (%)	BCC present n = 24[a] (%)	Tumour free n = 26[b] (%)
A	Dermatologist	Academic	5	120	7 (14)	22 (92)	16 (62)
B	Dermatologist	Nonacademic	7	140	10 (20)	23 (96)	15 (58)
C	Dermatologist	Academic	15	105	17 (34)	21 (88)	22 (85)
D	Pathologist	Academic	8	80	8 (16)	16 (67)	26 100)
E	Pathologist	Nonacademic	4	90	10 (20)	24 (100)	23 (89)
F	Pathologist	Academic	8	100	12 (24)	16 (67)	26 (100)

Percentage were rounded.

BCC, basal cell carcinoma; MMS, Mohs micrographic surgery; n, number.

[a] Numbers of slides that were equally diagnosed as the reference diagnosis of 'BCC present' out of 24.

[b] Numbers of slides that were equally diagnosed as the reference diagnosis of 'tumour free' out of 26.

Experts' interpersonal and intrapersonal agreement

Interpersonal agreement between the two experts was substantial on BCC presence (K = 0.61, 95% CI 0.41-0.79) and moderate on BCC subtype (K = 0.45, 95% CI 0.31-0.61) (Table 3). Equal to the interpersonal agreement, the overall intrapersonal agreement within the two experts was substantial on BCC presence (K = 0.75, 95% CI 0.60-0.86) and moderate on BCC subtype (K = 0.58, 95% CI 0.47-0.69)

Interpersonal levels of agreement between each rater and the reference diagnosis

Overall, interpersonal agreement and the reference diagnosis was substantial on BCC presence (K = 0.66, 95% CI 0.58-0.73) and moderate on BCC subtype (K = 0.45, 95% CI 0.39-0.52) (Table 4). Overall, BCC location on the slide was equal to the reference diagnosis in 95% (range 88-100%). Levels of agreement on BCC presence differed significantly only between raters B and E. Rater B had a significantly lower interpersonal level of agreement (K = 0.49, 95% CI 0.27-0.69), while rater E had a higher interpersonal level of agreement (K = 0.89, 95% CI 0.72-0.97), p = 0.01. Levels of agreement on BCC subtype did not differ significantly between the raters.

Table 3. Interpersonal agreement between the experts and intrapersonal agreement within the experts in 50 Mohs micrographic surgery slides.

Agreement	BCC presence K (95% CI)	BCC location on MMS slide equal (%)	BCC subtype[a] K (95% CI)
Interpersonal	0.61 (0.41-0.79)	100	0.45 (0.31-0.61)
Intrapersonal			
Expert 1	0.68 (0.44-0.85)	96	0.64 (0.47-0.79)
Expert 2	0.84 (0.64-0.95)	88	0.52 (0.37-0.68)
Overall	0.75 (0.60-0.86)	92	0.58 (0.47-0.69)

Percentage were rounded.
BCC, basal cell carcinoma; CI, confidence interval; K, Cohen's kappa; MMS, Mohs micrographic surgery.
[a] BCC subtypes included: superficial, nodular, micronodular, morpheaform, perineural invasion or any combination.

Table 4. Interpersonal agreement between each of the six raters and the reference diagnosis and intrapersonal agreement within each rater in 50 Mohs micrographic surgery slides.

Agreement	BCC presence K (95% CI)	BCC location on slide equal %	BCC subtype[a] K (95% CI)
Interpersonal			
Overall	0.66 (0.58-0.73)	95	0.45 (0.39-0.52)
A	0.53 (0.29-0.72)	95	0.41 (0.25-0.57)
B	0.49 (0.27-0.69)	96	0.35 (0.21-0.51)
C	0.73 (0.50-0.88)	100	0.51 (0.35-0.66)
D	0.67 (0.46-0.84)	88	0.47 (0.32-0.64)
E	0.89 (0.72-0.97)	92	0.55 (0.41-0.70)
F	0.67 (0.46-0.84)	100	0.42 (0.28-0.58)
Intrapersonal			
Overall	0.68 (0.59-0.76)	86	0.55 (0.49-0.62)
A	0.66 (0.42-0.84)	89	0.67 (0.50-0.81)
B	0.57 (0.33-0.78)	85	0.51 (0.35-0.66)
C	0.64 (0.42-0.82)	89	0.51 (0.35-0.66)
D	0.69 (0.44-0.86)	77	0.58 (0.39-0.75)
E	0.75 (0.55-0.90)	89	0.59 (0.44-0.73)
F	0.79 (0.59-0.92)	88	0.46 (0.32-0.61)

Percentage were rounded.
BCC, basal cell carcinoma; CI, confidence interval. K, Cohen's kappa.
[a] BCC subtypes included: superficial, nodular, micronodular, morpheaform, perineural invasion or any combination.

Intrapersonal levels of agreement

Equal to the interpersonal agreement, overall intrapersonal agreement within each rater was substantial on BCC presence (K = 0.68, 95% CI 0.59-0.76) and moderate on BCC subtype (K = 0.55, 95% CI 0.49-0.62) (Table 4). Overall, BCC location similarly scored more

often interpersonally (95%) than intrapersonally (86%). Intrapersonal levels of agreement did not differ significantly between the raters on BCC presence and BCC subtype.

Risk factors for slides with discordant diagnosis on basal cell carcinoma presence

Raters' diagnosis on BCC presence and BCC location differed from the reference diagnosis in 17% (50/300). An independent risk factor for discordant diagnosis on BCC presence were slides that were scored as difficult to diagnose by the raters (OR 3.5, 95% CI 1.8-6.8) (Table 5). Other studied variables did not affect the risk in the univariable or multivariable analysis.

Table 5. Univariable and multivariable analysis of risk factors for slides with discordant diagnosis on BCC presence between raters and the reference diagnosis.

Variable	Univariable OR (95% CI)	Multivariable OR (95% CI)
MMS slides (n = 50)		
Tumour free (n = 26)	1.00	1.00
Nonaggresive BCC subtype (n = 9)[a]	1.17 (0.54-2.46)	1.38 (0.61-3.02)
Aggressive BCC subtype (n = 15)[b]	0.96 (0.50-1.84)	1.11 (0.54-2.24)
Raters profession (n = 6)		
Pathologist (n = 3)	1.00	1.00
Dermatologist (n = 3)	1.52 (0.51-4.27)	0.88 (0.06-6.60)
Difficulty of the interpretation (n = 300)		
Easy (n = 236)	1.00	1.00
Difficult (n = 64)	3.30 (1.71-6.26)	3.54 (1.81-6.84)
MMS experience (years)	1.00 (0.84-1.21)	0.99 (0.76-1.34)
Review duration (minutes)	1.01 (0.99-1.04)	1.02 (0.96-1.09)

BCC, basal cell carcinoma; CI, confidence interval; MMS, Mohs micrographic surgery; OR, odds ratio.

[a] Nonaggressive BCC subtypes included: superficial BCC and nodular BCC.

[b] Aggressive BCC subtypes included: morpheaform BCC, micronodular BCC and BCC with perineural invasion.

DISCUSSION

Reliability of interpretation of MMS slides is pivotal because the success of MMS depends mainly on the correct diagnosis of slides. This study showed substantial interpersonal and intrapersonal agreement on whether BCC was present and moderate agreement on BCC subtype, which is comparable with other fields of diagnostic reliability such as breast pathology and radiology.[8-16] Discordant diagnosis on BCC presence was more frequent when slides were self-scored as difficult to diagnose. This suggests that raters are aware of their uncertainty and should know when to consult others to reduce misin-

terpretation. Although interpersonal and intrapersonal agreement on BCC presence was found to be imperfect, the recurrence rate of skin cancer after MMS is extremely low.[1,2]

Previous studies show high interpersonal agreement between MMS surgeons and pathologists (95-99%) on BCC presence.[17-22] These studies overestimate the reliability of diagnosis from MMS slides because they report concordance rates instead of K values. In contrast to these studies, we oversampled difficult MMS slides, which resulted in an underestimated level of agreement. Besides our focus on challenging aspects of diagnosis from MMS slides, this study had several other unique aspects. Firstly, we established a reference diagnosis and we included six raters to determine interpersonal and intrapersonal agreement. Secondly, agreement on BCC presence, BCC subtype and BCC location on the slide was determined. Thirdly, we determined risk factors for interpersonal discordance.

Remarkably, interpersonal and intrapersonal agreement on BCC presence was comparable, while we expected to find a higher intrapersonal agreement. Intrapersonal diagnosis from MMS slides was found to be less consistent than we anticipated even among experienced raters. This might be because we oversampled slides that were difficult to diagnose.

In line with Nedved et al., we observed a somewhat lower level of agreement on BCC subtyping than on BCC presence.[23] This is logically explained because BCC presence (yes or no) is a binary question while the differentiation between BCC subtypes is less strict and mixed subtypes are common. To improve the diagnostic concordance in BCC subtyping, it might be necessary to further specify and simplify the current World Health Organization classification of BCC subtypes.

Our predictor analysis of discordant BCC diagnosis from MMS slides showed that slides that were self-scored as difficult to diagnose increased the likelihood of discordance three-and-half-fold (OR 3.5, 95% CI 1.8-6.8). As suggested in a previous study, a second opinion might prevent slide misinterpretation and thereby prevent skin cancer recurrence and unnecessary excision of healthy tissue.[24] Other possible measures to improve accurate slide diagnosis include cutting an additional deeper slide or obtaining a (paraffin) slide with additional histochemical stains.[5,25] In exceptionally difficult cases, these actions do not clear the diagnosis. In those cases, to minimize the risk of recurrence an additional small safety margin should be excised and examined microscopically.

A promising development that might further optimize diagnosis from MMS slides is the use of optical devices such as spectroscopy, which aim to eliminate the subjectivity of human diagnosis from MMS slides.[26]

Other studies show that MMS surgeons are as good as pathologists in evaluating MMS slides.[18,21,22] Although this study was not designed to assess differences between MMS surgeons and pathologists, the three MMS surgeons identified almost all 24 BCC-positive slides correctly (high sensitivity), while they were more likely to interpret benign structures as BCC (lower specificity). In contrast, the three pathologists had a lower sensitivity, but a higher specificity.

This study has several limitations. Crucially, there is no gold standard.[27] We assumed that the expert reference diagnosis was more accurate than the raters' diagnoses. Moreover, our study showed that interpersonal levels of agreement were equal between the experts and raters and intrapersonal levels of agreement were only a little higher among the experts than among the raters. Furthermore, the determined reliability is likely to be lower than the reality for the following reasons.[25,27] Firstly, difficult to diagnose slides were oversampled. Secondly, raters could not consult a colleague or pathologist to establish a consensus-derived diagnosis. Thirdly, raters could not ask for a deeper (paraffin) slide or additional staining. Fourthly, raters were not informed about the clinical context. In addition, the generalizability of our findings is limited because the number of participating clinicians was small (n = 6), although we included a heterogeneous group of raters (i.e. MMS surgeons and pathologists of academic and non-academic MMS settings). To further determine the reliability of interpretation of MMS slides, a large international web-based study assessing randomly selected MMS slides is warranted.

This study shows that interpersonal and intrapersonal levels of agreement on diagnosis from MMS slides were substantial for BCC presence and moderate for BCC subtype. Slides that were scored as difficult to diagnose were an independent risk factor for discordant diagnosis. A better understanding of the reliability of diagnosis from MMS slides might decrease slide misinterpretation and thereby prevent recurrences of skin cancer.

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Chapter 4

Additional review of Mohs slides to optimize Mohs micrographic surgery

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ABSTRACT

Background: One significant risk factor for recurrence after Mohs micrographic surgery (MMS) is misinterpretation of slides.

Objectives: To determine how often pathologists detected incompletely excised basal cell carcinoma (BCC) on MMS slides and to determine risk factors for incompletely excised BCCs.

Methods: This retrospective study included 1,653 BCCs treated with MMS in a university hospital between 2007 and 2011. For routine quality assurance, all slides were additionally reviewed by a pathologist within one week of the procedure. For this study, all cases that had divergent interpretations were re-evaluated by a MMS surgeon and a pathologist. Mixed-effects logistic regression models with MMS surgeon effects as random effects were used to determine risk factors for incompletely excised BCC.

Results: Incompletely excised BCCs were detected in 2% (31/1,653), in which defects > 20 mm in diameter were an independent risk factor (OR 3.6, 95% CI 1.6-8.3). Other studied variables (i.e. aggressive subtype, previously treated BCC, location on nose and > 2 MMS stages) did not affect the risk of incompletely excised BCCs.

Conclusions: The additional review of MM slides might increase accurate interpretation, especially in large BCCs.

INTRODUCTION

Due to a low recurrence rate and preservation of healthy tissue, Mohs micrographic surgery (MMS) is a superior treatment for aggressive or recurrent basal cell carcinomas (BCCs) located on the face.[1,2] These benefits are achieved because all margins are reviewed microscopically. Therefore, the success of MMS depends on correct interpretation of slides. At least 30% of skin cancer recurrences after MMS are due to misinterpretation of slides by the MMS surgeon.[3,4] It is unknown how often MMS surgeons miss tumour cells on slides and, to date, no study has been performed on methods to reduce the number of cases with missed tumour. In pathology, an additional review to detect slide misinterpretation is considered the gold standard.[5] The purpose of our study was to determine how often a pathologist detected misinterpreted slides that included incompletely excised BCCs. We also aimed to determine risk factors for these incompletely excised BCCs.

METHODS

This retrospective study included BCCs treated with MMS at the Department of Dermatology, Erasmus University Medical Center Rotterdam (EMC), between 2007 and 2011. Each month, the first 60% of BCCs treated with MMS were included. Other types of skin cancers were excluded. Included cases were operated on by one of 11 MMS surgeons. MMS surgeons were certified by the European Society for Micrographic Surgery and each had over five years' experience in MMS. During the study period, four of the MMS surgeons operated on a regular basis; the other six only operated for approximately six months. Well-trained histotechnicians prepared MMS slides, which were stained with haematoxylin and eosin; the distance between each section was 100 µm and the sections themselves were eight µm thick. The number of slides made per MMS procedure depended on the size of excised tissue and number of stages. For each tissue block, at least six slides were prepared and reviewed. The MMS surgeon reviewed slides intraoperatively and recorded the findings in a standard digital file. For a margin to be considered tumour free, at least two complete slides should be without tumour. For routine quality assurance, all slides and files were additionally reviewed by one of five pathologists within one week of the MMS procedure. Slides and files were additionally reviewed for the absence or presence and correct mapping of BCC. Whenever the pathologist's review diverged from that of the MMS surgeon, this was recorded by the pathologist in the pathology report.

We examined patient records, MMS files and pathology reports of the included BCCs. Whenever a pathologist's interpretation diverged from that of the MMS surgeon, this was recorded in our database. For this study, an MMS surgeon and a pathologist were appointed to re-evaluate the cases with divergent interpretations. The MMS surgeon and the pathologist appointed both had > 15 years' experience in the interpretation of MMS slides. They jointly determined if the cases with divergent interpretations were truly misinterpreted by the initial MMS surgeon. If they determined that the initial MMS surgeon had truly misinterpreted a slide, it was specified whether this resulted in an incompletely excised BCC. Incompletely excised BCCs were defined as follows: BCC present on slides at the margin but not marked on the MMS map; marking of BCC on wrong portions of the map; an inadequately sized specimen to encompass previous areas of BCC completely.[6] In the case of an incompletely excised BCC, the BCC subtype was specified. In the case of a mixed subtype, the case was categorized on the basis of the worst pattern: perineural invasion (PNI) > morpheaform > micronodular > nodular > superficial. If the subtype on the MMS slide differed from the biopsy, it was specified whether this subtype was more aggressive than the biopsy. Aggressive subtypes were considered to be morpheaform, micronodular, adenoid, basosquamous and BCC with PNI. Less aggressive subtypes were considered to be superficial and nodular BCC.[7]

The secondary outcome was to determine if the characteristics of the BCCs and MMS procedures were an independent risk factor for incompletely excised BCCs. A mixed-effects logistic regression model was used to test the effect of variables on incompletely excised BCCs. MMS surgeon effects were taken into account as random effects. Variables in the model were presumed to increase the risk of an incomplete BCC excision and included: aggressive BCC subtype; previously treated BCC; BCC located on the nose; final defect size > 20 mm in diameter; and total number of MMS stages > 2. To check if our sample size was sufficient, a simulation for power calculation based on the mixed-effects logistic regression model was performed. The simulation study indicated > 80% power to detect at least one of five risk factors for incompletely excised BCCs. To indicate significance, a two-sided P-value < .05 was used. Statistical analyses were performed using R version 3.1.1 (http://www.r-project.org).

RESULTS

A total of 1,653 cases were examined (50% men, 50% women). The median age of the patients was 69 years (IQR 59-77). BCCs were most frequently morpheaform or nodular (Table 1). The median number of MMS stages was two (IQR 1-2; range 1-6).

Table 1. Subtypes of completely and incompletely excised basal cell carcinoma with Mohs micrographic surgery.

BCC Subtype	Completely excised BCC, BCC subtype in biopsy prior to MMS n = 1,662 (%)	Incompletely excised BCC, BCC subtype in biopsy prior to MMS n = 31 (%)	Incompletely excised BCC, BCC subtype in outer MMS slide n = 31 (%)
Morpheaform	922 (57)	16 (52)	13 (42)
Nodular	552 (34)	13 (42)	3 (10)
Micronodular	76 (5)	1 (3)	1 (3)
Superficial	14 (1)	0 (0)	13 (42)
Adenoid	10 (1)	1 (3)	0 (0)
Basosquamous	3 (0)	0 (0)	0 (0)
Perineural invasion	0 (0)	0 (0)	1 (3)
Unknown	45 (3)	0 (0)	0 (0)

Percentages were rounded.
BCC, Basal cell carcinoma; MMS, Mohs micrographic surgery; n, number.

