Current skin cancer practice in primary and secondary care

Margit van Rijsingen

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Thesis Radboud university medical center, Nijmegen, The Netherlands
With summary in Dutch, 150p

ISBN
978-94-028-0094-4

Cover image
Margit van Rijsingen (adapted Marameisje by Mara Trienekens)

Design/lay-out
Promotie In Zicht, Arnhem

Print
Ipskamp Printing, Enschede

Current skin cancer practice in primary and secondary care

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus,
volgens besluit van het college van decanen
in het openbaar te verdedigen op

vrijdag 29 april 2016
om 12.30 uur precies

door

Margit Catharina Johanna van Rijsingen
geboren op 29 april 1983
te Eindhoven

Promotoren
Prof. dr. dr. P.C.M. van de Kerkhof
Prof. dr. G.J. van der Wilt

Copromotor
Dr. M.J.P. Gerritsen

Manuscriptcommissie
Prof. dr. W.J.J. Assendelft
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Dr. N.W.J. Kelleners-Smeets (MUMC)

everything will be okay in the end.
if it's not okay,
it's not the end.

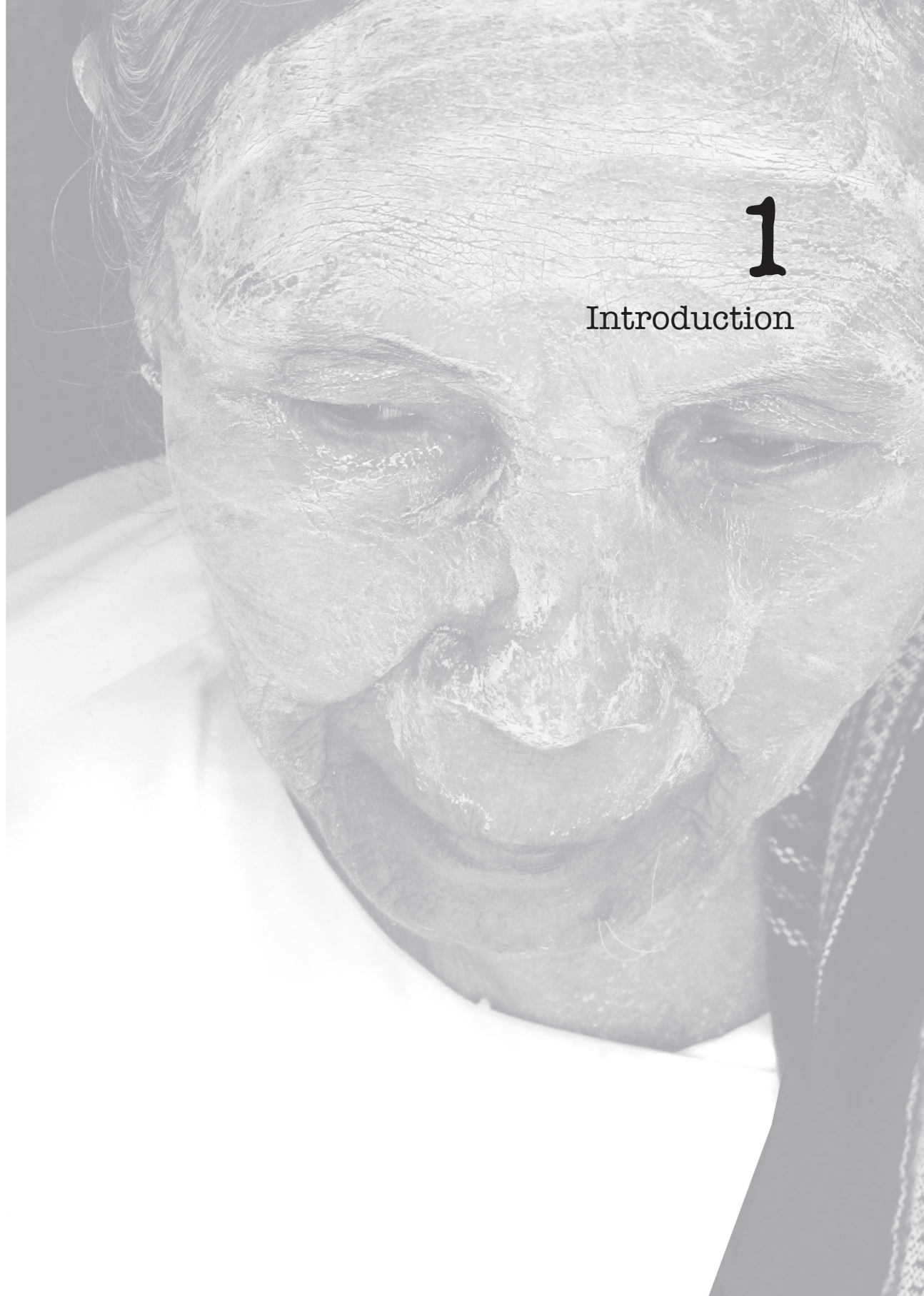
John Lennon

Paranimfen
Dr. I.A.W. van Rijsingen
Drs. J.M.P.A. van den Reek

Contents

List of Abbreviations

5-FU	5-fluorouracil
AK	actinic keratosis
ALA	5-aminolevulinic acid
BCC	basal cell carcinoma
BD	Bowen's disease
DR	dermatology resident
FU	follow-up
GP	general practitioner
iBCC	infiltrative basal cell carcinoma
IMI	imiquimod
ITT	intention-to-treat
LTFU	loss to follow-up
M0	baseline (0 months)
M3	3 months
M12	12 months
MAL	methyl aminolevulinate
mnBCC	micronodular basal cell carcinoma
nBCC	nodular basal cell carcinoma
NMSC	non-melanoma skin cancer
PDT	photodynamic therapy
PpIX	protoporphyrin IX
PPV	positive predictive values
PUVA	psoralen and ultraviolet A therapy
RCT	randomized controlled trial
RUNMC	Radboud University Nijmegen Medical Center
sBCC	superficial basal cell carcinoma
SC	skin cancer
SCC	squamous cell carcinoma
SD	standard deviation
SK	seborrheic keratosis
SPSS	statistical package for social science
TBE	total body examination
UV	utraviolet



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Introduction

Introduction

Skin cancer (SC) is the most frequent diagnosed cancer in the Caucasian population worldwide, and its incidence is rising year after year. The most important reason for this increase is ultraviolet (UV) radiation, due to sun exposure and the use of tanning beds.

SC comprises melanoma and non-melanoma skin cancer (NMSC). The incidence of NMSC is much higher as compared to melanoma. Basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and its precursors, actinic keratosis (AK) and Bowen's disease (BD), represent the vast majority of NMSC. Melanomas form a smaller group of SC, however their mortality rate is higher. Although not all NMSC demonstrate metastatic potential, their treatment may lead to functional and cosmetic loss. To lower SC related mortality and morbidity, early detection is crucial.

