Surgical treatment of non-melanoma skin cancer of the head and neck: expanding reconstructive options
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Chapter 1

General Introduction
EPIDEMIOLOGY AND ETIOLOGY OF NON-MELANOMA SKIN CANCER

Skin cancer is the most common malignancy in the Caucasian population with basal cell carcinoma (BCC) representing 75% and squamous cell carcinoma (SCC) 20% of all skin cancer cases. The remaining 5% include melanomas and other rare skin cancers such as skin adnex tumors, Merkel cell carcinoma and dermatofibrosarcoma protubers. This thesis deals with surgical treatment of BCCs and SCCs (together named non-melanoma skin cancer (NMSC)) and a number of reconstructive techniques.

In general, the risk for development of NMSC is associated with UV solar radiation exposure and the patient’s skin type. Fair-skinned individuals who frequently burn and never tan (Fitzpatrick skin types I) are at a much higher risk for developing NMSC than their darker-skinned, rarely burning individuals.

BCCs are more linked to intensive intermittent exposure resulting in sunburn whereas SCCs are predominantly associated with chronic long-term sun exposure. In both cancers, sun exposure in early life appears to be significant for the development of skin cancer later in life, sun exposure therefore is cumulative with development of skin cancers with increasing age. Caucasian individuals living in continents with a thinner ozone layer, such as Australia, have a higher risk for developing NMSC. Since they are exposed to a larger amount of damaging UV radiation than individuals living in the northern hemisphere.

The head and neck is the most sun-exposed area of the human body. As a consequence, eighty per cent of all NMSC occur in this region. UV exposure through recreational tanning, sun beds and therapeutic light units also increases the risk of skin cancer. Psoriasis treatment with oral psoralen and ultraviolet-A light (PUVA) is also related to increased frequency of BCC and SCC.

Over the last decades there has been a significant rise in the incidence of NMSC. For the Netherlands it is expected that there will be an increase of 80% in the total number of skin cancer patients over a 15-year period (from 20,654 in 2000 to 37,342 in 2015). For SCC there will be an increase among older males and females (aged ≥ 65) of 79% and for younger females (aged 35-64) of 93%. BCC is expected to increase by 66% in males, and 94% in females in the group aged 15-64. Thus most of the increase is to be found in women especially in sites other than the head and neck such as the trunk and legs. This is probably explained by intermittent exposure to UV radiation, as a result of the increasing popularity of sunbathing and the wearing of bikinis since the 1960’s. For BCC, a more recent study showed the age-adjusted incidence rates increased approximately threefold from 40 to 148 per 100,000 in males and from 34 to 141 in females. The lifetime risk of BCC was 1 in 5-6 for Dutch citizens. Disease prevalence in the Netherlands was 1.4% and almost four times higher than this (5.4%) in the oldest age group (aged >65). Predictions of future trends showed no signs of plateau in the number of cases. Therefore skin cancer is a significant public health problem in the Netherlands.

Physical and chemical exposure may also be associated with development of NMSC. Ionizing radiation has a threefold higher risk for developing NMSC and appears to be dose dependent, with larger fractioned doses (> 12-15
Grays) inducing tumor formation. Most of these NMSCs develop four to five decades after the initial irradiation. NMSCs, predominantly SCC, are also associated with chemical exposure (Arsenic, Tar, Soot, Tobacco, Asphalt, Mineral Oil, Polycyclic Aromatic Hydrocarbons, and Nitrogen Mustard) and develop many years after the initial exposure.\textsuperscript{17,18}

Patients with iatrogenic immune deficiencies such as solid organ transplant recipients are also known for their risk of developing NMSC. When compared to the general population, these patients are 40 to 250 times more prone to develop SCC and five to ten times more likely to develop BCC.\textsuperscript{19} Although a diminished immune surveillance is likely to occur after immunosuppression by Cyclosporine or Azathioprine, a direct carcinogenic effect of these immunosuppressives cannot be completely ruled out.\textsuperscript{19} Although the metastatic potential of cutaneous SCC is low, it is significantly higher in patients with solid organ transplantation.\textsuperscript{21}

Infection with oncogenic strains of HPV, such as 16 or 18, is also associated with SCCs.\textsuperscript{22} These lesions commonly arise in HIV-infected individuals and tend to develop in the perianal and anogenital regions. SCCs can also arise within scars and chronic wounds.\textsuperscript{1,22} The Marjolin’s ulcer, a cutaneous squamous cell carcinoma developing in an old scar, can have a latency period of as long as 30 years.\textsuperscript{1}

**PATHOGENESIS**

**Basal cell carcinoma**

Most BCCs are aneuploid and loss of heterezygosity (LOH) analysis has repeatedly demonstrated allelic loss of chromosome 9q in affected tumor cells.\textsuperscript{23} In approximately 69% of cases patched 1gene (PTCH) mutations, located on chromosome 9q, have been found. In 36% of BCCs allelic losses are found at 6q23-q27 loci, suggesting the presence of an additional tumor suppressor gene which remains unidentified. Genetic pathway mutations in BCC result in uncontrolled Hedgehog (Hh) signalling, which is required for proliferation of hair follicle epithelium.\textsuperscript{24-26} This may explain why most BCCs primarily develop in pilosebaceous skin units, which are mainly found in the head and neck, with the nose as one of the most affected sites. There is no known precursor lesion to BCC, such as actinic keratosis in SCC.