Of the 1,653 cases, a pathologist's review diverged from the initial interpretation of the MMS surgeon in 6% cases (n = 104) (Figure 1). These 104 cases were re-evaluated by the MMS surgeon and the pathologist appointed for this study. They jointly determined that 99 of these 104 cases were truly misinterpreted by the initial MMS surgeon. In 4% (68/1,653), initial misinterpretation did not result in an incompletely excised BCC (e.g. benign structures were misinterpreted as BCC). Benign structures that were interpreted as BCC were inflammatory cells; pronounced hair follicles; fibrotic cells; actinic keratosis; syringoma; and seborrhoeic keratosis. In 2% (31/1,653), initial misinterpretation resulted in an incompletely excised BCC.

The 31 incompletely excised BCCs were superficial in 42% (n = 13); morpheaform in 42% (n = 13); nodular 10% (n = 3); micronodular in 3% (n = 1); and with perineural invasion in 3% (n = 1) (Table 1). Subtypes of incompletely excised BCCs differed from their biopsy in 58% (n = 18). In 10% (n = 3), subtypes of incompletely excised BCCs were more aggressive than demonstrated in their biopsy, while in 48% (n = 12) incompletely excised BCC were less aggressive. The 13 incompletely excised superficial BCCs demonstrated different subtypes in their biopsy: 77% (10/13) biopsies demonstrated nodular BCCs; 15% (2/13) demonstrated morpheaform BCCs; and 8% (1/13) demonstrated adenoid BCC. The 13 incompletely excised morpheaform BCCs demonstrated consistent subtypes in 85% (11/13) biopsies and nodular BCCs in 15% (2/13) biopsies. The three incompletely excised nodular BCCs demonstrated a consistent subtype in 33% (1/3) biopsy and morpheaform BCCs in 67% (2/3) biopsies. The incompletely excised micronodular BCC was consistent with the biopsy. The incompletely excised BCC with PNI occurred in a case where the biopsy demonstrated a morpheaform BCC without PNI.

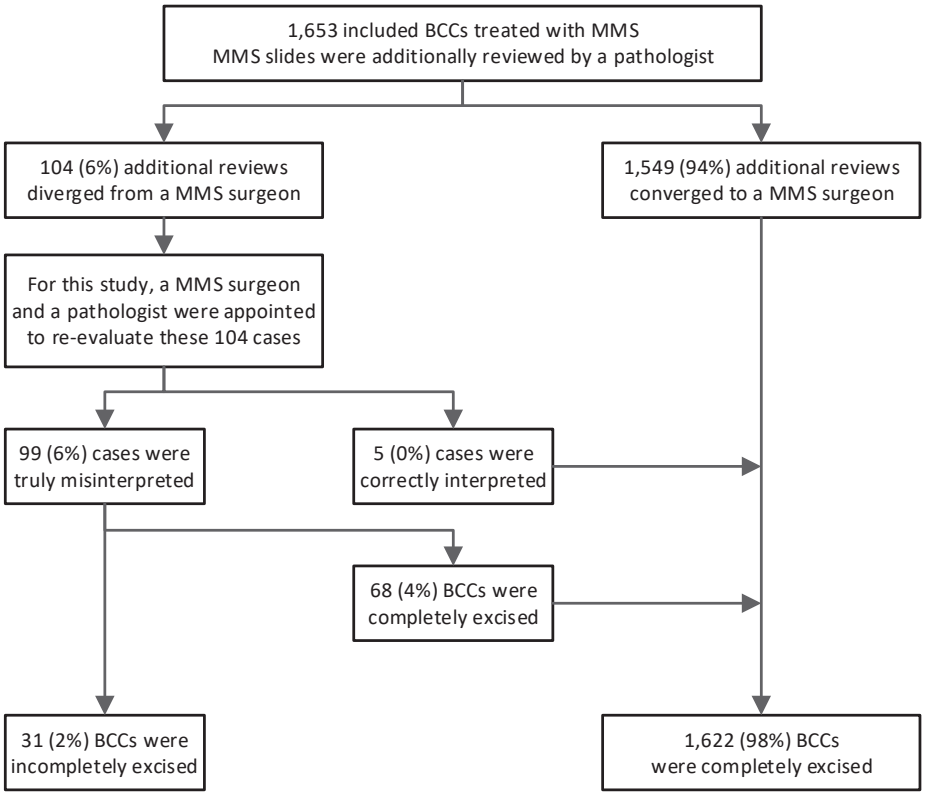

Figure 1. With the additional review of a pathologist, incompletely excised basal cell carcinomas were detected in 2% (31/1,653) Mohs micrographic surgery procedures.
BCC, Basal cell carcinoma; MMS, Mohs micrographic surgery.

Mixed-effects logistic regression models with MMS surgeon effects as random effects showed that a final defect > 20 mm in diameter was an independent significant risk factor for incompletely excised BCCs (OR 3.6, 95% CI 1.6-8.3) (Table 2). Other studied variables (i.e. aggressive BCC subtype; previously treated BCC; location on the nose; and total number of MMS stages > 2) did not impact the risk of incompletely excised BCCs ($P > .05$).

Table 2. Descriptive statistics and the results of variables in the mixed-effects logistic regression model with incompletely excised basal cell carcinomas as response and Mohs surgeons effects as random effects.

Variables	Completely excised BCC n = 1,622 (%)	Incompletely excised BCC n = 31 (%)	Adjusted OR (95% CI)
Previously treated BCC			
Yes	390 (24)	14 (45)	1.9 (0.9-4.2)
No	1,232 (76)	17 (55)	
Aggressive BCC subtype[a]			
Yes	1,011 (62)	15 (48)	0.6 (0.3-1.2)
No	611 (38)	16 (52)	
Location on nose			
Yes	640 (40)	14 (45)	0.5 (0.3-1.1)
No	982 (61)	17 (55)	
Number of stages > 2			
Yes	219 (14)	7 (23)	1.1 (0.4-2.7)
No	1,403 (87)	24 (77)	
Defect > 20 mm in diameter			
Yes	516 (32)	19 (61)	3.6 (1.6-8.3)
No	1106 (68)	12 (39)	

Percentages were rounded.

BCC, Basal cell carcinoma; CI, confidence interval; MMS, Mohs micrographic surgery; n, number; OR, odds ratio.

[a] Aggressive subtypes included: morpheaform, micronodular, adenoid, basosquamous and perineural invasion.

DISCUSSION

This study shows that pathologists detected incompletely excised BCCs on MMS slides in 2% of cases. This is in line with two other studies, although these studies included fewer cases than we did (207 and 102, respectively, vs. 1,653).[8,9] In our study, incompletely excised BCCs were most frequently morpheaform (42%) or superficial (42%) and, less frequently, nodular (10%). Both morpheaform and superficial BCCs were probably missed because both can be subtle in their appearance. Although superficial BCCs grow less aggressively than other BCC subtypes, they must be recognized on the MMS slides and treated (e.g. with nonsurgical therapies adjuvant to the MMS procedure) to prevent evolution to a more aggressive subtype. Micronodular BCCs and BCCs with PNI are less common; in our study, they counted for only 6% of the incompletely excised BCCs. Subtypes of incompletely excised BCCs differed from their biopsy in 58%. This is in line with two other studies, which show that biopsy subtypes differed from MMS slides in 41% and 51% of cases, respectively.[10,11] It is known that about 30% of BCCs demonstrate

mixed subtypes.[12] MMS surgeons might miss BCCs with mixed subtypes more easily if they focus on the detection of the subtype seen in the biopsy.

MMS procedures with misinterpreted slides that did not result in an incompletely excised BCC were found in 4% of cases, which is less than the 9% and 20% reported in two previous studies, respectively.[8,9] In some of these cases, healthy tissue might have been excised unnecessarily. In the falsely positive interpreted cases studied, areas with dense inflammation were, in some cases, misinterpreted as BCC. Areas of dense inflammation are suspicious for the presence of BCC as inflammation surrounds BCC in 52% of cases.[13,14] However, inflammation does not mask areas of tumour and therefore dense inflammation alone is no indication for a following MMS stage.

A final defect > 20 mm in diameter was found to be a significantly independent risk factor for incompletely excised BCCs (OR 3.6, 95% CI 1.6-8.3). This is probably because the number of slides to review is higher when the defect is larger and therefore the chance of misinterpretation is higher. Incompletely excised BCCs had a defect > 20 mm in diameter in only 61% of all cases. To detect the other 39% of incompletely excised BCCs, all MMS slides must be reviewed again.

Our results show that MMS surgeons should review slides carefully, paying special attention to morpheaform and superficial BCC. MMS surgeons should review slides with an open mind, without the limiting focus of the biopsy subtype, as some BCCs demonstrate mixed subtypes. In case of large defects, MMS surgeons should stay focused through the entire procedure. To verify their interpretations, they should record their findings and considerations in detail.

This study included 11 MMS surgeons and five pathologists; they were all trained in the Netherlands. Therefore, it is uncertain if our results can be generalized to other international MMS services. The percentage of incompletely excised BCCs found (2%) meets the MMS audit standard in the U.K., where a target rate of < 2% is suggested.[15] One can question if MMS training and the requirements for MMS credentials are sufficient to achieve a rate of incompletely excised BCCs of < 2%. An interesting study showed that approximately 1500 MMS procedures were required before one fellow reduced his misinterpretations to a minimum acceptable level of fewer than 1 per 100.[16] The number of MMS procedures required for MMS credentials is far fewer than 1,500 for both the American College of MMS Surgery and the European Society for Micrographic Surgery. Higher quantitative directives may be needed to ensure the quality of MMS surgeons. In addition to the quantitative directive, we suggest adding a qualitative directive for

MMS credentials (e.g. histopathological examination of MMS slides wherein a low level of misinterpretations must be achieved).

Although labour-intensive, the additional review has several important advantages. Firstly, detection and correction of incompletely excised BCCs will prevent recurrences. Secondly, detection of misinterpretations provides the MMS surgeon with the opportunity to learn from his or her mistakes, which is essential for personal quality improvement.[5,16] Thirdly, the number of misinterpretations and incompletely excised tumours are an excellent indicator for quality assurance and control for individual MMS surgeons and MMS services.[5,9] At the EMC, additional reviews were performed by a pathologist, which increased costs. Other studies show that the rate of slides interpreted in concordance by a MMS surgeon and a pathologist is high (95- 100%).[15,17-20] These studies conclude that MMS surgeons are able to review MMS slides as well as pathologists do. This suggests that the additional review can be performed by another MMS surgeon as well.

Even if all MMS slides were additionally reviewed in MMS practices, tumour will be missed and skin cancer recurrences will occur in some cases. Besides misinterpretation of slides, other risk factors for skin cancer recurrences are acceptance of poor-quality slides and incorrect initiation of later MMS stages.[3,4,6,14] These factors are under the control of the MMS surgeon. To further improve the effectiveness of MMS, research is needed to minimize all risk factors for skin cancer recurrence.

There are two limitations of this study. Firstly, this study was limited to retrospective data. However, for this study, slides with divergent interpretations were re-evaluated. Secondly, data was extracted from a single centre. However, the study involved several MMS surgeons and pathologists, and a large number (n = 1,653) of BCCs treated with MMS were included.

This study determined that a pathologist detected incompletely excised BCCs on MMS slides in 2% of cases. An independent risk factor for incompletely excised BCCs was a defect size > 20 mm in diameter. The additional review of MMS slides by pathologists and/or MMS surgeons optimizes the quality of MMS and may therefore prevent skin cancer recurrence.

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Part II

Squamous cell carcinoma

Chapter 5

Recurrence rates of cutaneous squamous cell carcinoma of the head and neck after Mohs micrographic surgery vs. standard excision: a retrospective cohort study

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ABSTRACT

Background: Recurrent cutaneous squamous cell carcinoma (cSCC) has been associated with an increased risk of local functional and aesthetic comorbidity, metastasis and mortality.

Objectives: To compare the risk of recurrence between Mohs micrographic surgery (MMS) and standard excision (SE) for cSCC of the head and neck.

Methods: This was a retrospective cohort study of all patients with a cSCC treated with MMS or SE at the departments of dermatology of a secondary or tertiary care hospital in the Netherlands between 2003 and 2012. To detect all recurrences, patients were linked to the Dutch pathology registry. To compare the risk of recurrence between MMS and SE, hazard ratios (HRs) were used adjusted for clinical tumour size > 2 cm and deep tumour invasion.

Results: A total of 579 patients with 672 cSCCs were included: 380 cSCCs were treated with MMS and 292 with SE. The risk of recurrence was 8% (22/292) after SE during a median follow-up of 5.7 years (IQR 3.5-7.8), which was higher than the 3% (12/380) after MMS during a median follow-up of 4.9 years (IQR 2.3-6.0). The cumulative incidence of recurrence was higher for SE than for MMS during the entire follow-up period of 8.6 years. Carcinomas treated with MMS were at a three times lower risk of recurrence than those treated with SE when adjusted for tumour size and deep tumour invasion (adjusted HR 0.31, 95% confidence interval 0.12-0.66).

Conclusion: MMS might be superior to SE for cSCCs of the head and neck because of a lower rate of recurrence.

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) represent 20% of all skin cancers. CSCC is the second most common skin cancer after basal cell carcinoma. At least one in 15 white people will develop a cSCC before the age of 85 and the incidence is still rising.[1-4] CSCCs rarely metastasize (4%) and the disease specific death rate is low (2%).[2,5] However, because of the frequent localization in the head and neck, treatment can lead to major functional and aesthetic comorbidity.

In the Netherlands, cSCC is commonly treated with standard excision (SE). In the Dutch cSCC guideline, Mohs micrographic surgery (MMS) is noted as an alternative for SE for stage ≥ II, especially when SE would lead to substantial functional or aesthetic comorbidity.[6] In the United States it is generally accepted that MMS is indicated in high risk cSCC and the American 'appropriate use criteria for MMS' state that it is also appropriate to use MMS for stage I cSCC.[7]

MMS is superior to SE for facial aggressive or recurrent basal cell carcinomas, because of the low recurrence rate and maximum preservation of healthy tissue.[8-10] Studies on cSCC recurrence rates after surgery are sparse and it therefore remains unclear if MMS is better than SE for cSCC. This large retrospective cohort study was conducted to determine if the risk of cSCC recurrence is lower after MMS than SE.

METHODS

This was a retrospective, comparative cohort study of cSCC treated with MMS or SE at the dermatology departments of a tertiary (Erasmus University Medical Center) or a secondary care hospital (Isala Hospital), both in the Netherlands, between 2003 and 2012. The study was exempted from approval by both institutional review boards.

Inclusion criteria were all histologically confirmed invasive cSCCs of the head and neck that were completely excised with MMS or SE; multiple cSCCs per patient were included. The cSCCs that were incompletely excised with MMS or SE were excluded from the analysis and described separately. For SE, incomplete excision was postoperatively defined by a pathologist with the standard vertical bread loaf technique if cSCC was detected on the excision margin (stage I) or if a tumour free margin was ≤ 2 mm (≥ stage II).[6] For MMS, incomplete excision was postoperatively defined by a pathologist within the routine quality check if cSCC was detected on the outermost fresh frozen MMS slide. The study involved four pathologists; all had special training in skin cancer pathology and MMS.

The inclusion period differed per treatment modality and study centre. Patients treated with MMS were included at the tertiary care hospital between 1 January 2009 and 31 December 2012 because in the Netherlands MMS for cSCC was only offered at the tertiary care hospital since 2008. Inclusion started from 2009 to exclude the effect of a presumed learning curve during the first MMS year and continued until 2012 to have at least 5 years of follow-up. To prevent selection bias, cSCCs treated with SE were included at the tertiary care hospital between 1 January 2003 and 31 December 2007. At the secondary care hospital, SE was the only surgical treatment option during the entire study period and patients were included from 1 January 2008 to 31 December 2012. Selection bias because of the different inclusion periods was not expected because the Dutch cSCC guideline did not change during the entire study period (2003-2012).[6] In both hospitals, it was recommended that patients should visit a dermatologist routinely postoperatively for the following 5 years.[6]

The following variables were extracted from electronic patient files including pathology reports and standardized digital MMS files[11]: patient age and sex, tumour location (in the H-zone), recurrence before MMS or SE, clinical tumour size > 2 cm, defect size > 2 cm and deep tumour invasion (i.e. beyond the subcutaneous fat). These tumour characteristics were recorded because they have been associated with a high risk of cSCC recurrence.[12] Vital status, including date of death, was obtained from the Dutch Municipal Population Register until 1 August 2017.

Study outcome

The main outcome was cSCC recurrence. Recurrence was defined as a histologically proven cSCC in or within 1 cm of the scar. Furthermore, histologically confirmed cSCC metastasis was recorded. To detect all histopathologically proven recurrences and metastases, patients were linked to the nationwide network and registry of histology and cytopathology (Dutch acronym: PALGA) on 1 August 2017.[13] In the Netherlands, all histopathology reports from every biopsy, excision or MMS procedure are recorded in this database.

Follow-up

As explained above, the inclusion period for SE started earlier (2003) than for MMS (2009). Therefore, the median follow-up time after SE was suspected to be longer than after MMS. This was accepted because all patients had a follow-up of at least 5 years and the majority of cSCC recurrences occur within 5 years.[14] The maximum follow-up time for patients treated with SE was restricted to the maximum follow-up possible for patients treated with MMS (i.e. 8.6 years, which was the time between the start of MMS inclusion on 1 January 2009 until the PALGA search on 1 August 2017).

Surgical procedures

SE was performed in a standard manner by a dermatologist (n = 7), or a resident (n = 10) under supervision of a dermatologist. The cSCCs were excised with margins of five mm for stage I and ten mm for ≥ stage II.[6] Specimens were postoperatively assessed by a pathologist with the standard vertical bread loaf technique and haematoxylin and eosin staining.