Concomitant to the rise in SC prevalence, costs for SC care are rising, leading to a substantial burden on healthcare services.

In this introduction we will mainly focus on the most common types of SC: BCC, SCC, melanoma, and the pre-malignancies AK and BD.

1.1 Epidemiology

Several studies with respect to the epidemiology of (pre-)malignancies of the skin have been performed. In spite of this, accurate figures on the incidence and prevalence of NMSC in the Netherlands are difficult to obtain. BCCs are only registered in one part of the Netherlands. Moreover, only the first histologically confirmed BCC or SCC is registered, although an extensive part of the population develops multiple SC. Pre-malignancies, e.g. AK and BD, are not included in national registries, therefore their actual incidence is unknown.

BCC is the most common form of SC. In Australia, BCC and also other types of SC, form an enormous health care problem. A longitudinal study in a subtropical Australian population in 2009, showed an overall age-standardized incidence rate of BCC of 1,541 people affected per 100,000 person-years at risk[1]. In the Netherlands, an approximately threefold increase in age-adjusted incidence rates has been noted between 1973 and 2008[2]. In 2008, one in five men and one in six women had developed a BCC before the age of 85[2].The predictions are that for the upcoming years the incidence will continue to increase[2].

The chance of developing an additional BCC in patients with a previous BCC is almost 30%, which, as described above, is probably a conservative estimate[3]. Male sex and age 60 or over are associated with high BCC counts and patients with high numbers of AK are most likely to experience the highest number of BCC[4]. It has also been shown that BCCs occur more and more in younger patients, mainly in young women[5].

SCC is the second most common SC. The incidence of SCC has increased over the last years, and is predicted to rise further to 2020 and reach a European Standardised Rate of 46.9 per 100,000 inhabitants for males and 28,7 for females[6]. A 5-year relative survival curve, calculated over patients included between 1989 and 2008, remained stable over time[6].

Since AK is mostly diagnosed clinically, incidence figures are difficult to assess. However, in a recent study conducted in the Netherlands, AK prevalence of 49% in men and 28% in women was found in a cohort of participants aged 45 years or older[7]. In a German study, a prevalence of 16.36% in men and 6.29% in women was found in the age group 61-70 years in a working population[8]. Epidemiological studies on the incidence of BD are scarce and outdated[9].

The incidence of melanoma was assessed in a study performed in the Netherlands[10]. An increase in incidence was found in age-standardized incidence (ESR per 100.000 person years) from 11.3 in 1989 to 21.7 in 2008. Furthermore, mainly due to improved awareness and early diagnosis, an increase in 10-year relative survival was found for both men and women over time.

1.2 Risk factors

The rising incidence of SC is most likely caused by UV radiation due to increasing exposure to sun and tanning bed use. BCC is related to intermittent and intense sun exposure especially in childhood and adolescence[11,12], whereas SCC is associated with cumulative sunlight exposure[13]. In melanomas, intermittent sun exposure and (severe) sunburn during childhood constitute high risk factors[14] (table 1). In a large, multicentre case-control study it was found that subjects with a sun-sensitive skin type (Fitzpatrick I) had a statistically significant increased risk on developing BCC, SCC, and melanoma[15]. The presence of AK represents a marker of sun damage and increased risk of NMSC development[16].

Other significant risk factors for BCC are higher age, red hair[18], exposure to ionizing radiation, use of photosensitizing medication, chronic immunosuppression, HIV sero-positivity and genetic syndromes e.g. nevoid basal cell carcinoma syndrome[19]. Most of these risk factors are also of importance in patients with SCC. However, SCC may also appear in chronically injured skin and ulcers[20]. For SCC, the presence of AK and BD form a risk factor, as they are pre-malignancies of SCC. Although AK and BD are not directly related with BCC, it has been demonstrated that a high number of solar keratoses confer a greater than 3-fold risk for BCCs of both the head and the trunk. BCC of the trunk have a particularly strong association with the number of reported sunburns and solar lentigines[21]. Another study demonstrated that patients with high numbers of solar keratoses were most likely to experience the highest BCC counts overall[4]. Moreover,

Table 1 Association of the most important risk factors in the development of basal cell carcinoma, squamous cell carcinoma and melanoma.

Risk factor	BCC	SCC	Melanoma
UV exposure:			
sunburn (young age)	++	+	++
intermittent	++	+	++
cumulative	+	++	+
phenotype	++	++	++
age	+++	+++	+
male sex	++	++	+
educational level	+	-	+
immunosuppressives	++	+++	+
high dose PUVA	++	+++	+
smoking	-	++	-

Abbreviations: basal cell carcinoma (BCC), squamous cell carcinoma (SCC), psoralen and ultraviolet A therapy (PUVA)
Modified from Holterhues C, de Vries E, Nijsten T. De epidemiologie van huidkanker: zorg om de zorg. Ned Tijdschr Dermatol. Venereol, 2009 sept;19(8):451-455[17].

BCC on the head, trunk and on the limbs were strongly associated with high numbers of solar keratoses on these sites.

SCCs are more often seen in patients who chronically use immunosuppressive medication, e.g. transplant recipients[22]. The most common risk factors for melanoma besides UV exposure are family history, fair skin, multiple moles and chronic immuno-suppression use[23].

1.3 Prevention

Since UV radiation is considered the most important environmental risk factor for the development of SC, primary prevention is based on the reduction of UV exposure, especially in childhood and adolescence. The World Health Organisation's sun protection advice includes: the avoidance of sunlamps and tanning parlours, the limitation of exposure to midday sun, to watch for the UV-index, to use the shade wisely, to wear protective clothing and to use sunscreen[24]. The preventative properties of sunscreen in various types of skin cancer have been studied. In a community-based randomised trial with a 2 by 2 factorial design, individuals were assigned to four treatment groups: daily

application of a sun protection factor 15-plus sunscreen to the head, neck, arms, and hands, and beta-carotene supplementation (30 mg per day); sunscreen plus placebo tablets; beta-carotene only; or placebo only[25]. It was found that SCC but not BCC could be prevented by regular application of sunscreen. After a further 8 year follow-up it was found that BCC tumour rates tend to decrease, although not significantly[26].

Secondary prevention is performed with the purpose of early detection and treatment, e.g. total body examination performed by a physician or the patient himself.

1.4 Clinical presentation and diagnosis

Basal cell carcinoma

The clinical presentation of BCC is dependent on the subtype. The most common types are nodular and superficial BCCs. Nodular BCC (nBCC) may present as a shiny pearly nodule with teleangiectasias and elevated edges. Crusting may be present overlying the central depression or the lesion may ulcerate. Most nBCCs occur on the face. Superficial BCC (sBCC) may present as well-circumscribed scaly erythematous papules or plaques, sometimes with small pearly papules forming a thin rolled border. sBCCs are mainly seen on the trunk and the extremities. In young patients sBCC is the most common BCC subtype. A third group is formed by infiltrative BCCs (iBCC), they are the least common type of BCC and present as shiny indurated, sometimes depigmentated nodules that may resemble a scar. Also less frequently seen are micronodular BCCs (mnBCC) which present as papules or slightly elevated plaques, they may clinically appear as nBCCs.

