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 ≈ 87), followed by appendageal tumours (n ≈79), and neural tumours (n ≈ 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.

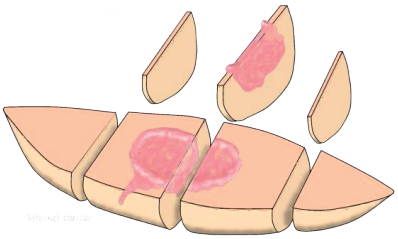

Figure 1. Standard excision with bread loaf sectioning method and missed incompletely excised tumour cells.

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.

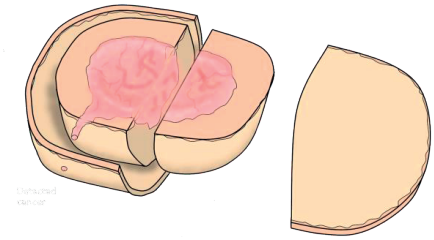

Figure 2. Sectioning method of Mohs micrographic surgery with detected incompletely excised tumour cells.

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-

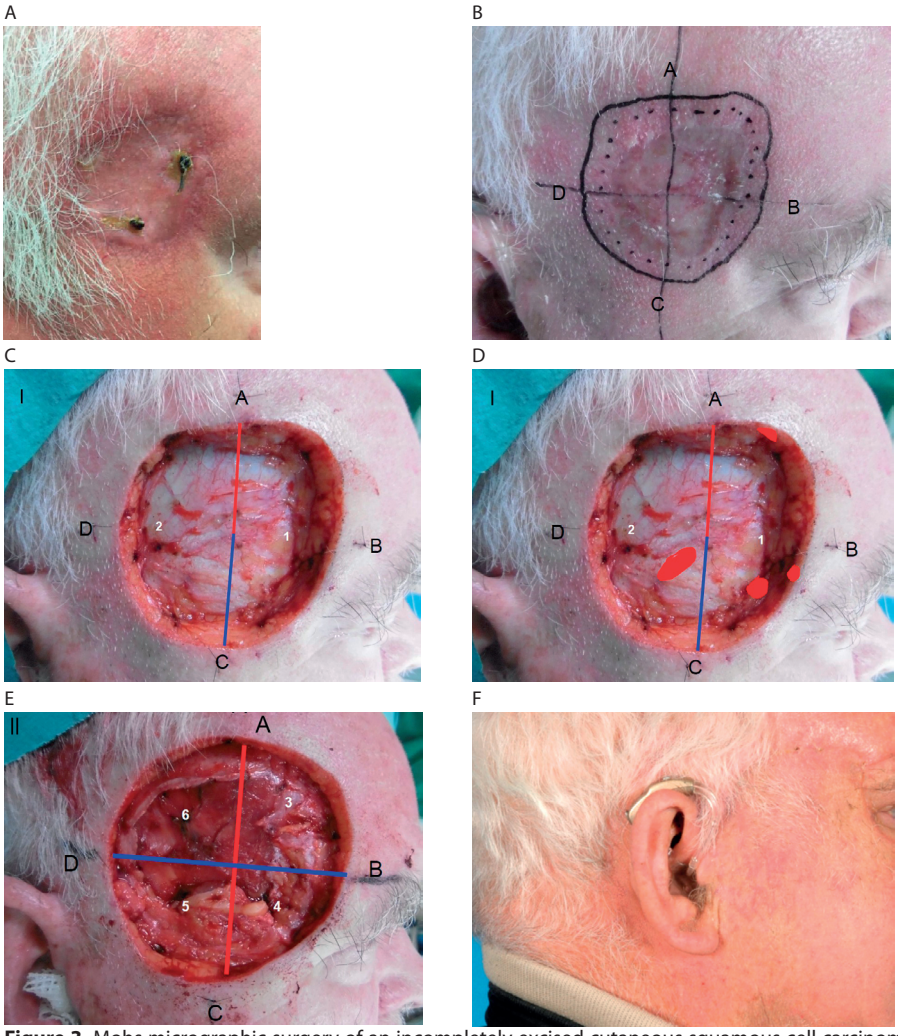

Figure 3. Mohs micrographic surgery of an incompletely excised cutaneous squamous cell carcinoma. A. Pre-operative clinical appearance. B. Demarcation of the first stage. C. Defect after excision of the first stage. D. Demarcation of the tumour cells corresponding to the fresh frozen slides. E. Final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