MMS was performed in a standard manner by experienced MMS surgeons (n = 6, all dermatologists certified by the European Society for Micrographic Surgery), or a resident (n = 10) under supervision of a MMS surgeon. The cSCCs were excised with a minimal margin of clinically tumour free tissue. The sample was directly compressed, frozen and sliced horizontally by a trained MMS technician. The entire excision margins were microscopically examined on the fresh frozen slides by a MMS surgeon. Residual tumour was mapped and subsequently excised. The procedure was repeated until tumour clearance was achieved.

Statistics

Differences between MMS and SE regarding the studied variables were assessed with an exact test for binary variables and with an independent sample T-test with bootstrapping for continuous variables, to take within-patient correlation into account. The length of follow-up per patient was calculated as the number of years between surgery and end of study (linkage to PALGA on 1 August 2017) or date of recurrence or date of death, whichever occurred first. Difference between the rate of recurrence after MMS and SE was assessed with a cumulative incidence curve to take into account the competing risk of death. Comparison of the risk of recurrence after MMS and SE was assessed with univariable and multivariable Cox proportional hazards regression adjusted for clinical tumour size > 2 cm and deep tumour invasion. The 95% confidence interval (CI) and P-value for the univariable and multivariable regression were obtained by applying bootstrapping to take within-patient correlation into account. The proportional hazards assumption was confirmed by log minus log plots. P-values less than 0.05 (2-sided) were considered significant. SPSS 24.0 for Windows (IBM, Armonk, NY, U.S.A.) and SAS 9.4 (SAS Institute Inc., Cary, NC, U.S.A.) were used for statistical analyses.

RESULTS

In total, 631 patients with 738 cSCCs of the head and neck were reviewed of which 383 cSCCs were treated with MMS and 355 with SE (Figure 1). Of the 355 cSCCs that were treated with SE, 34% (n = 122) were included at the tertiary care hospital and 66%

(n = 233) at the secondary care hospital. The baseline characteristics, the rate of incompletely excised cSCCs and the rate of recurrences did not differ between the included cases at the tertiary care hospital and secondary care hospital.

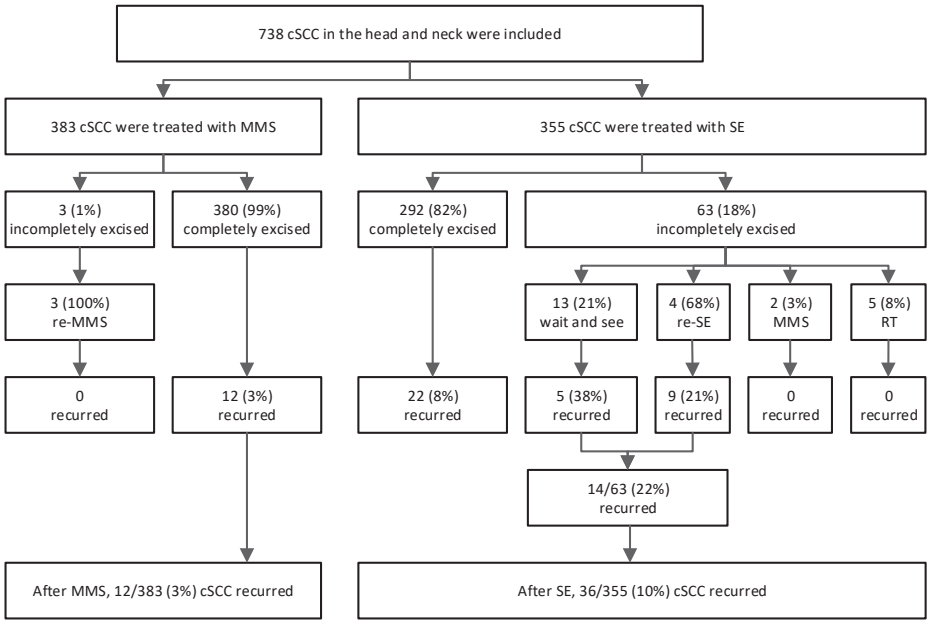


Figure 1. Flowchart of the cutaneous squamous cell carcinomas of the head and neck that were treated with Mohs micrographic surgery or standard excision.
cSCC, cutaneous squamous cell carcinoma; MMS, Mohs micrographic surgery; RT, radiotherapy; SE, standard excision.

Of the 738 cSCCS, three treated with MMS and 63 treated with SE were excluded because of an incomplete cSCC excision. All three treated with MMS were additionally completely excised with re-MMS and did not recur or metastasize. Of the 63 incomplete SE cases, no additional treatment was given in 21% (13/63), after which 38% (5/13) developed a recurrence and 15% (2/13) metastasized. Of the incomplete SE cases, an additional treatment was given in 79% (50/63): 68% (43/68) were re-excised with SE, 8% (5/63) received radiotherapy, and 3% (2/63) were re-excised with MMS. Of the 43 incomplete SE cases which were re-excised with SE, 21% (9/43) developed a recurrence and 2% (1/43) metastasized. Of the incomplete SE cases which were additionally treated with radiotherapy (n = 5) or MMS (n = 2), none developed a recurrence or metastasis.

Baseline characteristics

A total of 579 patients (69% men, overall median age 76 years, IQR 69-82) with 672 completely excised cSCCs were included; 380 cSCCs were treated with MMS and 292 with SE. There were 513 patients with one included cSCC, 50 patients with two cSCCs, eight patients with three cSCCs, six patients with four cSCCs, one patient with five cSCCs and one patient with six cSCCs.

For MMS, most cSCCs were located on the nose (22%), forehead (19%) and scalp (17%) followed by the auricular region (15%), cheek and maxilla (11%), periocular region (8%), perioral region and lips (6%) and neck (2%). For SE, most cSCCs were located on the auricular region (24%), scalp (21%), cheek and maxilla (20%) and forehead (20%), followed by the nose (7%), perioral region and lips (5%), neck (3%) and periocular region (2%).

The cSCCs treated with MMS were significantly more often: located in the H-zone, previously recurrent tumours, clinically > 2 cm and more often had deep tumour invasion (Table 1). Defects after MMS were more often ≤ 2 cm than after SE. Median number of MMS stages needed for tumour clearance was one (range 1-4).

Cutaneous squamous cell carcinoma recurrence

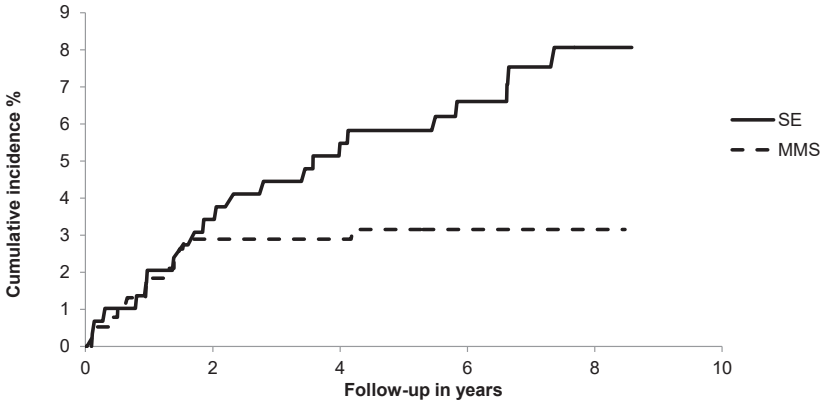
The risk of recurrence was 8% (22/292) after SE during a median follow-up of 5.7 years (IQR 3.5-7.8), which was higher than the 3% (12/380) after MMS during a median follow-up of 4.9 years (IQR 2.3-6.0). The cumulative incidence of recurrence was higher for SE than for MMS during the entire follow-up period of 8.6 years (Figure 2).

After adjusting for tumour size and deep tumour invasion, cSCCs treated with MMS were at a three times lower risk of recurrence than SE (adjusted HR 0.31, 95% CI 0.12-0.66) (Table 2). Of the 12 cSCC recurrences after MMS, 33% (n = 4) were located in the H-zone, 50% (n = 6) were previously recurrent tumours, 58% (n = 7) had a clinical tumour size > 2 cm, 67% (n = 8) had a defect size > 2 cm, 67% (n = 8) had a deep tumour invasion and none metastasized. Of the 22 cSCC recurrences after SE, 32% (n = 7) were located in the H-zone, 9% (n = 2) were previously recurrent tumours, 9% (n = 2) had a clinical tumour size > 2 cm, 77% (n = 17) had a defect size > 2 cm, 27% (n = 6) had a deep tumour invasion and 5% (n = 1) metastasized.

Table 1. Differences between cutaneous squamous cell carcinomas that were treated with Mohs micrographic surgery or standard excision regarding the characteristics and events during follow-up.

	MMS n = 380 (%)	SE n = 292 (%)	P-value
Sex[a]			
Men	262 (69)	219 (75)	0.101
Women	118 (31)	73 (25)	
Age in years, median (IQR)[a]	76 (69-81)	76 (68-82)	0.694
Anatomical location			
Head and neck, not H-zone	153 (40)	161 (55)	<0.001
H-zone	227 (60)	131 (45)	
Surgical history			
Primary cSCC	311 (82)	266 (91)	0.001
Previously recurrent cSCC	69 (18)	26 (9)	
Tumour size			
≤ 2 cm	256 (67)	274 (94)	<0.001
> 2 cm	124 (33)	18 (6)	
Defect size			
≤ 2 cm	231 (61)	93 (32)	<0.001
> 2 cm	149 (39)	199 (68)	
Tumour invasion			
Dermis	153 (40)	250 (86)	<0.001
Deep	227 (60)	42 (14)	
Events during follow-up			
Follow-up in years, median (IQR)	4.9 (2.3-6.0)	5.7 (3.5-7.8)	0.001
Recurrence			
No	368 (97)	270 (92)	0.013
Yes	12 (3)	22 (8)	
Metastasis			
No	377 (99)	287 (98)	0.304
Yes	3 (1)	5 (2)	
Deceased (cause unknown)			
No	209 (55)	133 (46)	0.016
Yes	171 (45)	159 (55)	

Percentages were rounded.
cm, centimetre; cSCC, cutaneous squamous cell carcinoma; IQR, inter quartile range; MMS, Mohs micrographic surgery; n, number; SE, standard excision.
[a] 575 Patients with 672 cSCC were included. Numbers in the table represent cSCCs.



MMS					
N at risk	380	291	246	96	17
N of recurrences	0	11	12	12	12
SE					
N at risk	292	246	206	134	71
N of recurrences	0	10	16	19	22

Figure 2. Cumulative incidence curve of recurrence of cutaneous squamous cell carcinoma of the head and neck after Mohs micrographic surgery compared with standard excision.
MMS, Mohs micrographic surgery; N number; SE, standard excision.

Table 2. Cox regression for the recurrence risk of cutaneous squamous cell carcinoma of the head and neck.

	Non-recurred cSCC n = 638 (%)	Recurred cSCC n = 34 (%)	Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Intervention						
SE	270 (42)	22 (65)	1	0.031	1	0.004
MMS	368 (58)	12 (35)	0.49 (0.23-0.94)		0.31 (0.12-0.66)	
Tumour size						
≤ 2 cm	504 (79)	26 (77)	1	0.346	1	0.119
> 2 cm	134 (21)	8 (24)	0.70 (0.32-1.82)		1.89 (0.64-4.06)	
Tumour invasion						
Dermis	383 (60)	20 (59)	1	0.593	1	0.164
Deep	255 (40)	14 (41)	0.82 (0.41-1.69)		1.80 (0.71-4.13)	

Percentages were rounded.
CI, confidence interval; cm, centimetre; cSCC, cutaneous squamous cell carcinoma; HR, Hazard ratio; MMS, Mohs micrographic surgery; n, number; SE, standard excision.

DISCUSSION

Until now, a wide range of cSCC recurrence rates after MMS (0-6%) and SE (0-15%) has been reported.[15] One systematic review with pooled analysis by Lansbury et al. showed a lower, but nonsignificant average recurrence rate after MMS (3.0%, 95% CI 2.2-3.9%; ten studies, n = 1,572) compared with SE (5.4%, 95% CI 2.5-9.1%; 12 studies, n = 1,144).[15]

However, the included studies had heterogeneous inclusion criteria, small numbers of included patients and a short follow-up duration with limited information on those lost to follow-up.

Our study showed a lower recurrence risk of cSCC of the head and neck after MMS (3%) than after SE (8%) during a median follow-up of 5 years (IQR 3-7). Although the median follow-up after SE was longer (5.7 years, IQR 3.5-7.8) than after MMS (4.9 years, IQR 2.3-6.0), the cumulative incidence of recurrence was higher for SE than for MMS during the entire follow-up period of 8.6 years (Figure 2). 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) (Table 2). The difference in risk of recurrence was probably underestimated because we could not adjust for all high risk tumour characteristics. However, because of confounding by indication of MMS (i.e. selection bias), cSCCs treated with MMS were more often high risk tumours than cSCCs treated with SE (Table 1).

The lower risk of recurrence after MMS than SE is most likely because of the fact that with MMS the entire excision margin is histologically reviewed. In contrast, for SE only a small portion of the excision margin is histologically reviewed, increasing the risk of a false negative result (i.e. an undetected incomplete cSCC excision).

The excluded 18% of incompletely excised cSCCs with SE in our study was higher than expected based on the study of Lansbury et al., which showed a pooled average estimate of 8.8% (95% CI 5.4-13.0%; 11 studies, n = 2,343).[15] However, the included studies had heterogeneous inclusion criteria (e.g. cSCC on the head and neck and elsewhere) and used a wide range of excision margins (2 to > 10 mm, or unspecified). A recent retrospective review of cSCCs of the head and neck reported 14% (51/364) of incompletely excised cSCCs. However, this study included invasive as well as in situ cSCCs.[16]

We found an extremely high recurrence rate (38%) and metastasis rate (15%) for incompletely excised cSCCs that did not receive additional treatment. This underlines the importance of a complete cSCC excision. In only 1% of the MMS cases, an incomplete cSCC excision was found with the routine postoperative external histological quality check. This shows that the MMS surgeons were very well able to detect cSCC on fresh frozen MMS slides and that MMS is an excellent treatment to achieve tumour clearance.

Another advantage of MMS compared with SE, beside the lower risk of cSCC recurrence and the excellent tumour clearance, is the maximum preservation of healthy tissue.[10] Consistently, we found that after MMS, defects were more often ≤ 2 cm (60%) compared

with after SE (32%), while cSCCs treated with MMS were more often > 2 cm (33%) compared with SE (6%).

Strengths of this study are the comparative design, the large number of included cSCCs, the precise detection of recurrences (elimination of loss to follow-up by the use of PALGA), the long-term follow-up and the use of the cumulative incidence curve. This study shows that it is important to report follow-up data of at least five years: after SE, 77% (17/22) of the recurrences occurred within five years whereas only 45% (10/22) of the recurrences occurred within the first two years.

Our study was limited to a retrospective design. As a result of missing data, we could not determine: tumour stage (mm of tumour invasion, perineural invasion, lymphovascular invasion and cSCC differentiation), disease specific death, and high risk patients (i.e. immunosuppressed patients). We excluded all SCCs that were treated with MMS during the first year that MMS was performed for SCC at the tertiary care hospital. It is uncertain if the learning period of one year was long enough to exclude the presumed bias of a learning curve.

It is uncertain if our results can be generalized to other international dermatology and MMS services. Firstly, in this study MMS and SE were performed by dermatologists, residents and MMS surgeons who were trained in the Netherlands. Secondly, the recommended excision margins in the Dutch cSCC guideline are wider (i.e. five mm for stage I and ten mm for ≥ stage II) than the British and American guidelines recommend (i.e. four mm for stage I and six mm for ≥ stage II).[6,17,18]

In conclusion, this study shows that MMS is an excellent treatment option for patients with cSCC of the head and neck. Although the results imply superiority of MMS compared with SE for cSCC of the head and neck as a result of fewer recurrences, conclusions must be made carefully because of the limitations of the study design.

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Chapter 6

Rate and characteristics of incompletely excised cutaneous squamous cell carcinoma: a large prospective study, systematic review and meta-analysis

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ABSTRACT

Background: Incomplete excision of cutaneous squamous cell carcinoma (cSCC) has been associated with an increased risk of recurrence, metastasis and mortality.

Objectives: To determine the rate and characteristics of incompletely excised cSCC.

Methods: Prospective study of all patients who gave their informed consent, with a cSCC treated with standard excision (SE) at one of six Departments of Dermatology in the Netherlands between 2015 and 2017. Pathology reports were screened to detect all incompletely excised cSCCs. Additionally, a systematic review was conducted with pooled average estimate of incompletely excised cSCC.

Results: A total of 592 patients with 679 cSCCs were included whereby the majority of cases were low risk cSCC (89%). The rate of incompletely excised cSCC was 4% (n = 26) and all were high risk cSCC of which 24 invaded the deep excision margin. The systematic review included 36 studies (n = 11,235 cSCCs) of which the majority was retrospectively designed (n = 31). The included studies used heterogenic inclusion criteria, different excision margins and heterogenic treating physicians. The pooled average estimate of incompletely excised cSCC was 12% (95% confidence interval 10-16, I^2=92%, range 0-39%).

Conclusions: Conclusions on the efficacy of SE for cSCC must be made carefully. Although the current prospective study showed that the risk of an incompletely excised cSCC was low (4%) for a cohort that was dominated by low risk cSCCs, the systemic review showed a wide range of rate of incompletely excised cSCC among studies that included heterogenic cases.

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer after basal cell carcinoma (BCC).[1-4] At least one per 15 Caucasians will develop a cSCC before the age of 85 and the incidence is still rising.[1-4]

In The Netherlands, cSCC is commonly treated with standard excision (SE).[5] The rate of incompletely excised cSCC is an important indicator for the quality of care. Incompletely excised cSCC has been associated with an increased risk of recurrence and, although rare, with metastasis and disease-specific death.[6-8] Therefore, it is recommended to re-excise residual cSCC.[5-11] For the patient, a re-excision is injurious because it can lead to local functional and aesthetic comorbidity. For society, a re-excision leads to higher costs.