All BCC types may be pigmented. BCCs can be classified as low risk or high risk BCC (table 2).

Table 2 Prognostic factors basal cell carcinoma.

	low risk	high risk
histological subtype	non-aggressive (nodular, superficial)	aggressive (infiltrative, micronodular)
location	trunk	H-zone (eyes, ears, lips, nasolabial fold, nose)
size	< 2 cm	≥ 2 cm
previous therapy	primary tumour	recurrent tumour

Modified from Kelleners-Smeets NWJ dHE, Beljaards RC, Ingels KJAO, Corten EML, Buis PAJ, et al. Evidence-based Richtlijn Basaalcelcarcinoom (modulaire update 2014)[27].

Squamous cell carcinoma and Bowen's disease

SCCs mainly appear on the sun-exposed areas of the skin. Their clinical presentation may vary from a small nodule to a nodule with central ulceration and hyperkeratosis. Lesions may be reported as painful.

BD presents as sharply demarcated scaly or crusted erythematous plaques. BD mostly occurs on the sun-exposed areas of the skin, but may also be seen on other body sites. BD may progresses to invasive disease if not treated[20].

Actinic keratoses

AKs also occur on the sun-exposed areas of the skin and present as scaly erythematous papules, which may vary in size from a few millimetres to nummular plaques. They may also have a brown or pink colour and are generally more easily felt, as rough lesions, than seen.

AKs can occur as single lesions or as multiple lesions, sometimes in close proximity (field AK). Lesions may spontaneously regress, recur or progress into SCC. The risk of progression of one single lesion into SCC is estimated from 0% to 0.075% per year[28]. In patients with a history of NMSC the rate of progression from AK to SCC is estimated 0.53% per lesion. However, most patients have multiple and recurrent AKs, the reason why AK can be seen as a chronic disease, making the risk on SCC higher.

Melanoma

Melanomas demonstrate various clinical features. They mostly appear as hyperpigmentated nodules or macules. Complains as itching, bleeding, ulceration and pain may be present.

Diagnosis

BCC, SCC and BD are generally diagnosed by performing a diagnostic biopsy. In case of high clinical suspicion treatment can be started without a prior biopsy. Dermatoscopic examination can contribute in establishing the diagnosis of BCC, since it allows for visualization of arborizing telangiectasias[29]. In case of a biopsy, it should be noted that there may be disagreement between the histological subtype diagnosed by biopsy as compared to the histological results of the excision[30,31]. This is caused by sampling error, which means that the most aggressive part of the tumour is missed by the performance of a biopsy. The diagnosis of AK is a clinical diagnosis, in case of diagnostic doubt a biopsy should be performed.

Pigmented lesions can also be judged with a dermatoscope. In case of suspicion of a melanoma a diagnostic excision with a margin of 2 mm must be performed[32]. Lesions should be excised completely, since incomplete excisions (e.g. diagnostic biopsy, shave) may lead to sampling error with respect to Breslow thickness, the most important marker for prognosis, thereby influencing the accuracy of pathological staging.

1.5 Treatment

Basal cell carcinoma

Several treatments are available for BCC. The treatment type depends on the BCC subtype, the size and the location of the tumour and patient characteristics. All BCC subtypes can be adequately treated with surgical excision with predetermined margins. A 3 mm margin is used for sBCC and nBCCs. In case of a tumour size >1 cm and/or an infiltrative or micronodular subtype a margin of 5 mm is preferred[27]. After excision, histological examination of the BCC subtype, as well as the excision margins is performed by a pathologist to assess peripheral clearance of the tumour. In case of incomplete excision a re-excision is recommended. Recurrent BCCs and high risk primary BCCs located in the head-neck region, may be indications for treatment with Mohs surgery[33], a surgical technique by which the complete skin cancer can be excised, while doing minimal damage to surrounding healthy tissue. There are several additional treatment options, all of which have the disadvantage of lack of histological control. However, these therapies are non-invasive; they include imiquimod (IMI), 5-fluorouracil cream (5-FU), and photodynamic therapy (PDT). IMI is a topical immunomodulating cream, which is registered for the treatment of sBCC. The working mechanism is described as induction of pro-inflammatory cytokines and chemokines which eventually lead to the mounting of a profound T-helper mediated anti-tumour immune response[34].

5-FU, a topical treatment for sBCC, is a chemical agent which inhibits thymidylate synthase, which is needed for DNA synthesis.

PDT is registered for the treatment of superficial- and nodular BCC. The first step is the application of the topical photosensitiser (5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL)). After a three-hour incubation time, in which protoporphyrin IX (PpIX) is upregulated in the target cells, the treatment area is irradiated with a red light source. During light exposure, reactive oxygen species are produced and apoptosis is induced, leading to cell death of the tumour cells.

Occasionally destructive surgical techniques are used for low risk BCC including curettage and cautery, cryosurgery and carbon dioxide laser[33]. In specific cases, if other treatment options are deemed inappropriate, BCC can be treated with radiotherapy.

Squamous cell carcinoma and Bowen's disease

Excision is the first choice of treatment in SCC. The margins of the excision are based on the type of tumour. Primary and low risk tumours are excised with a margin of 5 mm, recurrences and high-risk tumours with a 10 mm margin[35]. The distinction between high and low risk tumours is based on the size of the tumour, the location and aggressive pathological features. In patients who have inoperable tumours or who do not tolerate surgery, radiation therapy may be an appropriate alternative[20].

For BD, also several therapeutic options are available. Cryotherapy, which is inexpensive and easily performed at the outpatient clinic. Topical 5-FU, PDT and surgical excision are also adequate therapies in BD. The choice of treatment is based on the clinical features of the tumour and the physical condition of the patient.

Actinic keratosis

Since AKs have a risk of progression into SCC, treatment of all AKs is advised in the Dutch guideline[36], especially in patients with multiple or field AKs. Treatment of AKs can be lesion-directed or field-directed (table 3).

Cryotherapy is the most common used lesion-directed treatment. It is performed with liquid nitrogen (-195.8 °C), most frequently used as an open spray method. The advantage of this therapy is that it is easy, non-expensive and effective[37]. The disadvantage is that healthy surrounding skin may also be destroyed. Moreover, cryotherapy may cause scarring and loss of pigmentation in the skin[38].

Field-directed treatments like 5-FU, IMI, ingenol mebutate and PDT have the advantage of being more selective, thereby destroying only atypical cells, with better cosmetic outcomes. The comparison of (dis)advantages of these treatments are presented in table 3. In this table ingenol mebutate is not yet included, as this agent is only recently available in the Netherlands.