Nevoid basal cell carcinoma syndrome (NBCCS, basal cell naevus syndrome, Gorlin syndrome) is an autosomal dominant disorder, also caused by the occurrence of mutations in the PTCH gene.\textsuperscript{27} It is characterized by multiple basal cell carcinomas across the whole skin, keratocysts of the jaws, palmar and plantar pits, cerebral ectopic calcification and several skeletal anomalies. Occasionally, patients with NBCCS develop other neoplasms, particularly medulloblastomas and ovarian fibromas, indicating that the PTCH gene is a tumor-suppressor gene affecting many organ systems.\textsuperscript{27}

Xeroderma pigmentosum is a rare disorder transmitted in an autosomal recessive manner, characterized by photosensitivity, pigment changes, premature skin aging, and malignant tumor development.\textsuperscript{28} These manifestations are due to a cellular hypersensitivity to UV radiation resulting from a defect in DNA repair. Other genetic syndromes, associated with multiple NMSCs, are oculocutaneous albinism, epidermodyplasia verruciformis and dystrophic epidermiolysis bullosa.\textsuperscript{27,29}
Actinic keratosis and squamous cell carcinoma

UV-induced p53 gene mutation is the most common genetic abnormality found in actinic keratosis and SCCs. It is believed that cutaneous SCCs develop through a multistep process and accumulating genetic changes in the epidermis leading to genetic instability. The progressive genetic changes are clinically represented by the evolution of precancerous actinic keratosis to SCC in situ, followed by invasive SCC, and finally resulting in metastatic SCC. Actinic keratosis histologically demonstrates mild-to-severe squamous cell dysplasia within basal layers of the epidermis. Severe squamous cell dysplasia, involving the full thickness of the epidermis, is synonymous with SCC in situ, also known as Bowen’s disease. The risk of an individual actinic keratosis developing into invasive SCC is estimated to be less than 0.1% per year.

CLINICAL FEATURES OF NON-MELANOMA SKIN CANCER

Basal Cell Carcinoma

BCCs are characterized by different clinical and histopathological phenotypes, with different prognostic impact. For practical clinical purposes a distinction is made between non-aggressive (nodular and superficial BCCs) and aggressive (e.g. infiltrating, micro-nodular, sclerosing BCCs) characteristics. Progression to metastatic disease is extremely rare but if left untreated BCCs can enlarge to several centimetres and become locally destructive to surrounding tissue, including bone and cartilage. The clinical course of BCC is unpredictable; it may remain small for years with little tendency to grow, or it may grow rapidly or proceed by successive spurts of extension of tumor and partial regression.

Superficial BCCs assume a primarily horizontal growth pattern and present as thin, erythematous plaques with variable amounts of telangiectasias (Figure 1). A large proportion of these superficial BCCs occur on the trunk, extremities and head and neck region. Over time superficial BCCs can become more invasive and demonstrate increasing induration, surface ulceration and nodule formation.

Figure 1. Superficial BCC, a thin erythematous plaque.

Nodular BCCs are the most common variant comprising 60% of all BCCs. They occur predominantly on the face and present as waxy, translucent, raised papules or nodules with intralesional telangiectasias (Figure 2). The center of the lesion often ulcerates as the tumor enlarges, with a rolled appearance at the tumor margin. Nodular BCCs sometimes contain blue, brown, or black pigment and are referred to as pigmented BCCs.
Infiltrating BCCs present as ill-defined, indurated red or white plaques that can be slightly elevated or depressed and atrophic (Figure 3). They often have overlying teleangectasias and can be mistaken for scars with contracted areas of skin. These lesions frequently have finger-like, subclinical extensions of tumor cells that exceed beyond the clinically visible borders of the lesion. Other BCC subtypes, which often exhibit subclinical extension and present in a similar subtle clinical fashion, include micronodular, sclerosing, and morpheaform BCCs. Some of these BCCs can show perineural invasion, finger-like tumor spread along the small nerves, and might be painful.

Certain BCCs can demonstrate features of true BCC as well as squamous cell carcinoma. These tumors are termed basosquamous carcinomas. Some of these tumors may represent the collision of a BCC and a SCC; however, others are likely to be BCCs demonstrating significant squamous metaplasia with metastatic capacity.

Actinic Keratosis
Actinic keratosis occurs on body surfaces with prolonged and continuous sun exposure, i.e. head, neck, and upper extremities. Within these sites, they are most frequently located on the helix of the ears, forehead, nasal bridge, cheeks, dorsal aspect of hands, and extensor forearms. The primary lesion is an erythematous papule or plaque with varying degrees of rough overlying white or yellow scale. (Figure 4) Their size ranges from a few millimetres to several centimetres in diameter. Sometimes advanced lesions can form thick cornified columns of scale that protrude the skin, leading to a “Cutaneous horn”. A biopsy specimen should always be obtained from cutaneous horns, because approximately 15% of these demonstrate invasive SCC at their bases. A clinical variant of actinic
keratosis is actinic cheilitis, which occurs on the sun-damaged skin of the lower lip.

**Squamous Cell Carcinoma in situ**
**Bowen’s disease**
SCC in situ, also known as Bowen’s disease, typically presents as an erythematous, scaly, slightly elevated plaque occurring on sun-damaged skin. These lesions can arise de novo or from pre-existing actinic keratosis. SCC in situ is histologically differentiated from actinic keratosis by the presence of severe squamous cell dysplasia involving the full thickness of the epidermis.

**Squamous Cell Carcinoma**
Invasive SCCs present as erythematous, keratotic papules, plaques or nodules occurring on sun-damaged skin. Often, there is a history of intermittent bleeding (Figure 4). The growth rate differs from slow to rapid depending on the degree of differentiation.

SCCs have been histologically categorized into two major groups: well-differentiated versus moderately, poorly or undifferentiated subtypes. The latter are associated with a higher risk of recurrence and metastasis. Additional aggressive, high-risk subtypes include adenoid or acantholytic, adenosquamous, and desmoplastic SCCs. Deeper invasion of SCC into the dermis and subcutaneous fat, measured either in millimetres or by Clark level, as in Melanoma, also correlates with an increased risk of recurrence and metastasis, particularly if depth of the lesions is > 4mm. Perineural growth, more frequently associated with SCC, also significantly increases the risk of loco-regional recurrence and distant metastasis.

More advanced lesions can become indurated, hyperkeratotic, and sometimes ulcerative. The metastasizing capacity of cutaneous SCC is low, concerning only 5% of cases, but for those involving ears and lips, this figure rises to 9%-14%. SCC of the forehead, cheek, eyelids, and ears usually metastasize to parotid lymph nodes, while lip, nasal and perioral tumors metastasize to levels I-II of the neck.

**Keratoacanthoma**
Keratoacanthomas present as a rapidly enlarging nodule with a central crater filled with keratinaceous material (Figure 5). They generally occur on sun-exposed skin and typically present as solitary lesions. As there are no clinical or histological criteria to classify a potential keratoacanthoma as a benign tumor that might spontaneously regress or as an SCC with metastatic potential it is often necessary to completely excise the lesion. If in the history of the patient,
the lesion has diminished in size or at least has stopped growing, a conservative approach can be chosen but careful follow-up is essential.