To prevent incompletely excised cSCC and to decrease cSCC recurrence rates, in America it is generally accepted that Mohs micrographic surgery (MMS) is indicated for both T1 and T2 cSCC.[12] While in the Dutch cSCC guideline from 2012, MMS was only mentioned as an alternative to SE if SE would lead to extensive functional or aesthetic comorbidity.[5] Since a recent update of the Dutch cSCC guideline, MMS is only indicated as appropriate for facial cSCC (T1 and T2) when it is aimed to preserve the healthy tissue and thereby to decrease the functional or aesthetic comorbidity.[13]

The rate of incompletely excised cSCC varies widely among studies whereby the studies are mainly retrospectively designed and use heterogenic inclusion criteria.[14] Therefore, conclusions on the efficacy of SE for cSCC are inconsistent. To assess the efficacy of SE for cSCC, this study determined the rate and detailed characteristics of incompletely excised cSCC in a prospectively designed multicentre observational study and in a systematic review with meta-analysis. This study is part of an on-going observational study that compares the efficacy of MMS with SE regarding rates of recurrences, metastasis and disease specific death.

METHODS

This was a prospective study of all patients who gave their informed consent, with a cSCC treated with SE at the Department of Dermatology in one of six study centres (two tertiary care hospitals, three secondary care hospitals and one private practice) in the Netherlands between 1 January 2015 and 31 December 2017. This study is part of an on-going observational study (i.e. not randomized) which compares MMS with SE for cSCC

regarding rates of recurrence, metastasis, and disease specific death after follow-up of at least five years. The inclusion period of this study closed on 31 December 2017 while the follow-up is ongoing. The study was exempted from approval by all institutional review boards.

Inclusion criteria were excisions of invasive cSCCs, i.e. cSCC of all body sites, primary and recurrent or previously incompletely excised cSCC. Multiple cSCCs per patient were included if located in different anatomical subunits according to the New York Classification. For the current study, we excluded all cSCCs that were treated with MMS. In each study centre, SE and MMS was available during the inclusion period. Since specific indication criteria for the use of SE or MMS for cSCC were lacking in the Dutch cSCC guideline of 2012, the treating dermatologist decided together with the patient which surgical treatment would be used (i.e. SE or MMS) whereby MMS was offered to patients with a cSCC of the head and neck or other area's (e.g. hands) if SE would lead to extensive functional or aesthetic comorbidity.[5]

Dermatologists recorded the following variables prospectively in a digital standardized study form: patient age, gender and immune status, tumour location, location in the H-zone of the face, surgical history, clinical tumour size, excision margin in mm, defect depth, whether the reconstruction was delayed until the result of the histology report and how the defect was reconstructed.

Dermatologists recorded the conclusions of the pathologist concerning the histological tumour free margins, invasion depth in mm, differentiation, and perineural or lymphovascular invasion. The outcome of interest was an incompletely excised cSCC. According to the Dutch cSCC guideline, an incomplete excision was defined as histological cSCC extending to the inked surgical margin or in case of a ≥ T2 cSCC with a histological tumour free margin < 2 mm.[5,13] The eight edition of the American Joint Committee on Cancer (AJCC) system was used to stage the cSCCs whereby T1 cSCCs were classified as cSCCs at low risk of poor outcome and ≥ T2 as high risk cSCCs.[15]

Excisions were performed in a standard manner by a dermatologist (n = 29) or resident (n = 54) under supervision of a dermatologist. Specimens were postoperatively assessed by a pathologist (n = 25) with the standard vertical bread loaf technique and haematoxylin and eosin staining. Pathologists did not know if specimens were included in the study.

Statistics

Descriptive statistics were used to report the baseline characteristics of patients, cSCC, treatment and study outcome. Risk factors for an incomplete excision were not assessed with logistic regression due to small subgroups through which the risk analysis would be underpowered. SPSS 24.0 for windows (SPSS Inc., Chicago, IL) was used for statistical analyses.

Systematic literature review and meta-analysis

The systematic review was conducted and reported according to the MOOSE guidelines for meta-analysis of observational studies. The protocol for this systematic review was recorded in the International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42018096312.

In this systematic review, the following databases were searched: Embase, Medline Ovid, Web of science, Cochrane Central, and Google scholar from inception of the databases to 5 May 2018, for original articles in English reporting on the rate of incompletely excised cSCC . Additionally, the bibliography of included studies and previously published review articles were checked for other relevant articles. Articles were included if the rate of incomplete excision was specific for cSCC (i.e. not mixed with other tumours or in situ cSCC) and standard excision (i.e. not mixed with other treatment modalities). Articles were excluded if they were non-English, if the full text was not available, if the study was not original, or if the study included less than five cases.

Two review authors (CBL, AP) independently screened the titles and abstracts. Full texts were reviewed of those articles which potentially met the inclusion criteria. After consensus was reached on the included articles, data was extracted by the two reviewers independently, using standardized extraction forms. Risk of bias of individual studies could not be evaluated because of the lack of a relevant validated tool.

Raw proportions of incompletely excised cSCC were calculated for each study (events divided by the total number of included cSCCs). The pooled average estimates of incomplete cSCC excision was calculated using a random effect model with 95% CI. Index I^2 was used to quantify the impact of heterogeneity and to assess inconsistency. R studio (R core team, Vienna, Austria) was used for the meta-analysis.

RESULTS

Results of the prospective study

A total of 592 patients (348 man, overall median age 76 years, IQR 69-82) with 679 cSCCs were included (Table 1). Overall, 90% (n = 533) of the patients had one cSCC, 7% (n = 42) had two cSCCs, and 3% (n = 17) had three or more cSCCs.

Table 1. Differences between completely and incompletely excised cutaneous squamous cell carcinoma.

	Completely excised cSCC n (%)	Incompletely excised cSCC n (%)
Patient characteristics, n = 592	569 (96)	23 (4)
Sex		
Men	333 (59)	15 (65)
Women	236 (42)	8 (35)
Age in years, median IQR	76 (69-82)	76 (68-81)
Immunosuppression		
No	505 (89)	20 (87)
Yes	64 (11)	3 (13)
cSCC characteristics, n = 679	653 (96)	26 (4)
Location		
Body	288 (44)	3 (12)
Head and neck not H-zone	219 (36)	16 (62)
H-zone	146 (22)	7 (27)
Clinical size		
0-20 mm	628 (96)	16 (62)
≥21 mm	25 (4)	10 (39)
Surgical history		
Primary	626 (96)	25 (96)
Recurrent/incompletely excised	27 (4)	1 (4)
Invasion depth		
≤ 6 mm	446 (68)	11 (42)
> 6 mm	16 (3)	11 (42)
Unspecified	191 (29)	4 (15)
Differentiation		
Well or moderate	523 (80)	14 (54)
Poor	130 (20)	12 (46)
PNI or lymphovascular invasion		
Not visible	635 (97)	14 (54)
Yes	18 (3)	12 (46)

Table 1. (continued)

	Completely excised cSCC n (%)	Incompletely excised cSCC n (%)
High risk cSCC		
No	601 (92)	0
Yes[a]	52 (8)	26 (100)
Procedural characteristics, n = 679	653 (96)	26 (4)
Excision margin		
≤ 5 mm	627 (96)	16 (62)
> 5 mm	26 (4)	10 (39)
Excision margin[b]		
Conform Dutch guideline	622 (95)	14 (54)
Wider	16 (3)	6 (23)
Smaller	15 (2)	6 (23)
Defect depth		
Dermis	526 (81)	17 (65)
Deep	127 (19)	9 (35)
Timing of reconstruction		
Directly after the excision	619 (95)	18 (69)
Delayed[c]	34 (5)	8 (31)
Reconstruction type		
Simple[d]	601 (92)	19 (73)
Complex[e]	52 (8)	7 (27)

Percentages were rounded.

cSCC, cutaneous squamous cell carcinoma; IQR, inter quartile range; mm, millimetre; n, number; PNI, perineural invasion.

[a] High risk cSCC include ≥T2 cSCC according to the eight edition of the American Joint Committee on Cancer staging system.[15]

[b] According to the Dutch cSCC guideline five mm for T1 cSCC, and ten mm for ≥T2 cSCC.[5,13]

[c] Delayed reconstruction until the result of the histology report.

[d] Simple reconstruction include primary closure or healing by secondary intention.

[e] Complex reconstruction include all non-simple reconstructions, e.g. flaps and grafts.

Of the 679 cSCCs, location was in the head and neck in 57% (n = 388), of which cSCCs were most commonly located on the scalp 18% (n = 119), peri-auricular area 10% (n = 65) and forehead 9% (n = 58). CSCCs were located outside the head and neck in 43% (n = 291), locations were: leg 13% (n = 85), arm 10% (n = 69), trunk 10% (n = 68), hand 9% (n = 59), and feet 2% (n = 10).

The majority of cSCC were excised with a margin conform to the Dutch cSCC guideline (94%).[5,13] Although the Dutch cSCC guideline recommends to take a punch biopsy to histologically diagnose a skin tumour to plan an optimal treatment strategy, 17%

(n = 117) excisions were performed without prior biopsy.[5,13] Of the 562 excisions with prior histology (i.e. punch biopsy or previous excision), in 17% (n = 93) no cSCC was detected on the histology of the excised specimen (e.g. tumour cells could be missed due to the vertical bread loaf technique or the immune system eliminated the cSCC).

CSCCs were incompletely excised in 4% (26/679) which were all high risk cSCC (i.e. T2), while only a few completely excised cSCC were high risk tumours (52/653). The rate of incompletely excised cSCC did not differ between the six study centres (p = 0.277). Of the 26 incompletely excised cSCC, 77% (n = 20) involved the deep margin, 15% (n = 4) involved both deep and side margins, and 8% (n = 2) involved the side margin. CSCC invaded the margin in ten patients, and the histological tumour free margin was < 2 mm in 16 patients. Eight of these 16 patients with an incompletely excised cSCC did not receive an additional treatment. The other 18 patients were additionally treated with re-excision (n = 10) or MMS (n = 8).

Results of the systematic review and meta-analysis

The systematic review included 36 observational studies[11,16-50] including the current study (Table 2, Figure 1). A total of 11,235 cSCCs were included in the review. Study size varied from 13 to 2,536 tumours, with a median of 91. The majority of included studies had a retrospective design (n = 31). The studies used different definitions for incomplete excision (i.e. unspecified, or cSCC extending to the inked surgical margin and/or cSCC close to the surgical margin on histology). Of the 36 studies, 22 included all locations, four included only head and neck cSCCs, two included only periocular cSCCs, one included only lip cSCCs, and the location was unspecified in seven studies. Of the 36 studies, 24 included only primary cSCCs, one included only re-excisions, four included both primary cSCCs and re-excisions, and the surgical history was unspecified in six studies. Only ten of the studies reported the used excision margin, which ranged from one up to ten mm. The excisions were performed by dermatologists in seven studies, by other hospital based specialties in 18 studies (i.e. plastic surgeons, general surgeons, ophthalmologists or ENT physicians), by general practitioners in six studies, and by a mixed group of physicians in five studies. One third of the studies were performed in the United Kingdom (n = 13), seven in Australia, three in New Zealand, three in the United states of America, three in The Netherlands, and seven in other countries.

The pooled average estimate of incompletely excised cSCC was 12% (95% CI 10-16, I^2 92%, range 0-39%) (Figure 2). From the seven studies that reported which margins were tumour positive, six reported that the majority of incompletely excised cSCCs involved the deep margin and one reported that the lateral margins were more often involved.

Table 2. Overview of included studies.

Study	Total cSCC included n = 11,235	Incompletely excised cSCC % range 0-39%	Location	Surgical history	Excision margin
Ang 2004	63	16	All	Primary	4-6 mm
Babington 2003	51	28	Lip	Primary	Unspecified
Baker 2001	227	7	Head and neck	Primary	Unspecified
Bhatti 2006	260	31	All	Primary	Unspecified
Bogdanov 2005	369	7	All	Primary	3-6 mm
Bovill 2009	676	18	All	Primary	Unspecified
Bovill 2012	84	29	All	Re-excision	Unspecified
Chan 2011	82	9	All	Primary	Unspecified
Cook 1993	478	12	Unspecified	Primary	Unspecified
Corwin 1997	28	36	All	Primary	Unspecified
Cox 1992	18	8	All	Primary	Unspecified
Delaney 2012	880	16	Unspecified	Primary	Unspecified
Fernández 2006	117	5	Unspecified	Unspecified	Unspecified
Griffiths 2002	93	4	All	Primary	Unspecified
Hansen 2009	2536	6	Unspecified	Primary	Unspecified
Haw 2014	114	21	Unspecified	Primary	Unspecified
Immerman 1983	84	29	All	Primary	Unspecified
Jowkar 2015	58	16	Head and neck	Primary	5 mm
Khan 2013	633	8	All	All	4-6 mm
Matteucci 2011	30	13	Unspecified	Unspecified	Unspecified
Mirshams 2010	273	18	All	All	Unspecified
Mourouzis 2009	218	12	Periocular	Primary	5 mm
Nemet 2006	68	25	Periocular	Primary	5 mm
Pua 2009	69	0	All	Primary	>5 mm
Ribero 2016	81	17	All	Unspecified	>4 mm
Riml 2013	89	6	All	Unspecified	5 mm
Robertson 2018	848	3	All	Primary	Unspecified
Seretis 2010	54	6	Head and neck	Primary	>4 mm
Stewart 2014	81	6	All	Unspecified	>4 mm
Stewart 2018	954	9	All	Unspecified	Unspecified
Tan 2007	480	6	All	Primary	Unspecified
Thomas 1994	54	11	Unspecified	Primary	Unspecified
Thomas 2003	38	0	All	Primary	1-4 mm
van Lee 2018	355	18	Head and neck	All	Unspecified
van Rijsingen 2015	13	39	All	Primary	Unspecified
Current study	679	4	All	All	1-10 mm

Percentages were rounded.

cSCC, cutaneous squamous cell carcinoma; mm, millimetre; n, number.

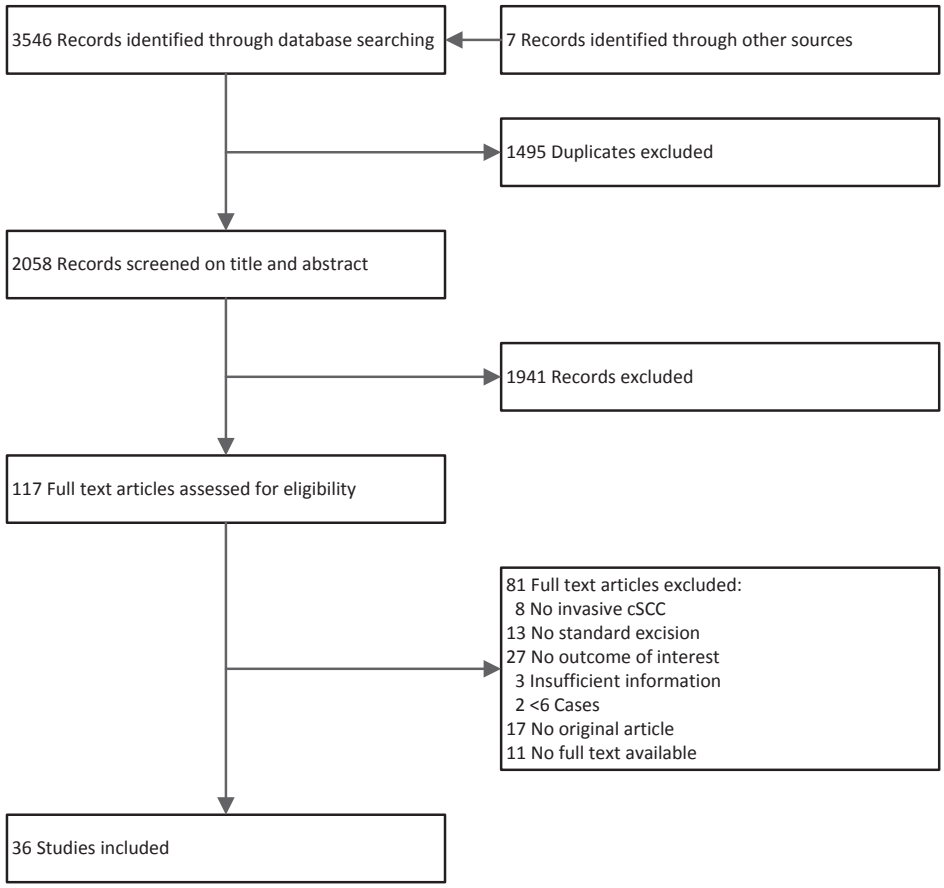

Figure 1. Flow-chart of the systematic review.
cSCC, cutaneous squamous cell carcinoma.