Table 3 Comparison of the advantages and disadvantages of the different treatment techniques for actinic keratosis (based on Dutch guideline).

based on:	cryotherapy	5-FU	imiquimod	PDT	Peeling/ laser
lesion characteristics					
single lesion(s)	****	***	***	**	*
multiple lesions	**	****	****	****	****
hypertrophic AK	**	*	*	*	*
patient characteristics					
low compliance	****	**	**	****	****
high compliance	**	****	****	**	**

**** = treatment of first choice
*** = best alternative after first choice treatment
** = medium alternative
* = not recommended
Abbreviations: actinic keratoses (AK), 5-fluorouracil (5-FU)
Modified from Beljaards RC, Borgonjen RJ, Engelen JWM, Everdingen JJE, Marion AMW, Munte K, et al. Richtlijn Actinische keratose[36].

In the Netherlands, 5-FU is available as a 5% cream and used twice daily until erosions of the skin appear. In AKs, IMI is used three times per week during four weeks. Four weeks after the end of the treatment the efficacy is evaluated. If necessary, the treatment should be repeated.

PDT is another form of field-directed treatment. It is performed in the hospital. The mechanism of action is the same as described for BCC. A disadvantage of this treatment, mainly in AK, is that it can be painful. For this reason, daylight PDT has become recently available. In daylight PDT the incubation time of the photosensitizer is shortened and daylight is used instead of red light, leading to comparable efficacy rates, but patients experience less pain[39].

A new therapy is ingenol mebutate. This is a topical treatment suitable for field AK. The mechanism of action is not fully elucidated, but seems to be based on induction of necrosis and the production of cellular cytotoxicity of residual cells[40].

Furthermore laser, chemical peels, and surgical techniques as curettage, shave and dermabrasion can be used in the treatment of AKs. Surgical techniques are preferably used for single thick hyperkeratotic lesions. Laser is an effective but expensive treatment. The Dutch guideline recommends peels as an option for patients with a low compliance[36].

Melanoma

As mentioned previously, the diagnosis of melanoma is performed by a diagnostic excision with a 2 mm margin. In case the diagnosis of a melanoma is confirmed a therapeutical re-excision needs to be performed, with excision margins based on the Breslow thickness of the tumour[41,42].

1.6 Organisation and costs of skin cancer care

Organisation of care

In the Netherlands 554 dermatologists and 8865 general practitioners (GP) are registered[43,44]. The number of persons who will develop skin cancer in the Netherlands is estimated to be 1 in 5[2] and one-third of these patients will develop at least a second primary skin cancer[3]. Pre-malignancies have not even been included in this calculation. At present most of these patients are treated by dermatologists[45]. However, in the Netherlands, patients visit their GP first with their health related questions. Performing this gatekeeper role, GPs may treat patients themselves, or in case of clinical doubt refer to a medical specialist.

In a study performed in the Netherlands, it was found that in 2009 more than 50% of dermatologists' time was spent on skin cancer and skin neoplasms[46]. In a Dutch study performed in general practice, an annual increase of 7.3% in the demand for care due to skin lesions suspected of malignancy was found between 2001 and 2010[47]. The benign : malignant ratio had changed from 17.5 : 1 in 2001 to 10.2 : 1 in 2010.

Skin cancer diagnosis and treatment in primary care

In the Dutch medical curriculum, courses in dermatology are most frequently taught during the Bachelors, followed by a (sometimes optional) clinical rotation in dermatology during the Masters[48]. With respect to GP trainees' training in dermatology there is no national consensus, therefore this may vary per university[48]. As mentioned above, high numbers of patients with skin diseases present themselves to GPs, while the intensity of training programmes in dermatology is limited. Several studies, mostly international, have been performed to provide insight in the skills of GPs in diagnosing and treating SC.

It was found that GPs have difficulties diagnosing SC. In a study performed in Irish GPs a 54% agreement between the clinical diagnosis of the GP and dermatologist was found[49]. In this study, a total of 38 of the referred patients had pathologically proven skin malignancies. These were diagnosed accurately by the GP in 22% of patients[49].

In Australia, a continent with an extremely high incidence of SC and a substantial contribution of GPs in skin cancer care, it was found that skin cancer physicians and GPs have the same overall sensitivity for diagnosing skin cancer, resp. 0.94 and 0.91[50]. In one of the few studies performed in the Netherlands, the sensitivity for the clinical diagnosis of a malignant lesion was 38% in lesions excised by GPs[51]. In the same study it was found that 4.7% of all excised lesions included pre-malignancies or malignancies. Furthermore, 49.1% of lesions clinically diagnosed as (pre-)malignant were pathologically diagnosed as benign.

In previous European studies completeness of excisions performed by GPs showed a complete excision rate for BCC of 67.9%-79.8%, in SCC of 72.1%-85.5%, and 65.4% in case of melanoma[52-54].

Health care costs

The rising incidence of SC is associated by an increase in SC-related costs. In a study performed in the U.S. it was found that the average annual cost for SC increased from $3.6 billion in 2002-2006 to $8.1 billion in 2007-2011, an increase by 126.2%[55]. With these costs, NMSC is in the top five most costly cancers to Medicare in the U.S[56]. In Sweden an increase of 27% was seen in SC costs (including pre-malignancies and melanocytic naevi) from 2005 to 2011[57]. The direct SC costs in 2011 were €102.2 million, the total indirect costs (e.g. production loss due to morbidity and mortality) €177.6 million[57]. In England future SC costs are estimated to be over £180 million in 2020[58].

1.7 Aims and outline of this thesis

Aims of the thesis

As reported above, the number of patients with SC as well as the number of patients with multiple skin tumours is rising. However, data on the complete number of (pre-) malignancies in this population remains unclear.

Besides the increasing burden on dermatological care, rising numbers of SC have an impact on the healthcare related costs. Early detection and adequate treatment may help to control this development. In the Dutch healthcare system, GPs act as gatekeepers, playing an important role in secondary prevention and adequate referral.

At present, the majority of SC patients are diagnosed and treated by dermatologists, thereby also spending substantial time on AK and low-risk BCC. The question rises whether these SC patients need to be treated in secondary or tertiary care centres. In near future it may be discussed to shift parts of low-risk SC care to primary care settings. Therefore, it is important to gain insight in the willingness of GPs to play a more extensive role in SC care. Also, to guarantee appropriate quality with respect to SC care, information is needed on the current knowledge and skills of GPs.

Evaluation of the cost and efficacy of common used SC diagnostics and treatment in hospital settings could contribute to improvement of SC care.

The following aims were formulated:

1. To investigate the tumour characteristics of NMSC populations in different hospital settings

2a. To investigate the present role and skills of GPs in skin cancer care

2b. To explore the future role of GPs in SC care

3. To investigate the value of a diagnostic incision biopsy in BCC

4. To investigate patient characteristics, efficacy, and costs in patients with field AKs

Outline of the thesis

In **chapter 2** tumour characteristics are presented of patients with AK and BCC from university, as well as from general hospital settings.