DIAGNOSIS

Although many NMSCs can often be diagnosed clinically by their macroscopic appearance, a properly performed biopsy is a prerequisite to confirm the diagnosis and to guide management. The most commonly used techniques are shave and punch biopsies. Shave biopsies only shave off the upper dermis and are suitable for histological examination of exophytic parts of skin tumors, especially in diagnostic processing of atypical skin tumors. This technique does not lead to extra scar formation and leaves the deep and lateral margins of the tumor intact. However, histological examination of shave biopsies has its limitations and is not useful for flat skin lesions. In these cases, punch biopsies allow for better histological judgement, because deeper layers such as the reticular dermis and subcutaneous fat are included.

TREATMENT OF NMSC

A number of prognostic factors determine the chance of cure (Table 1). The histological features of BCC and SCC have already been discussed in the previous paragraphs.

Location

NMSCs located in the head and neck region are generally more likely to recur than those occurring on the trunk and extremities. The sites at highest risk for recurrence are collectively referred to as the “H-zone” of the face (Figure 6). These areas include the central face, eyelids, eyebrows, periorbital skin, nose, lips, preauricular and post-auricular skin.

Size and border

Tumor size in conjunction with location also affects the risk of recurrence. In general, any NMSC larger than 2 cm in diameter has a higher
Table 1. Clinical and histological findings associated with NMSC recurrence.

<table>
<thead>
<tr>
<th>Clinical Parameters</th>
<th>Low-risk-features</th>
<th>High-risk features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location and size</td>
<td>-Trunk/extremities &lt; 20 mm</td>
<td>-Trunk/extremities &gt; 20 mm</td>
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<td></td>
<td>-Cheeks, forehead, scalp, neck &lt; 10 mm</td>
<td>-Cheeks, forehead, scalp, neck &gt; 10 mm</td>
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<tr>
<td>Borders</td>
<td>Well defined</td>
<td>Poorly defined</td>
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<td>Immunosuppression</td>
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<td>Present</td>
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<tr>
<td>Failure of previous treatment</td>
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<td>Yes</td>
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<tr>
<td>Site of prior radiation *</td>
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<tr>
<td>Site of chronic inflammation*</td>
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<td>Yes</td>
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<tr>
<td>Rapidly growing tumor*</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Neurologic symptoms*</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Histologic Parameters</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Perineural or vascular* involvement</td>
<td>Absent</td>
<td>Present</td>
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<tr>
<td>Degree of differentiation *</td>
<td>Well-differentiated</td>
<td>Moderately or poorly differentiated</td>
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<tr>
<td>Adenoid, adenosquameus, or Desmoplastic subtypes*</td>
<td>Absent</td>
<td>Present</td>
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<tr>
<td>Depth: Clark level or thickness *</td>
<td>I, II, III, or &lt; 4 mm</td>
<td>IV, V, or ≥ 4 mm</td>
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<tr>
<td>BCC subtype</td>
<td>Nodular, superficial</td>
<td>Micronodular, infiltrating, sclerosing, morpheaform</td>
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</table>

* Applies only to SCC
rate of recurrence regardless of location. For SCC > 2 cm the recurrence rate doubles and the metastatic rate triples if compared to lesions less than 2 cm. NMSCs with ill-defined clinical borders are also more likely to recur.

Recurrent tumors
Recurrent tumors often represent an aggressive biology and indistinct margins, associated with significant subclinical growth, contribute to a therapeutic problem. Generally speaking, the cure rate of a given standard modality drops from 90% to 50% if the same treatment modality of the primary tumor is applied to the recurrence. It should be noted that even with Mohs’ micrographic surgery the entire scar including flap or graft, as well as a deep margin of original resection should be reexcised, because tumors tend to move into previously dissected planes and possible nests of discontinuous tumor may present after previous treatment.

Treatment Guidelines
In international literature several evidence-based guidelines have been published for treatment of NMSC (Table 2-5), with an emphasis on cure while achieving maximum preservation of function and cosmesis. However, all treatment decisions should be geared to individual patient characteristics and allow for patient preference.

Surgery
Standard surgical excision is effective for many primary NMSCs. Complete tumor clearance is confirmed by postoperative histopathologic assessment of the margins. Because NMSCs can have subclinical extension of tumor, excision requires removal of the clinically apparent visible tumor as well as a small margin of normal surrounding skin. Studies on treatment safety margins of NMSC provide clinical, albeit vague, recommendations, ranging from 2-10 mm. The magnitude of subclinical outgrowth in BCC is largely related to histologic type and size of tumor. Suggestions on treatment margins can be based on these specific characteristics. For example, a case of small primary nodular BCC with a diameter of 10 mm or less requires a 3 mm margin to include all tumor extensions in 80% of cases. Infiltrating BCCs are, however, notoriously deceptive, sending out subclinical extensions of 7 mm or more beyond clinical estimated borders. Recurrent tumors need notably larger margins than primary tumors. Most SCCs in high-risk locations, such as scalp, ears, eyelids, nose and lips need at least a 6 mm margin for excision. It is recommended that excision of all SCCs should include subcutaneous fat, because at least 30% invade to this level.

NMSCs can be treated surgically by either conventional excision (CE) or Mohs micrographic surgery (MMS). MMS is a surgical technique for removing NMSCs and other cutaneous carcinomas that allows for precise microscopic margin control by using horizontal frozen sections. A study comparing cure rates of CE and MMS in a randomized controlled fashion showed no significant difference in recurrence of primary BCCs between the treatment groups (2.5% in MMS versus 4.1% in CE). However, significantly fewer recurrences for facial recurrent BCC after MMS (2.4%) versus CE (12.1%) after five years follow-up were observed. For all NMSCs, MMS has been shown to have superior cure rates when compared to curettage and electrodessication, cryosurgery, topical
therapies and radiotherapy. MMS affords maximal normal tissue conservation and has been shown to be cost effective. MMS is primarily indicated for high risk NMSCs, as is also shown in the guidelines for NMSC by the American Academy of Dermatologists.