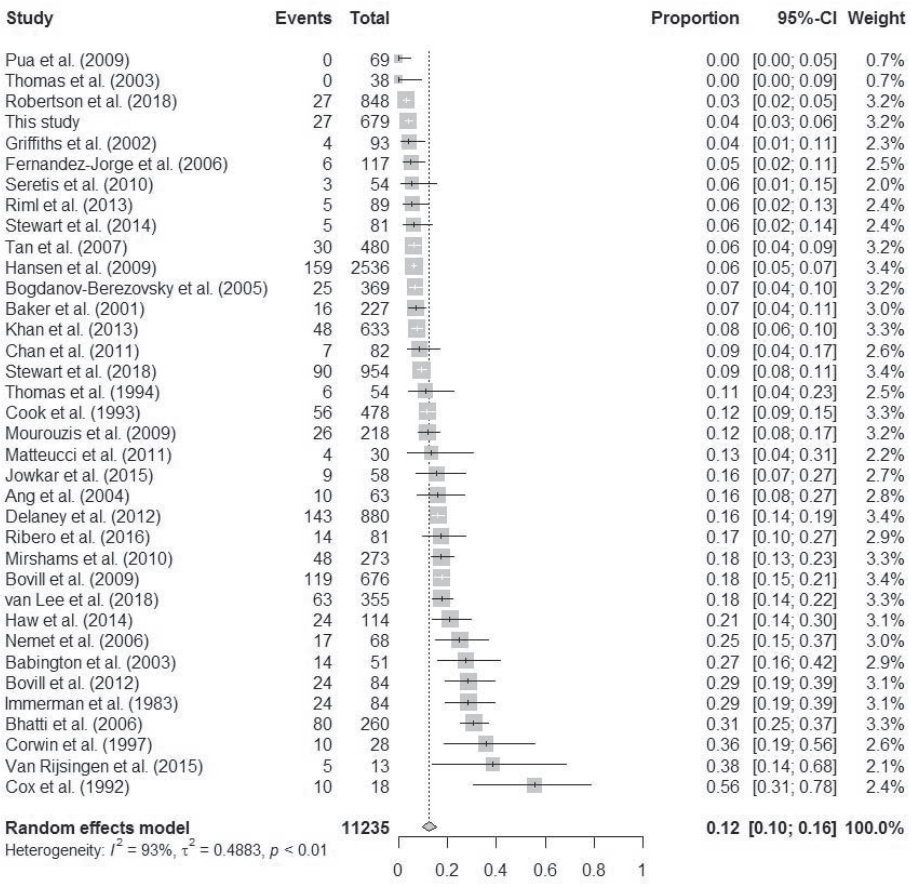

Figure 2. Proportions of incompletely excised cutaneous squamous cell carcinoma.
CI, confidence interval.

DISCUSSION

This prospective observational multicentre study showed that the rate of incompletely excised cSCC was only 4% for a cohort that was dominated by low risk cSCCs while all incompletely excised cSCC were high risk tumours. This indicates that the prescribed excision margin by the Dutch cSCC guideline of five mm for T1 cSCCs is sufficient and that dermatologists are well skilled to clinically demarcate the peripheral margins of cSCCs. The drawback of SE concerns the depth of excision, i.e. incompletely excised cSCCs involved the deep margin in 92%.

Until now, a wide range of incompletely excised cSCC has been reported (range 0%-39%).[11,16-50] This current study shows a lower rate of incompletely excised cSCCs

(4%) than the pooled average estimate of the systematic review (12%, 95% CI 10-16, I^2 92%) whereby the rate of incompletely excised cSCC found in our previous retrospective study was even higher (18%).[11]

The differences in rates of incompletely excised cSCC could be caused by selection bias. First, in our previous retrospective study, MMS was not yet used for cSCCs in the two study centres during the inclusion period of SE. While in this current study, MMS was available during the entire study period (2015-2017) in all six study centres whereby dermatologists and patients might have preferred MMS over SE when cSCCs had high risk features or were clinically hard to demarcate. Secondly, although cSCC location in the H-zone is not indicated as a high risk feature in the AJCC-8, it is suggested that cSCCs in the H-zone might be more often incompletely excised due to deep tumour invasion over the embryonic fusion plates just like it is assumed for basal cell carcinoma (BCC).[15,51] Our previous retrospective study included cSCCs in the head and neck area only, whereby 45% of cSCCs were located in the H-zone, while the majority of the studies in the meta-analysis as well as this current study included all tumour locations. In the current study, only 23% of SCC were located in the H-zone. Thirdly, the recommended excision margins in the Dutch cSCC guideline are wider (i.e. five mm for T1 and ten mm for ≥ T2 cSCC) than in the British, American and Australian guidelines (i.e. four mm for T1 and six mm for for ≥ T2 cSCC).[9,10,52] Fourthly, in this current study all excisions were performed by dermatologists (or residents under supervision of a dermatologist), while for the studies in the meta-analysis the excisions were performed by other specialities than dermatologists in 29 of the 36 studies (i.e plastic surgeons, general surgeons, ophthalmologists, ENT physicians, general practitioners). For BCC, it has been shown that the rate of complete excisions was higher for dermatologist (93%, $p < 0.001$) than for plastic surgeons (83%) and general practitioners (70%).[53] This could also be the case for cSCC as dermatologists are extensively trained and experienced in both BCC and cSCC care compared to plastic surgeons and general practitioners.

Strengths of this study are the prospective multicentre design, the large number of included cSCCs, the detailed information of patient characteristics, cSCC characteristics, histological characteristics and procedural characteristics, and the addition of a systematic review with meta-analysis.

Our study was limited by selection bias because MMS was available in all study centres. The selection bias may be expected to have removed a group of higher risk cSCC. The amount of tumour invasion (mm) was missing in 27% and it was undescribed whether perineural invasion involved nerves lying deeper than the dermis or with a diameter ≥0.1 mm, therefore the numbers of cSCC with stage ≥ T2 were underestimated. Interest-

ingly, in 17% of the SE no cSCC was detected on the histological examination of the excised specimen. For these cases, although exceptionally rare, the cSCC might have been regressed spontaneously or the cSCC was missed by the cuts of the bread loaf technique. Therefore, the truth rate of incompletely excised cSCC might have been underestimated. The follow-up of this study has to clarify if any of these cases recur, which would indicate that they were incompletely excised instead of spontaneously regressed.

It is uncertain if our results can be generalized to other international health care services as the systematic review showed that the efficacy of SE for cSCC differs widely among different subgroups of patients, cSCC, physicians and countries (e.g. due to different recommended excision margins in cSCC guidelines).[5,9,10,52] The systematic review was limited by the retrospective design of the majority of the included studies and poor quality of reporting of the methods and included cases which made them prone to bias. Due to the absence of an applicable scoring tool, the articles included in the meta-analysis could not be scored for quality.

In conclusion, this study showed a low rate of incompletely excised cSCC in a cohort that was dominated by low risk cSCCs, while all incompletely excised cSCC were high risk tumours. This indicates that the prescribed excision margin by the Dutch cSCC guideline of five mm for T1 cSCCs is sufficient and that dermatologists are well skilled to clinically demarcate the peripheral margins of cSCCs. The drawback of SE concerns the depth of excision, i.e. incompletely excised cSCCs involved the deep margin in 92%. Although conclusions about the efficacy of SE must be made carefully as the systematic review showed a wide rate of incompletely excised cSCC. Moreover, 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.

Acknowledgement

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Part III

Rare skin tumours

Chapter 7

Mohs micrographic surgery of rare cutaneous tumours

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ABSTRACT

Background: Recurrence rates after Mohs micrographic surgery (MMS) for rare cutaneous tumours are poorly defined.

Objective: To investigate the recurrence rate after MMS for rare cutaneous tumours at a university centre.

Methods: Retrospective review of all rare cutaneous tumours treated with MMS at a large university centre between January 2008 and December 2012. To detect all recurrences, patients were linked to The Nationwide Network and registry of histology and cytopathology (PALGA).

Results: In total, 80 patients with 80 tumours were included. Tumour types included dermatofibrosarcoma protuberans (27), atypical fibroxanthoma (22), Merkel cell carcinoma (8), microcystic adnexal carcinoma (9), sebaceous carcinoma (6), extramammary Paget's disease (2) and other (6). Mean follow-up time was 3.7 years (SD 1.4) during which two atypical fibroxanthomas recurred (2.5%).

Conclusion: This large case series shows that MMS is an appropriate treatment for rare cutaneous tumours with a recurrence rate less than 3%. To improve the quality of treatment, MMS for rare cutaneous tumours is preferably performed in centres where multidisciplinary experts work together.

INTRODUCTION

Mohs micrographic surgery (MMS) for the treatment of skin cancer is associated with low recurrence rates and maximal preservation of healthy tissue.[1] Most studies focus on the surgical treatment of basal cell carcinomas (BCC) and squamous cell carcinomas (SCC), as these are the most common cutaneous cancers among Caucasians.[2-5] Studies about the treatment of rare cutaneous tumours are sparse.

Rare cutaneous tumours are commonly treated with wide standard excision, whereby excision margins range from 2 to 5 centimetres. Despite these margins, incomplete excisions and recurrences occur frequently.[6,7] Few studies, which investigated MMS for rare cutaneous tumours, all reported low recurrence rates.[8–10] However, conclusions were based on small numbers of patients and limited information on follow-up. Therefore, large case series with adequate follow-up data are needed to obtain more in-depth information on recurrences after MMS for rare cutaneous tumours.

METHODS

Patient selection

This retrospective case series included all rare cutaneous tumours (i.e. excluding BCC and SCC) treated with MMS at the Department of Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands between 1 January 2008 and 31 December 2012. This time frame was chosen because at the study centre from 2008 and on, rare cutaneous tumours were structurally treated with MMS. Inclusion was stopped after 2012 to set a solid follow-up period. In the study period, all patients with rare cutaneous tumours were preoperatively discussed in a multidisciplinary team (i.e. dermatologist, head and neck surgeon, plastic surgeon, radiologist and a radiation oncologist) where MMS was considered as an appropriate treatment for operable rare cutaneous tumours. Dermatologists certified by the European Society for Micrographic Surgery performed the MMS procedures. Well-trained histotechnicians made MMS fresh frozen slides, which were stained with haematoxylin and eosin and evaluated by the MMS surgeon. Pathologists were available for an intraoperative consultation. For routine quality assurance, a pathologist additionally reviewed all MMS slides within one week after the MMS procedure. In some cases, depending on tumour type and MMS surgeon, an additional margin was excised after the MMS to confirm tumour clearance with immunohistochemical stains (e.g. CD34) on paraffin slides. When tumour clearance was achieved, the MMS surgeon or plastic surgeon reconstructed the defect. For follow-up after treatment, patients were recommended to visit a dermatologist at least once a year during the following five to ten years.

Outcome and data source

The primary outcome was a histologically proven recurrence in or within one centimetre of the MMS scar, in tumours which were completely excised with MMS. Patients who proved inoperable during the MMS procedure were reported separately. In the Netherlands, all histopathology reports from every biopsy, excision or MMS procedure are registered in The Nationwide Network and registry of histology and cytopathology (Dutch acronym: PALGA).[11] To detect recurrences, patient files were reviewed and the included patients were linked (through an encrypted identification code) to PALGA on 11 August 2015, assuming that lesions clinically suspicious of recurrence were histologically verified by biopsy or excision. In addition to this latter assumption, we recorded whether each patient visited a dermatologist for follow-up in the past six months. Vital status was obtained from the Dutch Municipal Population Register (Dutch acronym: GBA) until 18 June 2015. Follow-up duration was determined as the number of years between the MMS procedure and PALGA linkage (11 August 2015) or date of recurrence or date of death. The secondary outcome was the number of MMS stages needed for tumour clearance.

Patient, tumour and MMS characteristics

Patient, tumour and MMS characteristics were derived from electronic patient files including standardized digital MMS files and pathology reports. SPSS 22.0 for windows (SPSS Inc., Chicago, IL) was used for the descriptive summary statistics.

RESULTS

During the study period, a total of 4,258 cutaneous tumours were treated with MMS: 88% BCC, 10% SCC and 2% rare cutaneous tumours. In total, 86 patients with 87 rare cutaneous tumours were treated with MMS. Of these 87 tumours, 92% (n = 80) were completely excised and 8% (n = 7) turned out to be inoperable. The seven inoperable tumours were three extramammary Paget's disease (EMPD), two Merkel cell carcinoma (MCC), one microcystic adnexal carcinoma (MAC), and one trichilemmal tumour. The 80 completely excised tumours were 27 dermatofibrosarcoma protuberans (DFSP), 22 atypical fibroxanthoma (AFX), nine MCC, eight MAC, six sebaceous carcinoma (SEB CA), two EMPD and six other rare cutaneous tumours. In 30 cases, an additional margin was excised after the MMS to confirm tumour clearance with immunohistochemical stains (e.g. CD34 for DFSP) on paraffin slides. This was performed in 23 cases of DFSP, one AFX, two MCC, three MAC and one cutaneous angiosarcoma. In one MAC, there were still tumour cells present on the paraffin slides; however, the outer margins were tumour free.

In Table one, a description is given of the 80 completely excised rare cutaneous tumours. In total, there were 2.5% (n = 2) recurrences, both AFX, during a mean follow-up time of 4 years (SD 1). Overall mean age during time of MMS was 61 years (SD 19). Of all 80 patients, 19% (n = 15) died during the follow-up period, these patients were treated for an AFX (n = 6), SEB CA (n = 4), DFSP (n = 4), MCC (n = 1), MAC (n = 1), and porocarcinoma (n = 1). Of all 65 patients who finished the studied follow-up period, 77% (n = 50) patients had their skin checked in the past six months and 23% (n = 15) patients were lost to follow-up.

The two recurrences were both located on the scalp. Case one was a primary AFX tumour, which was excised in one MMS stage. Case 2 was an AFX which was previously three times incompletely excised. Case two was excised in two MMS stages. Both cases had a final defect of 4 centimetres in diameter and reached on to the skull. In both cases, bone milling was performed additionally to the MMS. The MMS slides were additionally reviewed by a pathologist in concordance with the MMS surgeon. The recurrences occurred three and seven months after the MMS procedure. Remarkably, the histopathology of the two recurrences was unclear, an AFX was considered, but an undifferentiated pleomorphic sarcoma could not be excluded. Case one developed lymphovascular and lung metastasis and died eight months after the MMS procedure. Case two was not additionally treated because of severe comorbidity and died 12 months after the MMS procedure.

Figure one shows an overview of the number of MMS stages needed for tumour clearance in all 80 cases. DFSP was the only rare cutaneous tumour that in certain cases needed six MMS stages, and DFSP had the highest percentage of cases with the largest defect size of more than ten centimetres.

Table 1. Patient, tumour and Mohs procedure characteristics of 80 completely excised rare cutaneous tumours.

	DFSP (%)	AFX (%)	MCC (%)	MAC (%)	SEB CA (%)	EMPD (%)	Other[a] (%)
Total number of tumours	27	22	9	8	6	2	6
Men	15 (56)	16 (73)	4 (44)	4 (50)	5 (83)	1 (50)	3 (50)
Mean age at MMS, years (SD)	44 (15)	72 (9)	74 (9)	68 (15)	74 (10)	65 (4)	58 (25)
Mean follow-up time, years (SD)	4 (1)	3 (2)	4 (1)	4 (1)	3 (2)	3 (1)	4 (1)
Recurrence[b]	0	2 (9)	0	0	0	0	0
Tumor location							
Head or neck	8 (30)	22 (100)	8 (89)	6 (75)	6 (100)	0	2 (33)
Trunk	10 (37)	0	0	1 (13)	0	0	1 (17)
Extremities	8 (30)	0	0	1 (13)	0	0	2 (33)
Hands or feet	0	0	0	0	0	0	1 (17)
Genital region	1 (4)	0	1 (11)	0	0	2 (100)	0
Pre-treatment							
None	10 (37)	15 (68)	4 (44)	6 (75)	5 (83)	2 (100)	3 (50)
Incompletely excised or recurrence	16 (59)	6 (27)	5 (56)	2 (25)	1 (17)	0	3 (50)
Radiotherapy	0	1 (5)	0	0	0	0	0
Imatinib	1 (4)	0	0	0	0	0	0
Defect size after 1st MMS stage							
0-2 cm	4 (15)	6 (27)	3 (33)	3 (38)	5 (83)	0	0
2.1-5 cm	5 (19)	13 (59)	5 (56)	1 (13)	1 (17)	1 (50)	5 (83)
5.1-10 cm	15 (56)	3 (14)	1 (11)	3 (38)	0	1 (50)	1 (17)
10.1-20 cm	3 (11)	0	0	1 (13)	0	0 (0.0)	0
Final defect size							
0-2 cm	2 (7)	5 (23)	3 (33)	2 (25)	5 (83)	0	0
2.1-5 cm	5 (19)	14 (64)	5 (56)	1 (13)	1 (17)	0	5 (83)
5.1-10 cm	11 (41)	3 (14)	1 (11)	1 (13)	0	1 (50)	1 (17)
10.1-20 cm	9 (33)	0	0	4 (50)	0	1 (50)	0
Final defect depth							
Subcutaneous fat	9 (33)	0	5 (56)	1 (13)	3 (50)	1 (50)	3 (50)
Muscle	14 (52)	12 (55)	2 (22)	3 (38)	3 (50)	1 (50)	2 (33)
Cartilage or bone	4 (15)	10 (46)	2 (22)	4 (50)	0	0	1 (17)
Mean number of MMS stages (SD)	2.6 (1.4)	1.5 (0.5)	1.6 (1.0)	2.1 (0.4)	1.3 (0.8)	2.5 (0.7)	1.3 (0.5)
Margin for histochemistry after MMS	23 (85)	1 (5)	2 (22)	3 (38)	0	0	1 (17)
Reconstruction							
Noncomplex[c]	16 (59)	14 (64)	6 (67)	1 (13)	5 (83)	0	3 (50)
Complex[d]	11 (41)	8 (36)	3 (33)	7 (88)	1 (17)	2 (100)	3 (50)

Table 1. (continued)

	DFSP (%)	AFX (%)	MCC (%)	MAC (%)	SEB CA (%)	EMPD (%)	Other[a] (%)
Reconstruction by							
Dermatologist	20 (74)	20 (91)	9 (100)	4 (50)	6 (100)	1 (50)	4 (67)
Plastic surgeon	7 (26)	2 (9)	0	4 (50)	0	1 (50)	2 (33)
Adjuvant treatment[e]	4 (15)	6 (27)	6 (67)	2 (25)	0	0	2 (33)

Percentage were rounded.