Chapter 3 is devoted to the current and future role as well as the current skills of GPs in SC care. The results from a study on the role and willingness of GPs to participate in SC care are discussed, as well as the need for additional training. Furthermore, the necessity and quality of referrals made by GPs in a population of patients with skin tumours were investigated. Also, the surgical skills of GPs with respect to skin tumours were studied.

In **chapter 4** a study of the added value of a diagnostic punch biopsy in BCC in dermatological practice is presented.

In **chapter 5** real life clinical data with respect to patient characteristics, efficacy, and costs in patients with field AK are shown and discussed.

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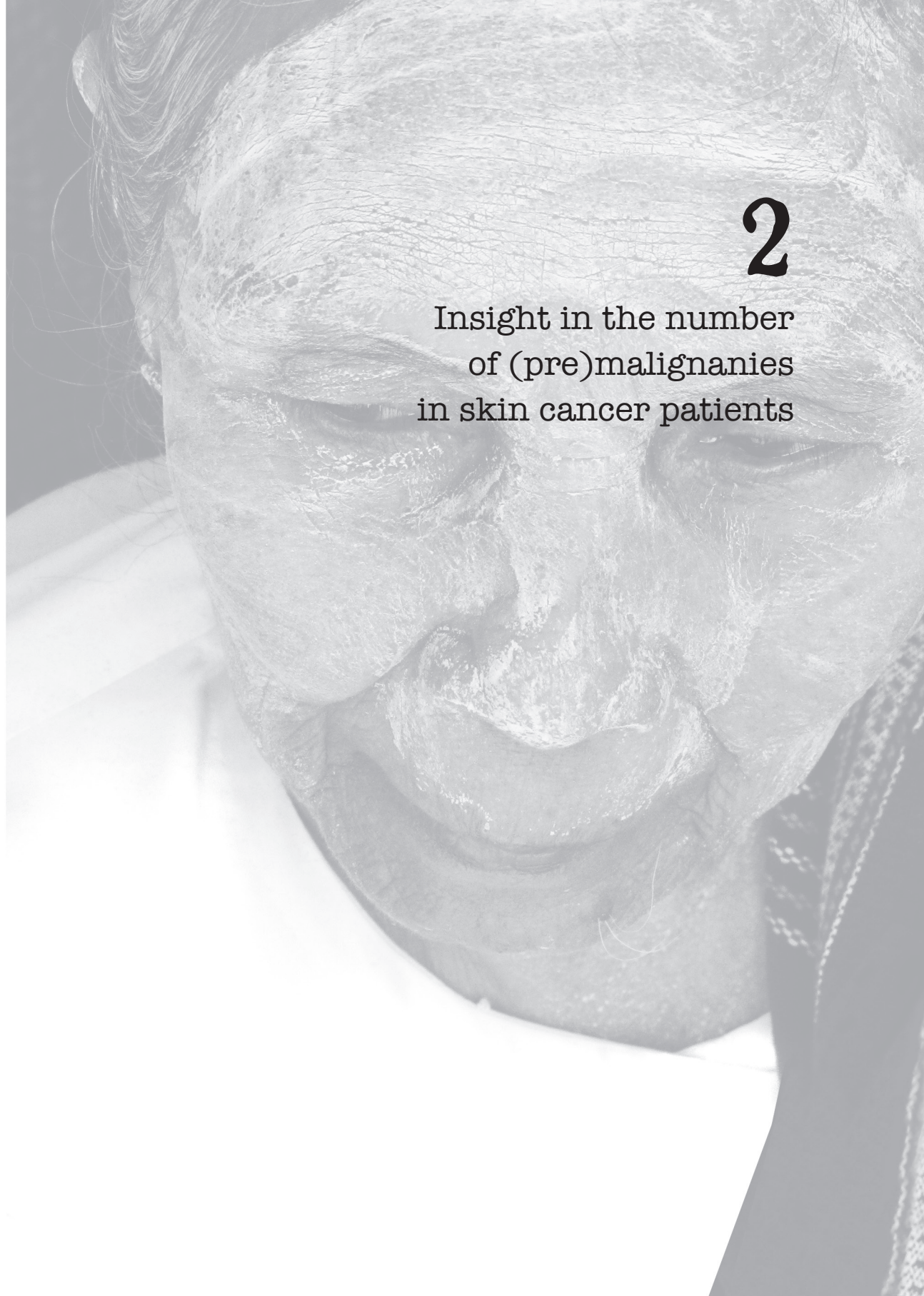

2

Insight in the number of (pre)malignanies in skin cancer patients

2.1

Insight into the number of pre-malignancies and malignancies of the skin in a hospital population in the Netherlands

M.C.J van Rijsingen
I. Seubring
M.B. Maessen-Visch
A.P.M. Lavrijsen
L.H. van Bergen
J.M.M. Groenewoud
M.J.P. Gerritsen

Eur J Dermatol. 2015 May-Jun;25(3):261-5

Abstract

Background
Skin cancer incidence is rising, placing a burden on healthcare systems worldwide. This problem may even be more extensive than expected, since registration of (pre)malignancies of the skin is poor.

Objective
To provide insight into the numbers of (pre)malignancies in patients with actinic keratosis (AK) or basal cell carcinoma (BCC) in 2 university and 2 general hospitals.

Methods
The types and numbers of previous tumours and of tumours during a two-year follow-up were collected from 574 patients.

Results
Mean time between the first diagnosed (pre)malignancy and time of inclusion was 6.6 years. Overall, 60% had multiple types of (pre)malignancies. In BCC patients 61% had multiple BCCs, in patients with squamous cell carcinoma (SCC), 40% had multiple SCCs. The combination 'BCC and SCC' occurred in 10%, 'BCC and AK' in 47%, 'SCC and AK' in 14%.

Conclusion
High numbers of patients with multiple (pre)malignancies were found in this patient population in university and general hospitals, which may well reflect the Dutch hospital population. We conclude that skin cancer patients are more extensively affected than was expected up till now. Consequently, the management of skin cancer may be in need of adaptation in near future and the question arises whether dermatologists have the capacity for providing care for all these patients.

Introduction

The incidence of skin cancer (SC) is rising, placing a burden on health care systems worldwide[1-3]. The largest group of SC is formed by the non-melanoma skin cancers (NMSC), which mainly include basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and its precursors. In the Netherlands, it has been found that 1 out of 5-6 people will develop at least one BCC during their life[4]. Furthermore, the 3-year cumulative risk for a subsequent tumour was found to be 44% for BCC and 18% for SCC[5], resulting in high numbers of patients with multiple tumours.