Curettage and Electrodessication
Curettage and electrodessication is a technique by which tumor is removed using a sharp curette followed by destruction on the base of the lesion with electrodessication. Successful outcomes rely heavily on careful selection of appropriate lesions (ideally small nodular or superficial BCCs), as well as the skill and experience of the treating physician. Variations in technique include the use of different types of curette and the number of treatment cycles. A literature review of all studies published since 1947 suggested an overall five-year cure rate of 92.3% for selected primary BCC (only small nodular and superficial BCCs). Curettage and electrodessication is

Table 2. Primary basal cell carcinoma (BCC): influence of tumor type, size (large = > 2 cm) and site on the selection treatment. (Adapted from British association of dermatologists, Telfer 2008).

<table>
<thead>
<tr>
<th>BCC type: histology, size and site</th>
<th>PDT</th>
<th>Topical imiquimod</th>
<th>Curettage and cautery</th>
<th>Radiation therapy</th>
<th>Cryosurgery</th>
<th>Excision</th>
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<td>Superficial, small and low-risk site</td>
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PDT = photodynamic therapy; *** = probable treatment of choice; ** = generally good choice; * = generally fair choice; ? = reasonable, but not often needed; – = generally poor choice; X = probably should not be used.
Table 3. Recurrent basal cell carcinoma (BCC): influence of tumor type, size (large = > 2 cm) and site on the selection treatment (Adapted from Britisch Association of Dermatologists, Telfer 2008).

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much less successful for recurrent BCC with an overall five-year cure rate of 60%.72

**Cryosurgery**

Liquid nitrogen cryosurgery uses the effect of extreme cold (tissue temperatures of -50 to -60 °C) to realize deep destruction of the tumor and surrounding tissues. Individual treatment techniques vary considerably, with both open and closed spray techniques and single or multiple cycles of freezing.73,74 The success of cryosurgery relies upon careful selection of appropriate lesions and individual experience.75 Cryosurgery can be used for treatment of low-risk BCC.76,77 Several retrospective studies with a five years’ follow-up showed recurrence rates for primary BCC of 2-18%.73,74,78 In a prospective randomized trial comparing cryosurgery to photodynamic therapy including 88 patients (non-aggressive BCCs; not on the nose) the recurrence rates were respectively 15 and 25%.79

Cryosurgery wounds generally heal with
Table 4  Management of local low-risk SCC, Adapted from the National Comprehensive Cancer Network, Basal and squamous cell skin cancers clinical practice guidelines in oncology (2010)

Local Low-risk SCC

- Curettage and electrodessication; If fat reached, surgical excision must be performed
- Excision with POMA: If lesion can be excised with 4-6 mm clinical margins and secondary intention, side-to-side repair, or skin graft
- Radiotherapy for non-surgical candidates

Follow-up:
- Full skin & regional lymph node exam every 3-6 months for 2 years, then every 6-12 months for 3 years, then annually for life

Recurrence
- Local: Follow treatment high risk SCC
- Distant metastasis: Multidisciplinary tumor board consult and therapy

Mohs or resection with CCPDMA or Re-excision with POMA for area L¹ or Radiotherapy

Margins

POMA = postoperative margin assessment
CCPDMA = complete circumferential peripheral and deep margin assessment with frozen or permanent section

1 L-area = trunk and extremities
Table 5. Management of local high-risk SCC. Adapted from the National Comprehensive Cancer Network, Basal and squamous cell skin cancers clinical practice guidelines in oncology. (2010)

1. any high-risk factor places the patient in the high-risk category
2. for complicated cases, consider multidisciplinary tumor board consultation
3. L-area = trunk and extremities

Local High-risk¹,² SCC

- Excision with POMA:
  Lesions ≥ 20 mm in area L,² with no other risk factors, if can be excised with 10 mm clinical margins + primary repair
- Mohs or resection with CCPDMA
- Radiotherapy for non-surgical candidates

Margins

+ → Mohs or resection with CCPDMA or Radiotherapy
- → Radiotherapy

If extensive perineural or large-nerve involvement, recommend adjuvant RT

Follow-up:
Full skin & regional lymph node exam every 3-6 months for 2 years, then every 6-12 months for 3 years, then annually for life

POMA = postoperative margin assessment
CCPDMA = complete circumferential peripheral and deep margin assessment with frozen or permanent section
minimal tissue contraction, resulting in good cosmetic results.\textsuperscript{75,76} However, when comparing the cosmetic results of cryosurgery with complete excisions of BCC in the head and neck, excision generally yields superior cosmetic results.\textsuperscript{80}

\textit{Imiquimod and fluorouracil}

Imiquimod is an immune-response modifier, which acts through the release of cytokines and chemokines, thereby promoting a cell-mediated immune response, which generates an anti-viral and anti-tumoral effect. Imiquimod is locally applied for five days a week during a six week period. Fluorouracil is a cytostatic drug and usually applied twice a day for six weeks. In a recent systemic review\textsuperscript{81} clearance rates of Imiquimod ranged from 43\% to 100\% for superficial BCC, 42\% to 100\% for nodular BCC, 56\% to 63\% for infiltrative BCC, 73\% to 88\% for SCC in situ, and 71\% for invasive SCC.

For Fluorouracil the following clearance rates were established: 90\% for superficial BCC and 27\% to 85\% for SCC in situ.\textsuperscript{81} Up to 100\% and 97\% of patients applying Imiquimod and Fluorouracil, respectively, experienced at least 1 adverse event like; erythema, pruritus, and pain ranging from mild to severe. Based on these experiences, the use of Imiquimod or fluorouracil should be limited to patients with superficial BCCs in low-risk areas.

\textit{Photodynamic therapy}

Photodynamic therapy is a topical therapy that involves the application of a photosensitizing agent [aminolaevulinic acid (ALA) or methylaminovulinic (MAL)] to a lesion and surrounding skin followed by illumination with a specific wavelength. Topical PDT is effective in the treatment of actinic keratoses, Bowen’s disease, superficial and thin nodular basal cell carcinomas, with good cosmetic results.\textsuperscript{82} PDT offers an advantage in the treatment of large, extensive and multiple superficial BCCs. A multicenter, randomized study compared MAL-PDT (102 lesions) with cryosurgery (98 lesions) in primary superficial BCCs. The four-year recurrence rate was not significantly different: 22\% after MAL-PDT vs. 19\% after cryotherapy.\textsuperscript{82} In another study 91\% of 131 superficial BCCs cleared following MAL-PDT, with 9\% of these tumors recurring during 35 months of follow-up.\textsuperscript{83} In the same study nodular BCCs were cleared in 89\% of 168 lesions. Photodynamic therapy is mainly useful for numerous actinic keratoses occurring on diffuse sun-damaged skin,\textsuperscript{84} particularly when it remains difficult to distinguish macroscopically the individual actinic keratosis from benign sun-damaged skin.