AFX, atypical fibroxanthoma; cm, centimeter; DFSP, dermatofibrosarcoma protuberans; EMPD, extramammary Paget's disease; MAC, microcystic adnexal carcinoma; MCC, Merkel cell carcinoma; MMS, Mohs micrographic surgery; SEB CA, sebaceous carcinoma; SD, standard deviation.

[a] Others included one trichilemmal carcinoma, one cutaneous angiosarcoma, one porocarcinoma, one nerve sheath myxoma, one granular cell tumour, one spiradenocarcinoma.

[b] Number of recurrences after MMS; this means that aborted MMS were excluded from this study and number of recurrences.

[c] Noncomplex reconstructions included primary closure or healing by secondary intention.

[d] Complex reconstructions included all noncomplex reconstructions, e.g. skin grafts, flaps.

[e] Adjuvant treatments included bone milling, radiotherapy, chemotherapy, imatinib or an combination of these treatments.

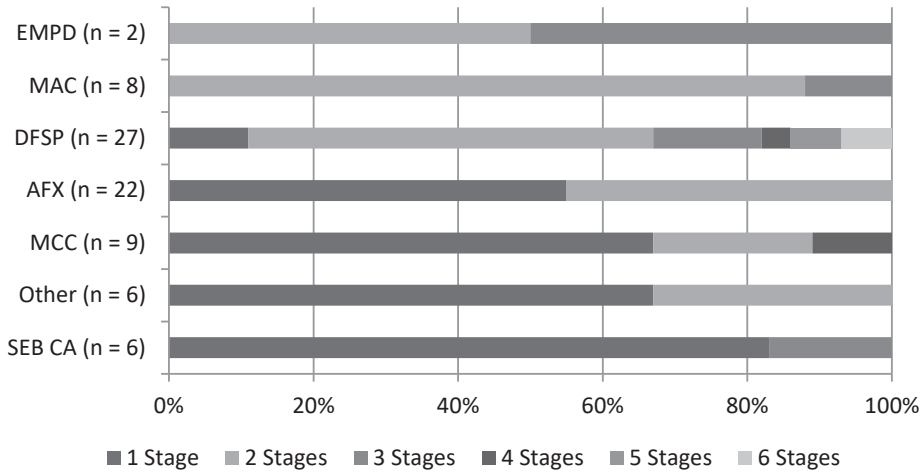

Figure 1. Number of Mohs micrographic surgery stages needed for tumour clearance in 80 rare cutaneous tumours.

AFX, atypical fibroxanthoma; DFSP, dermatofibroma sarcoma protuberans; EMPD, extramammary Paget's disease; MAC, microcystic adnexal carcinoma; MCC, Merkel cell carcinoma; n, number; SEB CA, sebaceous carcinoma.

Other included one trichilemmal carcinoma, one cutaneous angiosarcoma, one porocarcinoma, one nerve sheath myxoma, one granular cell tumour, one spiradenocarcinoma.

DISCUSSION

This Dutch case series showed that MMS for rare cutaneous tumours is an appropriate treatment, because only two of the 80 cases had a recurrence during our mean follow-up period of four years. This percentage is extremely low in comparison with standard excision, as for the latter recurrence rates up to 89% are reported.[8,12] In this study, most rare cutaneous tumours occurred at older age (except for DFSP) and men were relatively more often affected than women (except for MCC), which has also been observed by others.[8,9,13] Our study was limited by retrospective data and selection bias. Our observed low recurrence rate is in accordance with a study of the Geisinger Medical Center in Pennsylvania where only 4% of rare cutaneous tumours recurred after MMS during a mean follow-up period ranging from 11 to 39 months.[13] The three recurrences were MAC, the tumours which did not recur were 39 DFSP, 23 MAC, 10 EMPD. [13] Others also report low recurrence rates after MMS.[6,8,9,13-15]

The risk of missing recurrences during our follow-up period was low because patients were linked with PALGA. The two tumours that recurred were diagnosed as AFX based on the pre-MMS biopsy. The recurrences were classified as undifferentiated pleomorphic sarcoma, which must in retrospection already have been the initial diagnosis. These tumours have a very aggressive behaviour and a poor prognosis, wherefore MMS might be a less appropriate treatment.

DFSP was associated with many MMS stages and large defect sizes. This is probably explained because DFSP mainly grows in the reticular dermis and subcutis often sparing superficial dermis and epidermis whereby the clinical visible part of the DFSP is often much smaller than its microscopically spread.[16]

The seven cases which turned out to be inoperable had bone invasion or were limited by local anaesthesia. Even when adequate imaging has been performed (e.g. CT, MRI), it might be difficult to predict the extent of the tumour preoperatively. To prevent aborted MMS procedures, research should focus on instruments that will be perfectly able to assess tumour extent preoperatively. MMS seems an appropriate treatment for rare cutaneous tumours given the low recurrence rate observed in our case series and should definitely be considered in cases where a wide local excision could mutilate the patient (such as in the head and neck area). To improve the quality of treatment, it is recommended that MMS for rare cutaneous tumours is performed in centres where multidisciplinary experts work together.

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Chapter 8

Rates of re-excisions and recurrences of dermatofibrosarcoma protuberans in the Netherlands between 1989-2016

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ABSTRACT

Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumour of which the quality of care is poorly studied. Therefore, rates of re-excisions and recurrences were determined using data from the Netherlands Cancer Registry between 1989-2016. Of the 1,890 DFSP included, 87% were treated with standard excision, 4% with Mohs micrographic surgery (MMS), and 9% otherwise or unknown. Linked pathology data was retrieved for 1,677 patients. Half of all excisions (847/1,644) were incomplete 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). After MMS (n = 34), there were no recurrences during a median follow-up of four years (IQR 3-6). Due to the found high rate of incomplete standard excisions and recurrences after excision, this study supports the European guideline, which recommends treating DFSP with MMS to decrease the rate of recurrence.

INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumour which originates from a translocation of chromosome 17 and 22, resulting in tumour cell proliferation of fibrohystiocytic lineage. Unlike most skin cancers, DFSP is a non UV related skin cancer. The overall standardized incidence rates in the Netherlands and the United States are 4 per 1,000,000 person-years.[1-3] Men and women are equally affected and the peak incidence age is between 20 and 50 years.[4-6] Although DFSP mostly occurs in adults, DFSP rarely occurs in children (1.0 per 1 million). DFSP is commonly located on the trunk (50%), proximal extremities (20-30%) or head and neck (10-15%).[4-6] It presents as an asymptomatic, slowly growing, skin coloured indurated plaque. Although DFSP rarely metastasize, they do grow in a locally invasive manner into subcutaneous fat, muscles and sometimes to bone.[4,5,7] Clinically and with imaging tests (e.g. MRI or CT) DFSP are difficult to delineate because the tentacle-like invasion into subcutaneous tissue is often greater than suspected. As a result, multiple surgical procedures may be required to ensure complete clearance of DFSP.

Until 2015, DFSP guidelines were lacking and in The Netherlands the majority of DFSPs were treated with standard excision. The European consensus-based interdisciplinary guideline which is available since 2015, recommends to treat DFSP with Mohs micrographic surgery (MMS) in order to reduce the assumed high recurrence rate after standard excision.[8]

To date, outcome data for DFSP management are based on small patient cohorts with limited information on lost to follow-up.[5,9] Previous studies report a wide range of rates of DFSP re-excisions (3%-81%) and recurrences (0%-46%).[5-7,10,11] This nationwide cohort study with long term follow-up of DFSP aims to determine the rate of re-excisions and recurrences, which is needed to inform patients, clinicians, and health policy makers to plan optimal treatment strategies and surveillance schedules.

METHODS

Patients

This cohort study included all patients with a histologically confirmed DFSP in the Netherlands between January 1989 and December 2016 (Figure 1). Data were obtained from the Netherlands Cancer Registry (NCR), which collects data on all newly diagnosed cancer patients in the Netherlands since 1989. Registration is primarily based on notification by the nationwide network and registry of histopathology and cytopathol-

ogy (PALGA), which contains all pathology reports of all Dutch pathology laboratories. Completeness of NCR incidence data on cutaneous malignancies is 93%.[12] All used data for this study from the NCR (i.e. patients sex and age, DFSP location, type of treatment and physician) were collected from the medical records of hospitals by special trained NCR employees. Tumour localization and morphology were registered according to the International Classification of Disease (ICD-O-3). Location of the primary tumour was categorized into face/scalp/neck (C44.0-C44.4), trunk (C44.5), arm/shoulder (C44.6), leg/hip (C44.7), genital (C51.0, C51.9, C63.2) or other (C44.8, C44.9). Vital status and date of death or emigration of the included patients were obtained by annual linkage with the Dutch Municipality Registers.

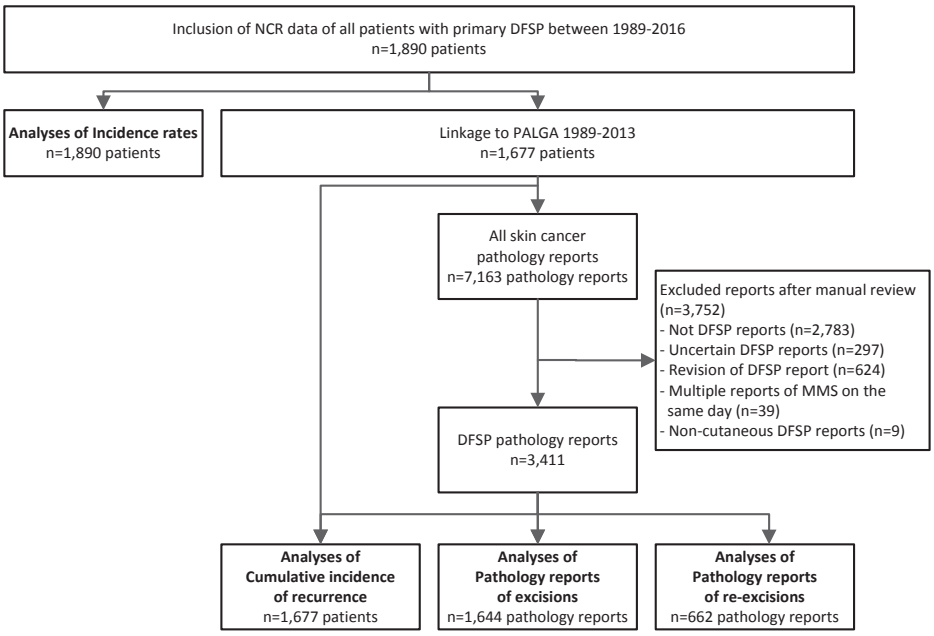

Figure 1. Flowchart of material and methods.
DFSP, dermatofibrosarcoma protuberans; MMS, Mohs micrographic surgery; n, number; NCR, Netherlands Cancer Registry; PALGA, Dutch nationwide pathology database.

Study outcome

The primary outcome was the rate of incomplete DFSP excisions and recurrences. The NCR registers DFSP only at time of the first primary diagnosis. Therefore, to detect all re-excisions and recurrences during follow-up, the included patients from the NCR registry were linked to PALGA. In order to have at least two years of follow-up, PALGA data were retrieved only for patients who were diagnosed with a DFSP before 1 January 2014. Follow-up time of the patients started on the day of the primary DFSP diagnosis

and ended on the day of death or emigration, or last date of NCR-PALGA linkage which was performed for this study at 1 February 2015.

Conclusions from the PALGA pathology reports were manually reviewed (WK,EIVC,LH,CBVL) and scored on the following variables: diagnosis (DFSP, possible DFSP, other), immunohistochemical staining with CD34 (positive, negative, not performed), anatomical location (according to ICD-O3), type of specimen (biopsy, diagnostic excision, wide local excision, re-excision, MMS, Breuninger surgery, other, unclear), histological clearance (yes, no, unknown, not applicable in the case of diagnostic biopsies), invasion into muscle (yes, no, possibly), fibrosarcomatous changes (yes, no, possibly) and clinical excision margins (in mm). Invasion into muscle, immunohistochemistry for CD34, fibrosarcomatous changes and clinical excision margins were missing for 50-99% cases and therefore not included in the final analysis.

All pathology reports with uncertain DFSP diagnosis (i.e. when the pathologist was in doubt of the diagnosis or if the pathology report was unclear) were excluded from the analyses (n = 297). Incompletely excised DFSP included DFSP which histologically invaded the inked surgical margin. Local DFSP recurrence included histologically proven DFSP that occurred at least four months after the previous pathology report, because it was assumed that re-excisions would occur within this period.

Statistical analysis

Annual incidence rates were calculated by sex, age groups and body sites per 1,000,000 person-years from 1989-2016, using the annual population size acquired from Statistics Netherlands (www.statline.cbs.nl). Standardized incidence rates were calculated using the European standard population (2013). Descriptive statistics were used to report the baseline characteristics of patients, DFSP, treatment and study outcome. In order to estimate the number of surgical procedures during follow-up (i.e., including the first surgical treatment of the primary DFSP and all re-excisions and/or recurrences), the mean cumulative count was calculated, which is equal to the sum of the cumulative incidences of all surgical procedures.[13] To estimate the probability of the first DFSP recurrence during follow-up, a cumulative incidence curve (CIC) was calculated, which takes the competing risk of death into account.[14] Statistical analyses were performed using STATA (version 15), SAS 9.4 statistical software (SAS Institute Inc., Cary, NS, USA), R statistical software version 3.4.1 (www.r-project.org). P-values < 0.05 (two-sided) were considered statistically significant.

RESULTS

Incidence and treatment of the first DFSP

A total of 1,890 patients were diagnosed with a DFSP in the Netherlands between 1989 and 2016 (Table 1). Both the crude and European standardized incidence rate of DFSP were 4.2 per 1,000,000 person-years. The incidence rate of DFSP was stable between 1989-2016. Incidence rates were comparable for men and women. Half of the 1,890 patients with a DFSP were women (51%) and overall median age at diagnosis was 41 years (IQR 31-41). DFSP were most commonly located on the trunk (45%) followed by arm/shoulder (24%), leg/hip (16%), head and neck (13%), and genital area (1%) (Table 1).

The majority of the 1,890 patients with a primary DFSPs were treated with excision (87%). Data from the NCR on the first primary DFSP showed that more than half of the 1,890 patients (56%) underwent a single standard excision, whereas 25% underwent two excisions and 6% underwent three or more excisions. Only 4% of patients underwent MMS as a primary treatment or as additional treatment after excision, and 1% were not treated at all. Nonsurgical treatments included postoperative radiotherapy (6%) and or other types of treatment, such as tyrosine kinase inhibitors (1%). The majority of the first treatment for DFSPs were performed by surgeons (38%), while dermatologists treated only 11% of DFSP. The other DFSPs were treated by plastic surgeons (6%), or general practitioners (2%), or by physicians who worked in a multidisciplinary team (13%), or it was unknown (30%).

Re-excisions

For 1,677 patients who were diagnosed between 1989-2013, linked pathology data were retrieved from PALGA (Table 2). Patient and tumour characteristics were similar to patients without linked pathology data [data not shown]. Of the 1,677 patients, 35% underwent a single surgical treatment for a primary DFPS during a median follow-up of 11 years (IQR 6-17). Half of all patients (51%: (588+180+78)/1,677) underwent multiple surgical treatments. The number of surgical treatments was unknown for 14% (n = 240) of all patients. Of all 1,644 pathology reports of DFSP excisions, 32% (n = 524) were completely excised, 52% (n = 847) were incompletely excised and histological clearance was unknown for 17% (n = 273) of all reports. Of all 662 pathology reports of DFSP re-excisions, 61% (n = 401) were completely excised, 29% (n = 192) were incompletely excised and histological clearance was unknown for 69 reports (10%). The mean cumulative count of surgical treatments per patient was 1.4 (95% CI 1.3-1.4) after a follow-up of six months and remained stable thereafter (Figure 2).

Table 1. Description of patients which were diagnosed with a primary dermatofibrosarcoma protuberans in the Netherlands between 1989 and 2016 according to data of the Netherlands Cancer Registry (NCR).

	DFSP patients 1989-2016 n = 1,890 (%)
Sex	
Men	926 (49)
Women	964 (51)
Age in years	
0-19	114 (6)
20-39	741 (39)
40-59	718 (38)
60-79	257 (14)
≥ 80	60 (3)
Anatomical location	
Trunk	848 (45)
Arms/shoulder	463 (24)
Leg/hips	305 (16)
Face/scalp/neck	239 (13)
Genitals	12 (1)
Other	20 (1)
Unknown	3 (0)
Surgical treatment for first primary DFSP	
1 Excision	1053 (56)
2 Excisions	469 (25)
≥ 3 Excisions	109 (6)
MMS	81 (4)
Non-surgical treatment	
Postoperative RT	119 (6)
Others[a]	18 (1)
Unknown	15 (1)
No treatment	14 (1)
Physician	
Surgeon	707 (38)
Dermatologist	209 (11)
Plastic surgeon	105 (6)
General practitioner	42 (2)
Multidisciplinary	240 (13)
Unknown	591 (30)

Percentages were rounded.

DFSP, dermatofibrosarcoma protuberans; MMS, Mohs micrographic surgery; n, number; RT, radiotherapy.

[a] Others included e.g. tyrosine kinase inhibitors.

Table 2. Re-excisions and recurrences of dermatofibrosarcoma protuberans which were primary diagnosed between 1989 and 2013 for whom followed-up until 31 December 2015 from the Dutch nationwide pathology database (PALGA) was retrieved.

	DFSP patients 1989-2013 n = 1,677 (%)
Follow-up in years, median (IQR)	10.5 (5.6-16.6)
Surgical treatments during follow-up[a]	
1	591 (35)
2	588 (35)
3	180 (11)
≥ 4	78 (5)
Unknown	240 (14)
Recurrences	
None	1,517 (90)
1	145 (9)
≥ 2	15 (1)

Percentages were rounded.