Additionally, SC patients may be affected by premalignant lesions: Bowen's disease (BD) and actinic keratosis (AK). In a recent Dutch study, conducted in the general population aged 45 years or above[6], a prevalence of AK was found in 49% of male and 28% of female participants. In a German study, conducted in a working population (employees of companies of various occupations), the AK prevalence was 16.4% in men and 6.3% in women in the age group 61-70 years[7].

In daily practice nowadays, it is noticed that many patients present with multiple pre-malignancies and malignancies of the skin. However, their registration is incomplete. BCCs are often not registered and if they are, most registries only register the first primary histologically confirmed BCC. Moreover, BCCs may be treated without pathological conformation. Since AKs are diagnosed clinically, they are never registered. Consequently, data on the total number and combination of pre-malignancies and malignancies in SC patients are incomplete.

The aim of the present study was to provide insight into the severity of SC in a patient population with AK or BCC in both university and general hospitals and to describe the type and number of tumours in these patients.

Methods

Patient characteristics

Patients in the present study were those who were included in an observational study on the cost-effectiveness of treatment of BCC and AK in the years 2010-2011. Patients included were cases of multiple (field) AKs located on the face and/or on the scalp or cases of nodular or superficial basal cell carcinoma(s). All patients were treated for the condition for which they were included. Patients were included at the outpatient clinics of four hospitals; two university hospitals and two general hospitals (Radboud University Medical Center, Leiden University Medical Center, Rijnstate Hospital, and Canisius Wilhelmina Hospital). Patients were included from a general outpatient clinic. Patients could be those with a previous history of SC or patients presenting for the first time with a skin tumour.

To create an overview of pre-malignancies and malignancies (referred to as (pre) malignancies)) in patients' histories and during a two years follow-up (FU), data were collected from patient records and the correspondence of referring doctors (e.g. general practitioner, dermatologist, surgeon).

The following data were collected: patient's age and sex, date of the first (pre) malignancy, and the number and type of (pre)malignancies during history and a two year FU. All (pre)malignancies diagnosed at the start and during the study were registered as 'occurred during FU'. (Pre)malignancies registered as 'history' were those diagnosed before inclusion. In all patients, at least one total body examination was performed during FU. At least two FU contacts were scheduled for the observational study.

Except for AK, which is diagnosed clinically, only histologically proven primary tumours were recorded. Patients with genetic disorders leading to multiple skin cancers were not included in this study. All other patients with various types of co-morbidities were included to provide insight in regular daily clinical practice. As this study had an observational design, most patients with field AK or BCC in the participating hospitals were willing to participate and were included in the study, thereby representing the SC population visiting the dermatological out-patient department well.

Statistics

Data collection and analysis were performed using Statistical Package for Social Science (SPSS 20.0, IBM Corp, Armonk, NY). Only descriptive statistics were used to present information: percentages in case of nominal variables, mean and standard deviation in case of continuous variables.

In cases of AKs, the number of lesions was not always registered in the patient's file. Therefore, we only registered if a patient had AK. AK numbers were not taken into the analysis.

Since data in the present study are collected from a selective patient population (hospital population), these numbers are not suitable for calculating incidence and prevalence. The outcome data were used to give an indication of the number and types of (pre)malignancies in a hospital population of patients with AK or nodular or superficial BCC.

Since data were collected in two different populations (AK and BCC patients), data are initially described for both groups separately, to provide insight into the different patient characteristics between these groups.

This study was approved by the ethics committee of all participating hospitals, all included patients gave consent to participate in this study.

Results

Patients were included in four hospital settings in the Netherlands. Two general hospitals and one university hospital were located in the eastern part of the Netherlands, whereas one university hospital was situated in the western part. A total of 574 patients were included in this study, 369 (64.3%) were female and the mean age at inclusion was 66.5 years (AK patients 70.6, BCC patients 61.6). Fifty-four percent of patients were included for AK, 45.6% for BCC. Of all the patients, 313 (54.5%) had (pre)malignancies of the skin prior to the start of the study. Of these patients, the mean time between their first diagnosed (pre)malignancy and inclusion was 6.6 years. A total of 333 (58.0%) patients were included in university hospitals. Three patients were transplant recipients.

History

Patients with AK had a mean time of 6.8 years (SD 6.3, range 1-34) between their first (pre) malignancy and inclusion, in BCC patients a mean time of 6.2 years (SD 5.4, range 1-29) was found. An overview of the number of (pre)malignancies prior to inclusion is provided in table 1.

Table 1 Overview of number of tumours in patients with a previous history of (pre) malignancies. *(n(%))*

	Actinic keratosis (n = 192 patients)			Basal cell carcinoma (n = 121 patients)		
	0 tumours	**1 tumour**	**> 1 tumour**	**0 tumours**	**1 tumour**	**> 1 tumour**
BCC	110 (57.3%)	47 (24.5%)	35 (28.2%)	17 (14.0%)	34 (28.1%)	70 (57.9%)
SCC	146 (76.0%)	28 (14.6%)	18 (9.4%)	110 (90.9%)	5 (4.1%)	6 (5.0%)
BD	144 (75.0%)	29 (15.1%)	19 (9.9%)	105 (86.8%)	9 (7.4%)	7 (5.8%)
Melanoma	181 (94.3%)	11 (5.7%)	-	114 (94.2%)	6 (5.0%)	1 (0.8%)
Dysplastic nevus	192 (100.0%)	-	-	116 (95.9%)	5 (4.1%)	-
Other	113 (93.4%)	8 (6.6%)	-	120 (99.2%)	1 (0.8%)	-
Total malignancies*	80 (41.7%)	52 (27.1%)	60 (31.2%)	10 (8.3%)	36 (29.8%)	75 (61.9%)
Number of different malignancies**	80 (41.7%)	77 (40.1%)	35 (18.2%)	10 (8.3%)	99 (81.8%)	12 (9.9%)

* Total number of all malignancies (BCC, SCC, Melanoma, other)
** Number of different types of malignancies (BCC, SCC, Melanoma, other)
Basal cell carcinoma (BCC), squamous cell carcinoma (SCC), Bowen's disease (BD)
Other are: lymphoma, atypical fibroxanthoma and lentigo maligna

The combination 'BCC and SCC' occurred in 16.7% of patients included with AK and in 11.6% of patients included with BCC, the combination 'BCC and AK' in respectively 51.6% and 72.7%, the combination 'SCC and AK' in respectively 29.2% and 10.7%, and the combination 'SCC, AK and BD' in respectively 16.7% and 5.8%.

Follow-up

In patients included with AK, the mean FU time appeared to be 22.0 months (SD 4.5, range 3-24); in patients included with BCC this was 23.5 months (SD 3.6, range 3-24). An overview of the number of (pre)malignancies during FU is provided in table 2.