\textit{Radiotherapy (RT)}

RT is a complex mix of different techniques including superficial RT (generated at up to 170kv), which is suitable for lesions up to 6 mm in depth, electron beam therapy (generated at higher energies), which penetrates into the deeper tissues, and brachytherapy, which is useful for lesions arising on curved surfaces. Poor long-term cosmetic results, consisting of depigmentation and radiation-induced teleangiectasias, which were once a significant problem are much less likely to occur with the use of modern tailored RT techniques.

Fractioned treatment regimes (which repeatedly exploit the difference in radio sensitivity between malignant and normal tissues) gener-
ally produce superior cosmetic results compared with single-fraction treatment, although this obviously requires multiple hospital visits. All RT treatments are a careful compromise between the likelihood of tumor destruction and an acceptable risk of radionecrosis. Different anatomical areas have different RT tolerances, with the head and neck generally tolerating RT well. However, certain areas such as the eyelids can be difficult to treat. The dorsum of the nose, where thin skin overlies bone, is often subjected to repeated minor trauma from spectacles and therefore at higher risk of developing radionecrosis.

Review articles have reported overall five-year cure rates following RT of 91.3\%53 for primary BCC and 90.2\% for recurrent BCC.60 Other studies suggest long-term (> four year) local control rates of 84\%85, 86\%86, 88\%87, 92.5\%88 and 96\%89 in BCCs.

Attempts have been made to compare RT with other treatment modalities in a randomized fashion. Surgical excision (91\% with frozen section margin control) of 174 primary facial BCCs (< 4 cm in diameter) has been compared with RT (mix of interstitial brachytherapy, contact therapy and conventional RT) for 173 lesions.88 The four-year recurrence rates were 0.7\% for surgery and 7.5\% for RT. Cosmetic outcome at four years was significantly superior following surgery (good cosmesis in 79\%) compared to RT (good cosmesis in 40\%) which led to altered pigmentation and teleangiectasia in over 65\% of RT patients, and radiodystrophy in 41\%.90 It has to be mentioned that this study refers to rather old radiation strategies, which harbour a higher risk for radiation damage than the modern fractionation techniques.

RT is an effective option in the treatment of primary BCCs and SCCs, as well as recurrent BCCs and SCCs after surgery,91 or as adjuvant therapy. It is probably the treatment of choice for high-risk disease in patients who are unwilling or unable to tolerate surgery for cosmetic reasons.91,92 However, when looking at the literature, it is clear that the various results are difficult to compare.

**FACIAL RECONSTRUCTION**

When reconstructing defects of the face with local skin flaps, it is important for the surgeon to consider the anatomical and physical properties of the skin (skin biomechanics) along with neurovascular and patient factors, in order to achieve an optimal cosmetic and functional result.

**Anatomy of the skin**

Many characteristics of the human skin (texture, thickness, and content of hair follicles and sebaceous glands) appear highly variable both inter- and intra-individually, varying from one anatomic region to the other. Skin may be divided into smooth, non-hair-bearing (glabrous) and hair-bearing (nonglabrous) areas, but is practically always hair-bearing. A complex organ system that is essential for all forms of mammalian life, skin may be viewed as a double-layered sheath, cushioned by the underlying subcutaneous fat, covering the entire surface of the body.

The outer layer of skin, known as the epidermis, is separated from the inner layer or dermis, by the basement membrane zone. The epidermis is stratified squamous epithelium that varies greatly in depth, ranging from the thick skin of the scalp to the delicate skin of the eyelid, (0.04
mm thickness), which is the thinnest skin of the body. The dermis is attached to the subcutaneous fat and underlying musculature by fibrous insertions. The dermis is primarily composed of connective tissue and contains important structures; such as epidermal appendages (hair follicles, sebaceous glands, and sweat glands), nerves, blood vessels, and immunologic cells (Figure 7).

Figure 7. Cross section of the skin; epidermis, dermis containing hair follicle, sebaceous gland, sweat gland, blood vessels and nerves.

Aesthetic (sub)units of the face
The concept of facial aesthetic units and sub-units, and the borders that separate them, is important when designing flaps for facial reconstruction. The face can be divided into specific areas or aesthetic units, which are covered by skin representing common characteristics (Figure 8). These skin characteristics include thickness, quantity of subcutaneous fat, degree of adherence to underlying fascia, color, and texture and hair growth. These facial units are separated from each other by ridges or valleys in the skin created by the facial skeleton or musculature. These ridges and valleys are known as aesthetic borders and are identified by facial landmarks including eyebrows, melolabial creases, mentol crease, philtrum crest, vermilion borders, and anterior hairline. Aesthetic units and their borders provide form, character, and individual uniqueness to the face. Some aesthetic units are subdivided into subunits and on the nose, lip and ear in particular division into subunits based on its complex topography can be discerned.

The preferred flap is frequently one that can be designed within the same aesthetic region as that containing the primary defect. Scars are best camouflaged by placing incisions along aesthetic borders. When a defect involves two or more aesthetic units, it is usually preferred to use separate repairs for each unit. Where 50% or more of a nasal sub-unit is involved, excision of the entire unit will improve the cosmetic result, as this will enable the surgeon to position the scars within the various boundary and function lines.93,94

Skin biomechanics
The skin has three unique physical properties, which have to be taken into account when reconstructing defects, i.e. nonlinearity, viscoelasticity and anisotrophy.
Nonlinearity
This mechanical skin property means that skin stretch differs depending on how much force is applied and that the maximal skin stretch is individually determined. Increasing amounts of pressure are required to further deform the skin.\(^9\) This represents a nonlinear relationship, which can be demonstrated with the stress-strain curve (Figure 9).\(^9\) This curve can be divided into three separate regions: 1) an initial flat region: little force causes large skin stretch; 2) a transition region: large force results in minimal increase; and 3) a terminal region: only little extension of skin despite great increases in applied force.