DFSP, dermatofibrosarcoma protuberans; IQR, inter quartile range; n, number.

[a] Surgical treatments during follow-up excluded biopsies, treatments of primary DFSPs, and treatments of cases of which the histological DFSP diagnosis was unclear. Surgical treatments included excision and Mohs micrographic surgery (n = 34).

Recurrences

During a median follow-up of 11 years (IQR 6-17), 9% (n = 145) of 1,677 patients experienced one local recurrence and 1% (n = 15) of patients had two or more local recurrences. The cumulative incidence curve showed that the majority of the recurrences occurred within five years (98 of 128, 77%), although some recurrences occurred even after ten years (Figure 3). After 20 years of follow-up, the cumulative incidence of local recurrence was 7% (95% CI 6-8). None of the 34 patients who underwent MMS between 1989 and 2013, experienced any recurrence during a median follow-up of four years (IQR 3-6).

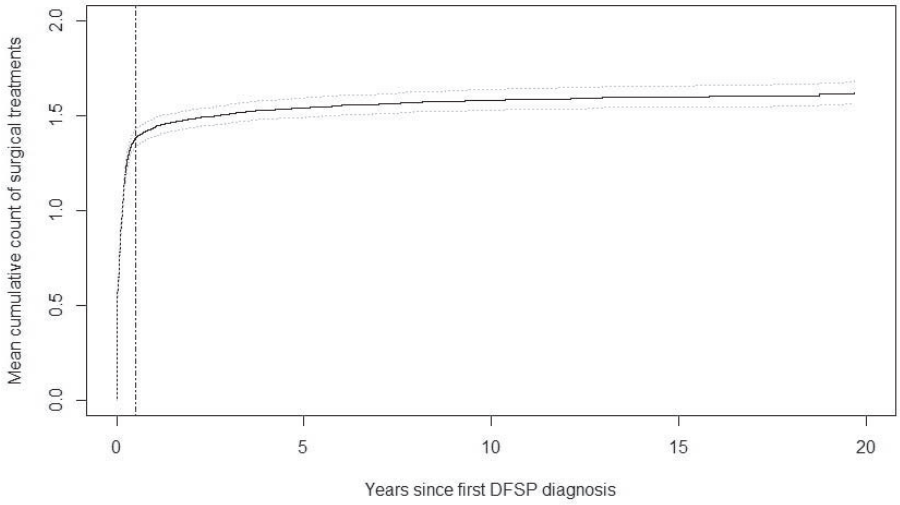

Figure 2. Mean cumulative count of surgical treatments of dermatofibrosarcoma protuberans which were diagnosed between 1989 and 2013 and followed-up until 2015 using data from the Dutch nationwide pathology database (PALGA). The majority of surgical treatments occurred within the first six months (indicated by the vertical line).
DFSP, dermatofibrosarcoma protuberans.

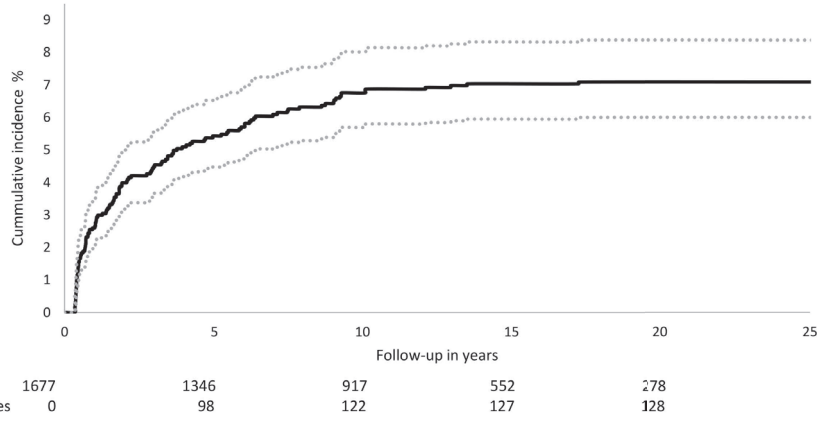

Figure 3. Cumulative incidence curve of the first recurrence with 95% confidence interval of dermatofibrosarcoma protuberans which were diagnosed between 1989 and 2013 and followed-up until 2015 using data from the Dutch nationwide pathology database (PALGA). The majority of recurrences occurred within 5 years of follow-up.
N, number.

DISCUSSION

This large nationwide cohort study of patients with a DFSP shows that the efficacy of standard excision is poor given the high rate of patients who underwent multiple surgical excisions (51%) to clear all tumour cells. This study also showed, that 10% of all patients experienced at least one recurrence during a median followed-up of 11 years (IQR 6-17).

In concordance with other studies, the ratio of incidence rate for men and women was 1:1.The majority of DFSPs occurred among young people (median age 41 years), and the most common location was the trunk (45%).[4,5]

The majority of DFSP excisions were performed by surgeons. This is due to the referral pattern of general practitioners in the Netherlands, who tend to refer patients with a sarcoma or a relatively large tumour to surgeons. Ideally, these patients are referred to dermatologists in specialized centres where multidisciplinary experts work together in order to plan optimal treatment strategies.

While the European guideline recommends to treat DFSP with MMS, this study shows that only 4% of all DFSP were treated with MMS.[8] The low percentage of patients that was treated with MMS is due to the introduction of the Dutch guideline in 2015 (while the cases were included between 1989-2016) and only in a single university medical centre DFSP are treated with MMS since 2008.

Only a few cases were treated with postoperative radiotherapy in our study, because it is still unclear, whether radiotherapy is effective in slowly growing tumours such as DFSP. Also, only a few cases were treated with tyrosine kinase inhibitors (imatinib), because systemic treatment for DFSP is only indicated for metastasized tumours or for tumours which could not be surgically treated, which is rarely the case for DFSPs.[15,16]

We observed that in our large population-based sample 51% of DFSPs were re-excised and 10% recurred. Rates of re-excision and recurrence range vary widely between studies, respectively between 3%-81% and 0%-46%.[5-7,10,11] This variation is most likely due to the small cohort size of the studies (range 14-451), and to the heterogeneity of included patients regarding anatomical locations (e.g. head and neck only versus all body sites), surgical treatments used (e.g. wide local excision versus MMS), clinical excision margin size (e.g. small versus wide), physician (e.g. surgeon, plastic surgeon, dermatologist), methodology of collecting follow-up data (e.g. from the patient files, patients consult

by phone or doctors visit), length of follow-up (few months up to several years) and numbers of patients lost during follow-up (often non specified).[5,9]

The observed DFSP re-excision rate of 51% is much higher than the known re-excision rates for basal cell carcinoma (BCC) (7-30%) and squamous cell carcinoma (SCC) (0-25%).[17-19] Multiple aspects contribute to the high re-excision rate for DFSP when compared to BCC and SCC. First, DFSP is a rare tumour and therefore physicians may be less familiar with the clinical recognition and delineation of the extent of a DFSP. Second, it is difficult to delineate the extent of a DFSP preoperatively because of the subcutaneous tentacle-like invasion, which might be invisible to the naked eye both clinically and on imaging tests (e.g. MRI or CT). Third, DFSP does not grow in a symmetrical manner around the clinical visible centre. Therefore, a clinical tumour free margin even up to several centimetres around the clinical visible tumour centre often results in histologically tumour positive margins at one side of the tumour while on the other side healthy tissue is unnecessarily excised.

Our observed recurrence rate of DFSP during a median follow-up period of 11 years (IQR 6-17) of 10% is within the range of known recurrence rates for BCC (12%), SCC (10%) and melanoma (12%).[18-21] Most likely, histopathological missed residual tumour continued to grow and presented in time as a recurrent DFSP. DFSP might be absent on the evaluated slides while still being present in the patient because with the standardized bread loaf technique only a few vertical slides through the excised specimen are examined representing only a small portion of the true excision margins.

Although this study only presented 34 patients that were treated with MMS, none of the patients developed a recurrence during a median follow-up of four years (IQR 3-6), which is in line with previous studies. A possible lack of aggressiveness of DFSPs treated with MMS compared to DFSPs treated with standard excision, cannot explain this finding, because only a single University centre performed MMS for all DFSPs treated in their centre since 2007. Other University centres performed standard excision for DFSPs. There were thus no referral patterns that could explain this finding. Therefore, our results suggests that MMS is an appropriate treatment for DFSP.[22-25]

The observation that the majority of DFSP recurrences occurred within the first five years of follow-up implies that follow-up of at least five years is reasonable, especially because of the difficulty to clinically distinguish a tumour's origin from a scar tissue or from a recurrence.[4,5]

Strengths of this study are the use of nationwide cancer registry data which resulted in a large number of DFSP cases, a robust dataset to detect re-excision and recurrence rates using the nationwide pathology database, and the long term follow-up period (up to 26 years). Limitations include a lack of information concerning high risk features for most pathology reports, such as invasion into muscle and fibrosarcomatous changes. Another limitation is that 17% of the pathology reports of primary excisions and 10% of the pathology reports of re-excisions did not contain conclusive information on the histological clearance. Therefore, the rate of DFSP incomplete excisions and recurrences was probably underestimated.

In conclusion, this study reports a high rate of incomplete DFSP standard excisions (51%) and a clinically relevant high recurrence rate (10%) during a median follow-up of 11 years. Multiple surgical procedures can lead to poor functional and cosmetic outcome for patients with higher costs to society. This study shows that there is a need to improve the quality of care for DFSP and the results support the current European guideline which recommend to treat DFSPs with MMS instead of excision (8).

Acknowledgment

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Chapter 9

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 an 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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Chapter 10

Summary / Samenvatting

SUMMARY

Chapter 1 contains a general introduction to this thesis. For basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC) and rare skin tumours general information is given regarding their epidemiology, clinical presentation and histological features. Furthermore, the procedures of a standard excision (SE) and Mohs micrographic surgery (MMS) are described. In this thesis, different aspects of the quality of SE and MMS are analysed and compared. The results presented in this thesis should help patients and clinicians to position MMS better in their skin cancer treatment strategies.

PART I BASAL CELL CARCINOMA

Chapter 2 concerns a study of the quality of BCC-care. Its goal was to investigate whether the quality of BCC care would be preserved when BCC care would be shifted from secondary to primary care. Therefore, differences were determined for the rate of completely excised primary BCC by general practitioners (GPs), compared to dermatologists and plastic surgeons in the Southwest area of the Netherlands between 2008 and 2014. In 2,986 pathology records, it was quantified that BCCs were completely excised by GPs in 70%, which was lower than the 93% by dermatologists and 83% by plastic surgeons ($p < 0.001$). This study shows that there is a strong need for an integrated care pathway including adequate training for GPs, before a shift of BCC care from secondary to primary care would be justifiable.

Chapter 3 and chapter 4 studies of the quality of histological diagnosis of MMS slides are presented. In **chapter 3** the reliability of the interpretation of MMS slides is assessed. The success of MMS largely depends on correct interpretation of slides. Therefore, the interpersonal and intrapersonal level of agreement was determined of the histological diagnosis from 50 randomly selected MMS slides. To determine a minimum level of agreement, difficult-to-diagnose slides were oversampled (21% versus 6% in daily practice). Agreement on BCC presence was substantial between six raters (three MMS surgeons and three pathologists) versus an expert panel (K = 0.66, 95% CI 0.58-0.73), as well as between each rater at T1 versus T2 two months later (K = 0.68, 95% CI 0.59-0.76). This study shows that the reliability of MMS slides is at least substantial. Especially for difficult to diagnose slides, it is recommended to consult a colleague intra-operatively to prevent misinterpretation and long-term BCC recurrence.

In **chapter 4** it the quality of MMS was assessed-after an additional review of MMS slides. It was determined how often pathologists detected incompletely excised BCC on MMS

slides by the additional review of 1,653 MMS procedures. The additional review was performed within one week after the MMS procedure in a university hospital between 2007 and 2011. Incompletely excised BCCs were detected in 2% (31/1,653) MMS procedures. This study shows that the use of an additional review of MMS slides increases accurate interpretation, which on the long term prevents skin cancer recurrences.

PART II SQUAMOUS CELL CARCINOMA

Chapter 5 focuses on the quality of MMS compared to SE for cSCC of the head and neck. Therefore, recurrence rates of cSCC of the head and neck for MMS and SE were compared at a secondary and tertiary care hospital in the Netherlands between 2003 and 2012. To detect all recurrences, patients were linked to the Dutch pathology registry (PALGA). In 579 patients with 672 cSCC, the risk of recurrence was 8% (22/292) after SE during a median follow-up of 5.7 years (IQR 3.5-7.8), which was higher than the 3% (12/380) after MMS during a median follow-up of 4.9 years (IQR 2.3–6.0, $p = 0.013$). Although cSCC treated with MMS were more often > 2 cm (33%) in diameter than cSCC treated with SE (6%), defects after MMS were more often ≤ 2 cm (60%) than after SE (32%). Therefore, to prevent cSCC recurrences in the head and neck and to preserve functional and cosmetic outcome, MMS is favourable to SE for cSCC in the head and neck.

Chapter 6 concerns a study of the quality of SE of cSCC. The rate of incomplete cSCC excisions was determined prospectively in six dermatology centres between 2015 and 2017, and additionally, a systematic review of the literature took place. In 592 patients with 679 cSCC a low risk (4%) of incomplete excision was found in a cohort that was dominated by low risk cSCCs while all incompletely excised cSCC were high risk cSCC. The drawback of SE concerns the depth of excision, i.e. incompletely excised cSCCs involved the deep margin in 92%. Although conclusions of the efficacy of SE must be made carefully as the systematic review showed a wide range of rate of incompletely excised cSCC, i.e. pooled average 12% (95% CI 10-16, range 0-39%).

PART III RARE SKIN TUMOURS

Chapter 7 presents a study of the quality of MMS for rare skin tumours. The recurrence rate of rare cutaneous tumours after MMS was determined at a University centre between 2008 and 2012. To detect all recurrences, patients were linked to to the Dutch pathology registry (PALGA). In 80 patients with 80 tumours, two atypical fibroxanthomas (AFX) recurred (3%) during a mean follow-up time of 3.7 years (standard deviation 1.4 years).

The other tumours did not recur, i.e. dermatofibrosarcoma protuberans (DFSP) (n = 27), AFX (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). The two AFX recurrences were classified as undifferentiated pleomorphic sarcoma, which must in retrospection already have been the initial diagnosis. Pleomorphic sarcoma has a very aggressive behaviour and a poor prognosis, wherefore MMS is a less appropriate treatment. Given the low recurrence rate of 3%, this study supports that MMS is an appropriate treatment for most rare cutaneous tumours.

Chapter 8 describes a study of the quality of SE for DFSP. The rates of DFSP re-excisions and recurrences were determined in a sample obtained from the Netherlands Cancer Registry (NCR) between 1989-2016. To detect all recurrences and re-excisions, all patients diagnosed with a DFSP between 1989-2013 were linked to the Dutch pathology registry (PALGA). Strikingly, half of all primary DFSP excisions were incomplete (847/1,644) and 29% (192/622) of all re-excisions were incomplete. The cumulative incidence of at least one DFSP recurrence was 7% (95% CI 6%-8%) during a median follow-up of 11 years (IQR 6-17). After MMS (n = 34), there were no recurrences during a median follow-up of four years (IQR 3-6). This study supports the European guideline, which recommends treating DFSP with MMS to increase the quality of care.

The studies presented in this thesis support that MMS is an excellent treatment choice for skin cancer. **Chapter 9**, discusses the present level of evidence of MMS for BCC, cSCC and rare skin tumours. Furthermore, recommendations are made to improve the quality of MMS and skin cancer care in the Netherlands.

SAMENVATTING

Hoofdstuk 1 geeft een algemene inleiding op dit proefschrift. Verschillende typen huidkanker worden beschreven, te weten basaalcelcarcinomen (BCC), plaveiselcelcarcinomen (PCC) en zeldzame tumoren. Daarna worden twee chirurgische behandelmethoden toegelicht, te weten standaard excisie (SE) en Mohs micrografische chirurgie (MMC). In dit proefschrift worden verschillende aspecten van de kwaliteit van SE en MMC geanalyseerd en met elkaar vergeleken. De resultaten zullen patiënten en clinici helpen om de MMC beter onderbouwd te kunnen positioneren in hun de behandelstrategieën voor huidkanker.

DEEL I BASAALCELCARCINOMEN

Hoofdstuk 2 beschrijft een onderzoek naar de kwaliteit van BCC-zorg, met de vraag of deze gewaarborgd blijft als de BCC-zorg wordt verlegd van de specialist naar de huisarts. Om daar een uitspraak over te kunnen doen, werd het percentage van radicaal geëxcideerde primaire BCC berekend van huisartsen, dermatologen en plastisch chirurgen in Zuidwest Nederland tussen 2008 en 2014. Uit 2.986 pathologieverslagen kwam naar voren dat excisies door huisartsen in 70% radicaal waren, terwijl dit voor dermatologen 93% was en voor plastisch chirurgen 83% ($p < 0.001$). Dit onderzoek toont aan dat een integraal zorgplan en specifieke training voor huisartsen noodzakelijk zijn, alvorens een verschuiving van BCC zorg van de specialist naar de huisarts verantwoord is.