Table 2 Overview of number of tumours during follow-up. *(n(%))*

	Actinic keratosis (n = 312 patients)			Basal cell carcinoma (n = 262 patients)		
	0 tumours	1 tumour	> 1 tumour	0 tumours	1 tumour	> 1 tumour
BCC	224 (71.8%)	45 (14.4%)	43 (13.8%)	0 (0.0%)	116 (44.3%)	146 (55.7%)
SCC	280 (89.7%)	23 (7.4%)	9 (2.9%)	250 (95.4%)	10 (3.8%)	2 (0.8%)
BD	273 (87.5%)	27 (8.7%)	12 (3.8%)	234 (89.3%)	21 (8.0%)	7 (2.7%)
Melanoma	310 (99.4%)	2 (0.6%)	-	259 (98.9%)	3 (1.1%)	-
Dysplastic nevus	312 (100.0%)	-	-	260 (99.2%)	2 (0.8%)	-
Other	311 (99.7%)	1 (0.3%)	-	260 (99.2%)	2 (0.8%)	-
Total malignancies*	202 (64.7%)	59 (18.9%)	51 (16.4%)	0 (0.0%)	111 (42.4%)	151 (57.6%)
Number of different malignancies**	202 (64.7%)	97 (31.1%)	13 (4.2%)	0 (0.0%)	243 (93.5%)	17 (6.5%)

* Total number of all malignancies (BCC, SCC, Melanoma, other)
** Number of different types of malignancies (BCC, SCC, Melanoma, other)
Basal cell carcinoma (BCC), squamous cell carcinoma (SCC), Bowen's disease (BD)
Other are: lymphoma, atypical fibroxanthoma and lentigo maligna

Table 3 Number of patients with multiple malignancies (all malignancies together). *(n(%))*

	0	1-5	6-10	>10	total
General hospital	77 (32.0%)	153 (63.5%)	9 (3.7%)	2 (0.8%)	241
University hospital	62 (18.6%)	184 (55.3%)	51 (15.3%)	36 (10.8%)	333
Overall	139 (24.2%)	337 (58.7%)	60 (10.5%)	38 (6.6%)	574

The combination 'BCC and SCC' occurred in 4.2% of patients included with AK and in 4.6% of patients included with BCC, the combination 'BCC and AK' in respectively 28.2% and 43.9%,the combination 'SCC and AK' in respectively 10.3% and 3.8%, and the combination 'SCC, AK and BD' in respectively 3.5% and 1.9%.

Overall (history and FU)

The total number of malignancies in these hospitals, during history and FU time together, are provided in table 3. Patients with higher numbers of multiple tumours were more frequently seen in university hospitals.

Overall and for both AK- and BCC-group combined, over 40% of all patients had more than one BCC, 5.8% had more than one SCC, and 6.8% more than one BD (table 4). Multiple melanomas or dysplastic nevi occurred in one patient. A total of 59.9% of all patients had more than one type of premalignancy and/or malignancy of the skin (table 4).

The combination 'BCC and SCC' occurred in 9.6% of patients, 'BCC and AK' in 47.4%, 'SCC and AK' in 13.9%, and the combination 'SCC, AK and BD' in 7.3%.

Of all patients with BCC, 61.3% (242/395) had more than one BCC (max. 33). Of all patients with SCC 40.2% (33/82) had more than one SCC (max. 17).

Table 4 Overview of number of tumours overall (history and follow-up). *(n(%))*

	AK and BCC together (n = 574 patients)		
	0 tumours	1 tumour	> 1 tumour
BCC	179 (31.2%)	153 (26.7%)	242 (42.1%)
SCC	492 (85.7%)	49 (8.5%)	33 (5.8%)
BD	466 (81.2%)	69 (12.0%)	39 (6.8%)
Melanoma	550 (95.8%)	23 (4.0%)	1 (0.2%)
Dysplastic nevus	568 (99.0%)	5 (0.9%)	1 (0.2%)
Other	562 (97.9%)	12 (2.1%)	-
Total malignancies*	139 (24.2%)	165 (28.7%)	270 (47.1%)
Number of different malignancies**	139 (24.2%)	359 (62.5%)	76 (13.2%)
Number of different (pre)malignancies***	-	230 (40.1%)	344 (59.9%)

* Total number of all malignancies (BCC, SCC, Melanoma, other)
** Number of different types of malignancies (BCC, SCC, Melanoma, other)
*** Number of different types of (pre)malignancies
Basal cell carcinoma (BCC), actinic keratosis (AK), squamous cell carcinoma (SCC), Bowen's disease (BD)
Other are: lymphoma, atypical fybroxanthoma and lentigo maligna

Discussion

An overwhelming number of patients included in the present study had multiple pre-malignancies and/or malignancies of the skin. Overall, almost 60% had more than one type of pre-malignancy and/or malignancy. Forty-seven percent had more than one malignant skin tumour. These numbers may be higher than those found in a general population, since inclusion criteria for our study were the presence of BCC or multiple AKs at the start of FU. Furthermore, it may be expected that patients with multiple AKs have a certain extend of actinic damaged skin, which makes them more at risk for the development of additional (pre)malignancies[8]. Multiple BCCs and the combination 'AK and BCC' occurred in almost half of the patients. In a recent review performed by Flohil *et al.* (2013) the pooled proportion for a subsequent BCC in a patient with a previous BCC was 29.2%, this percentage was based on previously performed studies[9]. The higher numbers found in the present study may be explained by the selective study population and by an increase in SC incidence in recent years. As the incidence of SCC and BD is lower, multiple tumours of these types occurred less frequent, but still in more than 5% of patients, whereas the combination 'SCC and AK' occurred in almost 14%. Furthermore, multiple SCCs and BD were found more frequently and in higher numbers in patients in the AK population. The latter findings may not be surprising, since AKs and BD are considered to be precursors for SCC[10]. Additionally, AK patients included in our study where those eligible for field therapy, indicating that these were patients with multiple AK, which is a risk factor for the development of SCC[11], also the existence of AK for multiple years could increase the risk of progression[12].

The combination of AK and BCC occurring in the same patient may be explained by sun exposure leading to both these tumours. It was found that the occurrence of (multiple) AK is associated with a higher risk in the development of BCC[8,13]. Patients with multiple dysplastic nevi or melanomas were rarely observed in this study. This is probably caused by our inclusion criteria, focussed on NMSC. In previous studies, in patients with melanoma, the number of patients with multiple melanomas was higher[14,15].

Patients with high numbers (>5) of malignancies were mainly included in university hospitals. These findings may be explained by the fact that in clinical practice it is common to refer severely affected patients to university hospitals for more specialized care. However, it should be noted that only a few of the patients in our study were organ recipients and that patients with genetic disorders leading to SC were excluded.

More than half of the patients had a previous history of (pre)malignancies and the mean time between the first tumour and inclusion was 5.1 years for general hospitals and 7.3 years for university hospitals. These numbers indicate that a substantial number of patients have a chronic skin cancer problem and may be in a life time follow-up, which contributes to high costs in health care.