As one might expect, the mechanical properties of skin show a marked age dependency. Loss of elastic fibers occurs with age, altering the shape of the stress-strain curve.\(^9\) Degeneration of the elastin network leads to a progressive loss in the elastic recovery of skin. As a result, aged skin deforms under its own weight, modifying region 1 of the stress-strain curve. Region 3 of deformation is unchanged suggesting that the stiffness of collagen does not change with age.

Viscoelasticity
One of the viscoelastic skin properties is stress relaxation. If a constant force is applied over a period of time to stretch the skin to a given length while maintaining that length, this will subsequently lead to a decrease of skin tension.

Another viscoelastic property of the skin is creep. Creep occurs when an increase in skin length is noted over time, when a certain tension is applied to a segment of skin. This property is employed when using tissue expanders and is due to numerous factors such as collagen re-alignment, tissue dehydration and migration of tissue.

Stress relaxation and creep are interrelated. If a skin flap is closed under excessive tension, a certain amount of relaxation occurs as the tissue creeps. Stress relaxation allows large lesions in elastic regions to be removed with serial excision. It also accounts for the improved vascularity observed in the first 24 hours of flaps closed under tension.

Anisotropy
This term refers to the fact that the mechanical properties of the skin vary with direction of closure. This property comes into play when surgeons are designing their incisions for defect closures. There is a wide variation in facial skin tension among the different anatomical units. For example the skin on the eyelids and cheek has much lower tension than the skin of fore-
head and nose. However, at any given point, the skin is under tension in every direction. This tension is continuously present and is modified by muscle action. This tension is responsible for the separation of the edges of a wound. The relaxed skin lines (RSTLs) are a series of imaginary facial lines, along which the skin has the least amount of tension for closure (Figure 10). These lines are usually not visible at rest, but can be visualized by the furrows occurring when pinching the skin together. Incisions placed parallel to these lines heal without stress or tension on the wound closure. A wound following these lines remains narrow, but if it is made perpendicular to the RSTLs, the edges may begin to widen or gap.

Another series of lines, which are important in the planning of incisions, are the lines of maximal extensibility (LME), which run perpendicular to the RSTLs. Extensibility is defined as the lengthening of the skin under tension, caused by stretching of the elastic fibers in the skin. This extensibility varies depending on the direction in which the tension is applied. The tension in the wound is smallest in the plane parallel to the LME, which allows for the largest amount of skin stretch at the widest area of the defect. Both lines, RSTL and LME, are important when recruiting adjacent tissues to close wound defects. The tension on the skin flap used for reconstruction is an essential matter for consideration because excessive tension may compromise the blood supply in the distal portion of the flap. Furthermore, the orientation of a wound has a direct correlation to the scar appearance. The defect of fusiform excisions should be closed in the direction of the LME, so that the scar or incision is situated in the facial RSTLs, allowing for the most acceptable orientation for the placement of surgical excisions.

**VASCULARITY OF THE FACE**

*Vascular supply*

Although understanding the vascular supply is vital to the operative planning of the reconstructive surgeon, soft tissue surgery on the head and neck usually heals particularly well due to a rich vascular system. This vascular system is a three-dimensional interpenetrating linkage of neighboring vascular territories. Major distributing vessels travel close to the underlying bony skeleton, emerging from the deep tissues at fixed points, either from bony foramina or where the deep fascia approximates the underlying bone. For instance, several branches of the external carotid (the occipital, posterior auricular, and superficial temporal arteries) emerge near the skull base, whereas the facial artery emerges along the lower border of the mandible. Other important facial vessels arise at the bony foramina of the maxilla and mandible (infraorbital and mental arteries) and at the orbital margins (the supraorbital, supratrochlear, dorsal nasal, and medial palpebral arteries.) The distributing arteries then
branch into smaller perforator vessels that comprise the basis for the muscular and cutaneous vascular systems. Typically, perforator branches enter their respective muscle groups on the deep surface, closely following the connective tissue architecture of the muscle as they divide and subdivide into smaller nutrient vessels before extending to the cutaneous surface.

Of importance in understanding the vascular system is the concept of angiosome. An angiosome is a composite segment of bone, muscle, nerve, and overlying skin, supplied by a common source vessel. These segments form the theoretical basis for the design of complex tissue flaps. A flap that is based on the source vessel of a single angiosome can frequently incorporate some tissues from an adjacent angiosome; nutrient blood will be supplied to the adjacent angiosome through collateral channels (Figure 11).

Most skin and subcutaneous tissue in the face are supplied by branches of the external carotid artery system, with the exception of a mask-like region in the center of the face that encompasses the eyes, the upper two-thirds of the nose, and the central forehead (Figure 11). These regions are mainly provided by the ophthalmic branch of the internal carotid system with anastomoses with the facial and superficial temporal branches of the external carotid system.

Cutaneous circulation
The cutaneous tissues and their nutrient vessels form a stack of interconnected vascular tissue planes called the vascular plexus, consisting of the fascial, subcutaneous, subdermal, dermal and subepidermal plexus (Figure 12). Branches of perforator arteries of the distributing facial arteries (e.g. facial or supratrochlear artery) extend to the cutaneous surface as either septocutaneous or musculocutaneous arteries. Septocutaneous vessels travel generally within the fascia (septa) of the muscle, whereas musculocutaneous vessels pass directly through the muscle tissue, providing multiple nutrient branches to the surrounding muscle as they travel vertically to the cutaneous tissues.

The deepest structure in the cutaneous vascular plexus is the fascial plexus, at the level of the deep muscle fascia, which derives its blood supply from small vessels that branch off from
septocutaneous and musculocutaneous arteries. Overlying the fascial plexus is the subcutaneous plexus, a significant network of vessels corresponding to the level of the superficial fascia or superficial musculoaponeurotic system (SMAS).