Hoofdstuk 3 en 4 gaan over de kwaliteit van de histologische diagnose van MMC coupes. In **hoofdstuk 3** staat de betrouwbaarheid van de beoordeling van coupes centraal. Het succes van de MMC hangt immers grotendeels af van de juiste interpretatie van de coupes. Om inzicht te krijgen in de mate van interpersoonlijke en intrapersoonlijke overeenstemming over de histologische diagnose is gekeken naar 50 willekeurig geselecteerde MMC coupes. Daarbij lag het aantal moeilijke coupes hoger lag dan in de dagelijkse praktijk (21% versus 6% in de dagelijks praktijk), om zo een minimaal niveau van overeenstemming vast te stellen. De overeenstemming over de aanwezigheid van BCC was substantieel, zowel interpersoonlijk tussen zes beoordelaars (drie MMC dermatologen en drie pathologen) en een referentie diagnose (vastgesteld na consensus door één MMC dermatoloog en één patholoog met beide > 15 jaar ervaring) ($K = 0.66$, 95% CI 0.58-0.73), alsmede intrapersoonlijk voor elke beoordelaar op T1 versus T2 twee maanden later ($K = 0.68$, 95% CI 0.59-0.76). Dit onderzoek toont aan dat de betrouwbaarheid van de beoordeling van MMC coupes ten minste substantieel is. Met name voor moeilijk te

beoordelen coupes is het verstandig om een collega intra-operatief om hulp te vragen ter preventie van misinterpretatie en uiteindelijk een recidief BCC.

In **hoofdstuk 4** werd onderzocht of een additionele beoordeling van coupes de kwaliteit van MMC verhoogt. Berekend werd hoe vaak een patholoog door de additionele beoordeling van 1.653 MMC procedures een irradicaal geëxcideerde BCC ontdekte. De additionele beoordeling vond plaats binnen één week na de MMC in een Universitair ziekenhuis tussen 2007 en 2011. De patholoog constateerde dat een BCC irradicaal was geëxcideerd met MMC in 2% (31/1.653) van de MMC procedures. Dit onderzoek toont aan dat een additionele beoordeling van coupes de kwaliteit van de MMC optimaliseert doordat irradicaal geëxcideerde BCC worden opgespoord wat uiteindelijk een recidief BCC voorkomt.

DEEL II PLAVEISELCELCARCINOMEN

In **hoofdstuk 5** ligt de focus op de kwaliteit van MMC in vergelijking met SE voor PCC in de hoofd-hals-regio. Het risico op een PCC recidief werd onderzocht na MMC versus SE in een secundair en tertiair ziekenhuis in Nederland tussen 2003 en 2012. Om geen enkel recidief te missen, werden alle patiënten gekoppeld aan de Nederlandse pathologie database (PALGA). Het risico op een recidief bleek 8% (22/292) voor SE tijdens een mediane follow-up van 5.7 jaar (IQR 3.5-7.8). Dit was hoger dan de 3% (12/380) voor MMC tijdens een mediane controle van 4.9 jaar (IQR 2.3–6.0, $p = 0.013$). De einddefecten na MMC waren vaker ≤ 2 cm (60%) dan na SE (32%), terwijl de PCC die werden behandeld met MMC vaker > 2cm in diameter waren (33%) dan de PCC die werden behandeld met SE (6%). De resultaten suggereren dat MMC superieur is ten opzichte van SE voor PCC in de hoofd-hals-regio.

In **hoofdstuk 6** wordt de kwaliteit van PCC excisie onder de loep genomen. Het percentage irradicale PCC excisies werd berekend in een prospectieve studie in 6 dermatologische centra tussen 2015 en 2017, aangevuld met een systematische literatuurstudie. Bij de in totaal 592 geïncludeerde patiënten met 679 PCC, werd 4% irradicaal geëxcideerd. De studiepopulatie bestond voornamelijk uit laag risico PCC, terwijl alle incompleet geexcideerde PCC hoog risico tumoren waren. De incomplete excisies waren in 92% in de bodem irradicaal. In de systematische literatuurstudie werden 36 observationele studies geïncludeerd, goed voor 11.235 PCC. De samengevoegde gemiddelde schatting van het percentage irradicale PCC excisies was 12% (95% CI 10-16, I^2=92%, variatie 0-36%). Omdat de percentages van irradicale PCC excisies zo uiteen lopen, is voorzichtigheid geboden in het maken van conclusies over de doeltreffendheid van excisies voor PCC.

DEEL III ZELDZAME TUMOREN

In **hoofdstuk 7** wordt de kwaliteit van MMC voor zeldzame huidkankers onderzocht. Het percentage recidieven werd berekend van zeldzame huidkankers na MMC in een Universitair ziekenhuis tussen 2008 en 2012. Om geen enkel recidief te missen, werden alle patiënten gekoppeld aan de Nederlandse pathologie database (PALGA). Van alle 80 patiënten die werden behandeld voor een zeldzame huidkanker recidiveerden er slechts 3%, dit waren twee atypische fibroxanthomen (AFX). De overige tumoren recidiveerden niet: DFSP (n = 27), AFX (n = 22), Merkel cel carcinoom (n = 8), microcysteus adnex carcinoom (n = 9), talgklier carcinoom (n = 6), extramammaire ziekte van Paget (n = 2), en overige (n = 6). Deze twee AFX recidieven bleken ongedifferentieerde pleomorfe sarcomen te zijn, wat in retrospectie al zo geweest zal zijn ten tijde van de MMC. Gezien het lage recidief percentage van 3% ondersteunt deze studie dat MMC een geschikte behandeling is voor de meeste zeldzame huidkankers.

In **hoofdstuk 8** wordt de kwaliteit van DFSP excisie onderzocht. Het percentage van DFSP re-excisies en recidieven werd bepaald op basis van data van de Nederlands Kanker Registratie (NCR) tussen 1989 en 2016. Om geen enkele re-excisie en recidief te missen, werden alle patiënten die werden gediagnosticeerd met een DFSP tussen 1989 en 2013 gekoppeld aan de Nederlandse pathologie database (PALGA). Zorgelijk genoeg bleek de helft van alle primaire DFSP excisies irradicaal te zijn (847/1,644) en nog eens 29% (192/622) re-excisies was wederom irradicaal. De cumulatieve incidentie van ten-minste één DFSP recidief was 7% (95% CI 6%-8%) tijdens een mediane follow-up van 11 jaar (IQR 6-17). Er waren *geen* recidieven na de 34 MMC operaties tijdens een mediane follow-up van vier jaar (IQR 3-6). Deze studie ondersteund het advies van de Europese DFSP richtlijn om patiënten met een DFSP bij voorkeur te behandelen met MMC.

De onderzoeksresultaten uit dit proefschrift ondersteunen het gebruik van MMC voor BCC, PCC en zeldzame huidkankers. In **hoofdstuk 9** wordt het huidige niveau van wetenschappelijk bewijs besproken van MMC voor BCC, PCC en zeldzame tumoren. Verder wordt besproken hoe de kwaliteit van MMC gewaarborgd en verbeterd kan worden.

Chapter 11

Appendices

List of abbreviations

List of co-authors

List of publications

PhD portfolio

Curriculum vitae

Dankwoord

LIST OF ABBREVIATIONS

AFX	Atypical fibroxanthoma
AJCC	American joint committee on cancer
BCC	Basal cell carcinoma
BWH	Brigham and Women's Hospital
CI	Confidence interval
cm	Centimetre
cSCC	Cutaneous squamous cell carcinoma
DE	Dermatologist
DFSP	Dermatofibrosarcoma protuberans
DICA	Dutch Institute for Clinical Auditing
DMTR	Dutch Melanoma Treatment Registry
EMPD	Extramammary Paget's disease
ENT	Ear-nose-throat
ESMS	European Society for Micrographic Surgery
GP	General practitioner
HR	Hazard ratio
IQR	Interquartile range
K	Kappa
mm	Millimetre
MMS	Mohs micrographic surgery
MCC	Merkel cell carcinoma
MAC	Microcystic adnexal carcinoma
n	number
NCR	Netherlands Cancer Registry
NVDV	Nederlandse Vereniging voor Dermatologie en Venereologie
OR	Odds ratio
PALGA	Dutch nationwide network and registry of histopathology and cytopathology
PNI	Perineural invasion
PS	Plastic surgeon
RCT	Randomized clinical trial
SE	Standard excision
SD	Standard deviation
SR	Systematic review
Seb ca	Sebaceous carcinoma
TNM	Tumour, node and metastasis

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LIST OF PUBLICATIONS

in chronological order, including publications not included in this thesis

I.E. Deckers, **C.B. van Lee**, R.R. van den Bos, S. Koljenović, K. Munte. Mohs micrografische chirurgie als behandeling voor het dermatofibrosarcoma protuberans. NTvDV. 2013 Dec;23(11):654-50.

K. Munte, **C.B. van Lee**. Handboek dermato-oncologie, Hoofdstuk 3.5.2: Dermatofibrosarcoma protuberans. Dchg. 2015.

C.B. van Lee, R.R. van den Bos. Het optimaliseren van Mohs micrografische chirurgie door de revisie van Mohs coupes. NTvDV. 2015 Okt;25(9):463-65.

C.B. van Lee, B. Graafland, S. Koljenović, H.A.M. Neumann, K. Nasserinejad, T.E.C. Nijsten, R.R. van den Bos, K. Munte. Additional review of Mohs slides to optimize Mohs micrographic surgery. Br J Dermatol. 2015;173:123-27.

C.B. van Lee, E.E.F. Ip Vai Ching, K. Nasserinejad, H.A.M. Neumann, M.G.W. Bol, P.K. Dikrama, N.W.J. Kelleners-Smeets, S. Koljenović, K. Munte, V. Noordhoek Hegt, H.C. de Vijlder, T. Nijsten, R.R. van den Bos. Reliability of diagnosis from Mohs slides: interpersonal and intrapersonal agreement on basal cell carcinoma presence and histological subtype. Br J Dermatol. 2016;175:549-54.

C.B. van Lee, S.C. Flohil, J. Beisenherz, M.A.M. Mureau, L.I.H. Overbeek, T. Nijsten, R.R. van den Bos. Mohs micrographic surgery of rare cutaneous tumours. J Eur Acad Dermatol Venereol. 2017;31(8):1285-88.

K. Ramdas, **C. van Lee**, S. Beck, P. Bindels, V. Noordhoek Hegt, L. Pardo, S. Versnel, T. Nijsten, R. van den Bos. Differences in Rate of Complete Excision of Basal Cell Carcinoma by Dermatologists, Plastic Surgeons and General Practitioners: A Large Cross-Sectional Study. Dermatology. 2018;234:86-91.

C.B. van Lee, B.M. Roorda, M. Wakkee, Q. Voorham, A.L. Mooyaart, H.C. de Vijlder, T. Nijsten, R.R. van den Bos. Recurrence rates of cutaneous squamous cell carcinoma of the head and neck after Mohs micrographic surgery vs. standard excision: a retrospective cohort study. Br J Dermatol 2018 September. Epub ahead of print.

C. van Lee, W. Kan, S. Gran, A. Mooyaart, M. Mureau, H. Williams, R. Matin, R. van den Bos, L. Hollestein. Rates of re-excisions and recurrences of dermatofibrosarcoma protuberans in the Netherlands between 1989-2016. Accepted Acta Derm.

C.B. van Lee, N. Kouloubis, M. Wakkee, A. Parfenkova, R. Nellen, A. van Rengen, H.C. de Vijlder, L.C.C. Wijne, N. Kelleners-Smeets, T. Nijsten, R.R. van den Bos. Rate and characteristics of incompletely excised cutaneous squamous cell carcinoma: a large prospective study, systematic review and meta-analysis. Submitted.

PhD PORTFOLIO

PhD student: C.B. van Lee
Erasmus University Medical Center: Department of Dermatology
PhD period: January 2013 - December 2019
Promotor: prof. dr. T.E.C. Nijsten and prof. dr. H.A.M. Neumann
Supervisor: dr. R.R. van den Bos

PhD training	Year	Work-load (Hours/ECTS)
Courses		
Systematic literature search and EndNote, Erasmus MC	2013	24 hours
Integrity in science, Erasmus MC	2013	24 hours
Basic introduction course on SPSS, Erasmus MC	2013	24 hours
How to build a career in research, Erasmus MC	2013	8 hours
Biomedical English writing, Erasmus MC	2013	28 hours
Research management for PhD students, Erasmus MC	2013	16 hours
Open Clinica, Erasmus MC	2013	8 hours
Regulation and organization of research (BROK), Erasmus MC	2013	28 hours
Effective use of your voice, Erasmus MC	2014	4 hours
Storytelling, Erasmus MC	2014	4 hours
DOO Communication, Erasmus MC	2015	8 hours
DOO Teach the teacher, Erasmus MC	2016	8 hours
DOO Collaborating, Erasmus MC	2017	8 hours
DOO Medical Ethics, Erasmus MC	2018	8 hours
Presentation techniques, Janssen Academy Utrecht	2018	8 hours
Subtotal		208 hours
Oral presentations		
Is an additional review of Mohs slides by a pathologist needed? 34th ISDS, Dubrovnik, Croatia	2013	1 ECTS
Mohs micrografische chirurgie ook voor zeldzame tumoren. Dermato-oncologie congres, Erasmus MC, Rotterdam, The Netherlands	2014	1 ECTS
Mohs Micrographic Surgery Today. New technology for rapid resection margin assessment in Mohs micrographic surgery. EPIC, Rotterdam, The Netherlands	2014	1 ECTS
Hoe betrouwbaar is de beoordeling van Mohs coupes? Wetenschappelijke vergadering NVDV, Rotterdam, The Netherlands	2014	1 ECTS
Reliability of Mohs slides diagnosis. 24th EADV, Copenhagen, Denmark	2015	1 ECTS
Who should diagnose Mohs slides and the misinterpretations we make. 37th ISDS, Amsterdam, The Netherlands	2016	1 ECTS
Squamous cell carcinoma treated with Mohs micrographic surgery versus Excision, NVED, Lunteren, The Netherlands	2017	1 ECTS
Mohs for rare skin tumours. 26th EADV, Geneva, Switserland	2017	1 ECTS
EADV Review on dermato-oncology. Utrecht, The Netherlands	2017	1 ECTS
Mohs micrographic surgery for squamous cell carcinoma, IKNL, Leiden, The Netherlands	2018	1 ECTS
Subtotal		**10 ECTS**

PhD training	Year	Work-load (Hours/ECTS)
Poster presentations		
Peer review of Mohs slides to optimize Mohs surgery. XV WCCS, Edinburgh, United Kingdom	2014	1 ECTS
Mohs Surgery for Microcystic Adnexal Carcinoma. 23th EADV Congress, Amsterdam, The Netherlands	2014	1 ECTS
Subtotal		2 ECTS
Attendence of conferences		
De spaarparadox: sparen we te veel of juist te weinig? Nederlandse werkgroep hoofd-hals tumoren, Erasmus MC	2013	16 hours
Image Guided Surgery, Erasmus MC	2013	8 hours
Network your way through your career! PhD-day, Erasmus MC	2013	8 hours
Verleiding, Wetenschapsdag, Erasmus MC	2013	8 hours
Gezichtstransplantatie, Capita Selecta, Erasmus MC	2013	8 hours
Your PhD Profile for Success! PhD-day, Erasmus MC	2014	8 hours
Dermatologie 2nd PhD weekend, Erasmus MC	2014	16 hours
Dermatologie PhD weekend, Erasmus MC	2017	16 hours
Cells to surgery, Erasmus MC	2017	16 hours
PhD-day: Where your PhD can take you, Erasmus MC	2018	8 hours
Cursus mondpathologie, VuMC	2019	8 hours
Cells to surgery, Erasmus MC	2019	16 hours
Subtotal		136 hours
Teaching		
Dermatologic oncology and dermatologic surgery for residents, each three weeks	2016-2017	28 hours
Subtotal		28 hours
Committees		
Organizing SPA III congress, Spa, Belgium	2014	1 ECTS
Organizing Dermatologic oncology conference, Erasmus MC	2014	1 ECTS
Subtotal		2 ECTS
Other		
Supervising 4 master theses: B. Graafland, J. Beisenherz, E. Ip Vai Ching, B. Roorda.	2014-2016	4 ECTS
Research meetings, Department of Dermatologie, Erasmus MC	2013-2014	1 ECTS
Journal clubs, Department of Dermatology, Erasmus MC	2013-2019	1 ECTS
Skintermezzo meetings, Department of Dermatology, Erasmus MC	2012-2019	1 ECTS
Development of the protocol for Mohs micrographic surgery procedure and training, Department of Dermatology, Erasmus MC	2013	1 ECTS
Development of the informative movie for patients about Mohs micrographic surgery, Department of Dermatology, Erasmus MC	2013	1 ECTS
Subtotal		9 ECTS
Total:		**36 ECTS**

CURRICULUM VITAE

Charlotte Barbara (Lotte) van Lee was born on December the 7th 1985 in Groningen, The Netherlands. After completing pre-university secondary education (VWO) at the Cals College in Nieuwegein, van Lee started her medical training at University Medical Center Groningen (2005). During her studies, van Lee participated in the organizing committee of the International Student Congress of Medical Sciences (ISCOMS). During her internship in the East of the Netherlands (ZGT Almelo), van Lee got excited about Dermatology and the surgical treatment of skin cancer specifically (2009). For her master thesis, van Lee conducted a study on Mohs micrographic surgery at the Erasmus University Medical Center and Mohs Klinieken Dordrecht under supervision of drs. Munte (2011). After obtaining her Medical Degree, van Lee started as ANIOS Mohs micrographic surgery at the Department of Dermatology, Erasmus University Medical Center. Under supervision of prof. Neumann, drs. Munte and dr. Koljenovic, van Lee developed her surgical and histological skills (2012). After a year of many clinical lessons learnt, van Lee started to conduct clinical studies to improve the surgical treatment of skin tumours guided by prof. Neumann, prof. Nijsten and dr. van den Bos at the Department of Dermatology, Erasmus University Medical Center. While continuing her research activities, van Lee started her residency in Dermatology at Erasmus University Medical Center in 2015 (residency program director dr. Thio, mr. dr. De Haas and dr. van Montfrans). One and a half year of her dermatology training was spent at Franciscus Gasthuis in Rotterdam (2016-2017, residency program directors dr. van Praag and dr. Loots). In 2007 van Lee started a relationship and she became a mother of three children between 2015 and 2017.

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