The subdermal plexus is the most significant of horizontal vascular layers and has a primary role in the distribution of blood to other components of the cutaneous system. The subdermal plexus lies at the junction between the reticular dermis and the underlying subcutaneous fat. Clinically this level corresponds with the phenomenon of dermal bleeding, which is often seen at the leading edge of skin flaps. Superficial to this major subdermal plexus lie the dermal plexus and the closely associated subepidermal plexus. These layers have two primary functions: the dermal plexus provides thermoregulation, whereas the capillary beds of the subepidermal plexus provide nutrients to the skin. The capillary density of the skin and the subcutaneous tissues is only a small fraction of that found in the muscular system.

One of the classification systems of tissue flaps is based on the vascular supply. Five categories are known: random cutaneous, arterial cutaneous, fasciocutaneous, myocutaneous or composite. Random cutaneous flaps are supplied by perforating septocutaneous and musculocutaneous vessels entering at the anatomic base of the flap. Perfusion of the distal flap segment occurs by way of the cutaneous (subdermal) vascular plexus. Random flaps are used extensively on the face and encompass the majority of transposition, advancement and rotation flaps performed in this region.

Arterial cutaneous flaps are based on the presence of axial aligned direct cutaneous arteries that permit large areas of skin to be raised. The flap may extend beyond the termination of the artery, depending on the degree of collateral flow through the cutaneous vascular plexus. Arterial cutaneous flaps may be used as pedicled or as free flaps for microvascular transfer. A clinical example in the face is the forehead flap.

Fasciocutaneous flaps are designed to include the underlying muscular fascia. Flap survival is improved due to circulation provided by the fascial plexus and the adjacent subfascial course of arteries. Clinical examples are the radial forearm flap and the deltopectoral flap.

RECONSTRUCTION OPTIONS
The ideal method of reconstruction aims at closure of the defect with good cosmesis with as little secondary morbidity as possible. Optimal results rely on a sound understanding of skin anatomy and flap physiology, careful analysis of the defect and recipient site, familiarity with multiple reconstructive options, and meticulous technique.

A variety of options is available for the surgeon and in order to organize these surgical options, a surgeon may bear in mind the concept of the reconstructive ladder. Each rung of the ladder represents a more complex surgical plan: healing through secondary intention, primary closure, skin grafts, local flaps, pedicled flaps and microvascular free flaps. The advantages and disadvantages of each step should be weighed carefully to individualize the treatment of choice.

WOUND HEALING
Each surgical reconstructive option has to deal with wound healing. It is a dynamic process consisting of complex and incompletely under-
stood molecular interactions between soluble mediators, blood cells and parenchymal cells, which will be discussed briefly. Wound healing follows three temporally overlapping phases: inflammatory, proliferation and remodeling. For optimal healing of wounds all these phases must take place in a coordinated sequence. The duration of wound healing depends on the size and depth of the wound. Contraction of wound edges also plays a major role.

**Inflammatory phase (0-5 days)**
The acute wound-healing process begins immediately after tissue injury and once hemostasis has been achieved. For the blood of the wound to clot, a combination of local vessel vasoconstriction, fibrin deposition, and platelet aggregation must take place. Fibrin deposition relies on the extrinsic coagulation pathway, and whereas the platelets begin to deposit on the vessel walls once they have been exposed to the local collagen and tissue factors circulating in the wound bed. Once 10 to 15 minutes have elapsed, the initial vasoconstriction changes to a period of vasodilatation, caused by the release of histamine, leukotrienes and prostaglandins from the endothelium. This phase gets its name from the infiltration of neutrophils that begin to predominate the wound bed. These cells patrol the wound and help prevent local infection by debriding foreign particles and digesting bacteria. These cells peak between one and two days and then begin to decline as the monocytes and macrophages move into the area, peaking around days four and five. Clinically the first phase is associated with erythema, edema, warmth and tenderness of the wound.

**Proliferative or granulation phase (6-14 days)**
The next phase in wound healing works to repair the epithelium, synthesize collagen, and promote the development of new blood vessels. Reepithelialization occurs through the migration of the epithelial cells near the wound edges along the fibrin scaffold to again cover the wound bed. Epithelial cells play an important role in this phase, and fibroblasts, crucial to the synthesis of elastin, proteoglycans; and collagen, start to become active during this period in wound healing. Initially, fibroblasts produce collagen type III, abundant in an early wound, which is later converted to type I collagen. Fibroblasts also change into myofibroblasts, which are critical in the contraction of wounds, seen around days 7 to 14.

Finally, the wound produces several angiogenic growth factors, such as vascular endothelial growth factor, which help to promote angiogenesis. It is this new blood vessel formation that is necessary to support the generation of the granulation tissue that exists in the wound bed.

**Remodeling or maturation phase (15 days-1 year)**
This is the longest phase and can last for up to a year. It is for this reason that many surgeons wait one year before attempting any surgical wound or scar revision procedure. In this phase the transition from the provisional fibrin and fibronectin matrix to the final matrix and collagenous scar occurs. Neovascularization stops, and the erythema that was originally seen in the wound from the vasculature turns a whitish color as the vessels regress. If one or more of these phases are impaired, delayed healing becomes apparent, resulting in more scar tissue. Clinically,
hypertrophic scars and keloids represent unbalanced collagen synthesis and remodeling. \textsuperscript{107}

**HEALING BY SECONDARY INTENTION**

The simplest way of repairing skin defects is secondary intention healing which shows all the phases of wound healing. It is an under-used reconstructive modality, as the wound requires a lengthy healing period. A moist healing environment accelerates re-epithelization, optimizes cosmesis and minimizes desiccation, necrosis and pain. \textsuperscript{103,108} Patients themselves have to be involved in the post-operative treatment by applying antibiotic ointment on the wound and daily cleaning with tap water. It usually takes several weeks for the skin defect to heal. If properly used, secondary intention healing gives better cosmetic results than other reconstructive modalities.

**PRIMARY CLOSURE**

This is often the quickest and simplest approach resulting in minimal incisions and scarring. Undermining of the skin edges helps to advance skin in the middle and allows dog-ears to settle at both ends. The benefit of undermining is achieved within the first 1 to 2 cm. Undermining beyond this distance causes injury to surrounding structures and may compromise blood flow. Primary closure of the face is ideally performed parallel to the relaxed skin lines or in the borders of the aesthetic (sub) units.

**SKIN GRAFTS**

Skin grafts can be categorized in full thickness and split-thickness skin grafts. Most grafts used for facial reconstruction are full thickness. Split-thickness grafts (consisting of epidermis with little or no dermis) have poor cosmesis and are used to resurface large areas only. The full-thickness skin graft (FTSG) consists of epidermis and full-thickness dermis. Given the technical simplicity and the general applicability of full thickness skin grafts, they can be used for a wide range of defects, provided there is adequate vascularity of the recipient site. For optimal cosmesis the defect location, and depth as well as graft donor site choice and delicate tissue handling are essential. Possible disadvantages of skin grafts are graft failure, graft contraction, poor color match, depressed contour, and donor-site morbidity. \textsuperscript{109}

**COMPOSITE GRAFTS**

Composite grafts by definition carry more than one structure in one graft. A most common example consists of skin and cartilage and is mainly used in small full-thickness defects (measuring less than 10 mm) of the nose. The helix of the auricle has a number of ideal donor areas for the reconstruction of the alar rim. The main disadvantage is the risk of graft failure, due to the need of vascular supply, which becomes critical if the grafts contain multiple layers of tissue.

**CUTANEOUS FLAPS**

A skin flap is an area of skin and subcutaneous tissue with a direct vascular supply that is transferred from its in-situ position to another site. The challenge in facial reconstruction is to design a flap that places the secondary defect in a region with minor functional or cosmetic importance if possible. Furthermore the donor area must have some skin laxity such as found in the cheek, glabella and neck region.

Many different classifications exist depending on the type of vascular supply, method of tis-
Sue transfer, configuration of flap or donor sites. In our opinion a classification system based on the method of tissue transfer is the most logical. This classification divides local flaps into sliding (e.g. advancement or rotation) and lifting (e.g. transposition, interpolation). For clarity, the most predominant type of movement dictates the term given to describe the flap. Clinical examples are the cervical cheek rotation flap used for a large cheek defect, which is a sliding flap, and a bilobed flap for the nose, which is a transposition flap or lifting flap.

AIMS AND OUTLINE OF THIS THESIS
As described in the introduction of this thesis many treatment modalities have been suggested for NMSC with a wide spectrum of indications. Nevertheless, surgery nowadays still remains the mainstay of treatment for NMSC of the head and neck. Surgery mainly distinguishes itself from all other treatments by the possibility of histopathological control of excision margins. Clearly the primary aim of surgery is to achieve clear resection margins, followed by appropriate reconstruction to obtain satisfactory cosmetic and functional outcomes after careful consideration of the individual skin biomechanics.

In this respect the head and neck region is demanding, as aesthetic and functional outcome are readily visible, often marred by functional impediments. The burden is on the surgeon to achieve optimal balance between tissue sacrifice and preservation of function and cosmesis. The increasing number of patients with NMSC, reaching epidemic magnitude in Western countries, plus the limited availability of healthcare facilities calls for a pragmatic surgical approach with minimal burden to the patient.

The simplest of “surgical closures” is secondary intention healing. However, most data on secondary intention healing are empirical and descriptive. In order to confirm the clinical value of secondary intention healing for skin cancer defects in the head and neck, wound-healing results need to be statistically analyzed.

Skin grafting has been a mainstay of closure of surgical wounds. Composite Skin perichondrial grafting is a variation on this theme. Given the sparse literature and lack of aesthetic comparison, the potential of this specific graft merits further evaluation.

Composite skin fat grafts with an extra tissue bulk to the skin defect have rarely been propagated. Investigating the value of these grafts as an alternative to local skin flaps may create an extra reconstruction modality.

By far the most common method to resurface middle to large (>1.5 cm) or complex nasal defects is the forehead flap. The paramedian design is mostly used but the need for increased effective length of the flap, without transposition of hairs, and the need for a favorable midline donor scar resulted in the use of the hybrid midline design. To prove the clinical value of this alternative design, vascular predictability, functional and cosmetic outcome should be evaluated.

OUTLINE OF THE THESIS
Chapter 1 is a general introduction to skin cancer treatment and facial reconstruction.

In Chapter 2 we compare the complex Mohs’ micrographic surgery (MMS) with conventional excision followed by delayed reconstruction in a series of 1504 patients. MMS has developed into an adequate treatment option for NMSC in the head and neck achieving the highest cure
rates. However, this type of surgery remains time-consuming and requires a logistically complex set-up allowing for immediate peroperative histological processing of the excised skin lesions, followed by immediate reconstruction. After conventional excision (CE), reconstruction is delayed as a result of conventional histological processing of tissue specimens (formalin fixation and H&E staining). Repeat excisions might be required until negative margins are reached followed by a delayed defect reconstruction. Usually CE leads to larger excision defects compared with defects after MMS. To compare both techniques, we will evaluate the oncological outcome and clinical findings.

In chapter 3 we analyze the value of secondary intention healing as an alternative for reconstruction by tissue transfer. Although still one of the simplest surgical options, it is often underestimated as an additional tool for skin defect closure. To investigate whether the cosmetic outcome can indeed be predicted by different wound characteristics and locations, a statistical evaluation of independent judgments of three investigators in a series of 89 patients undergoing secondary intention healing for NMSCs has been undertaken.

Chapters 4 to 9 focus on nasal reconstruction. Due to its cosmetic and functional vulnerability, this site calls for tailored medicine in NMSC surgery. New or modified surgical techniques are used for defect closure and nasal shape reconstitution. Chapter 4 focuses on the comparison between full-thickness skin grafts and perichondrial cutaneous grafts for defects located mainly on the nose. The results of composite skin-fat grafts for nasal reconstruction are described in chapter 5.

In chapter 6 free cartilage grafts and secondary intention healing of small nasal alar defects are analyzed. In chapter 7 the use of subcutaneous hinge flaps and secondary intention healing for defects containing a nasal portion and adjacent facial subunits are addressed.

Defect closures of large and deep skin defects of the nose by the use of subcutaneous soft tissue flaps and skin grafting are shown in chapter 8. Chapter 9 analyzes the clinical aspects of various forehead flap designs, including the hybrid midline design, for the reconstruction of large and/or complex nasal defects. This thesis ends with a general summary and concluding remarks in chapter 10.

References