As mentioned previously, data in the present study are based on a selective population and the results cannot be extrapolated to the whole skin cancer population. However, since appropriate SC registries are lacking, a population wide study based on cancer registries may not provide sufficient data to obtain a complete overview on all (pre)malignancies in our patient population. In our study, 574 patients from four hospital locations were included during a period of two years. As two general and two university hospitals participated, our results may reflect the situation with respect to characteristics of the patient population seen in West-European dermatological practices.

A potential limitation of our study might be that only patients with superficial and nodular BCC or multiple AKs were included. Furthermore, patients had various years of previous history and not all patients were followed during 24 month FU. However, these data do present an overview of the real life situation of these patients. If only a selection of years was included in the history data, this would not reflect the severity of this population as it appears to be in clinical practice, therefore we chose to use the full number of years in history and the total number of tumours.

Conclusion

Overwhelming numbers of patients with AK or BCC included in our study appeared to exhibit multiple (types of) pre-malignancies and/or malignancies of the skin.

Since these patients were included in four hospitals and were only followed during a short timeframe, the total number of severely affected patients will be much higher in the whole Dutch hospital-based SC population.

Consequently, the management of SC may be in need of adaptation in near future and the question arises whether hospital based dermatologists have the capacity for providing care for all these patients. Reimbursement should be well correlated to the severity of the SC patients in hospital settings. Additionally, those involved in SC care need to be aware of the fact that patients who present themselves with a first (pre) malignancy, may well have additional and future lesions, therefore total body examination and FU are recommended.

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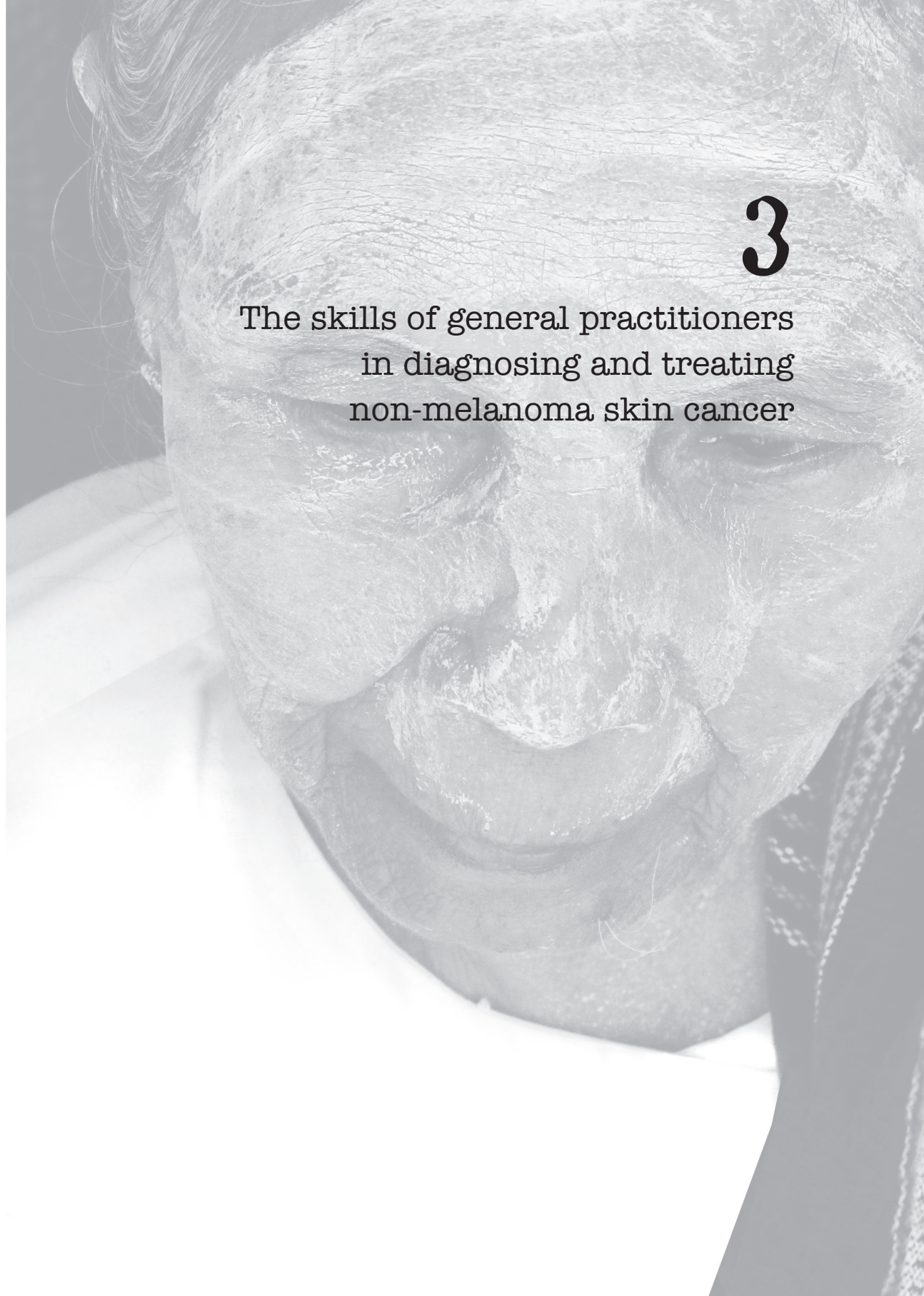

3

The skills of general practitioners in diagnosing and treating non-melanoma skin cancer

3.1

The current and future role of general practitioners in skin cancer care: an assessment of 268 general practitioners

M.C.J. van Rijsingen
B. van Bon
G.J. van der Wilt
A.L.M. Lagro-Janssen
M.J.P. Gerritsen

Br J Dermatol. 2014 Jun;170(6):1366-8

Abstract

Background
Given the increase in skin cancer (SC) it seems inevitable that general practitioners (GPs) will play a larger role in SC care in near future.

Objectives
To obtain insight into the opinion of GPs with respect to their role in SC care, and their SC knowledge and skills.

Methods
A self-administered questionnaire was sent to GPs in the region of Nijmegen, the Netherlands.

Results
In total 268 GPs (49%) responded. An overwhelming majority were willing to extend their role in SC care. Furthermore, we noted the following results:
(i) > 50% of GPs request additional SC knowledge; (ii) GPs often treat actinic keratosis (AK) themselves, primarily with cryotherapy; (iii) > 50% would treat (low-risk) basal cell carcinoma (BCC) after additional training; (iv) only a few GPs are familiar with BCC guidelines; (v) the majority of patients with high-risk SC are referred to dermatologists; (vi) only a few GPs perform total body inspection and palpation of lymph nodes; and (vii) a large number of GPs inform their patients on risk factors in SC development.

Conclusion
Most GPs are willing to extend their role in SC care; however, more training is requested and the usage of guidelines should be encouraged. Those willing to extend their role should focus on improving their clinical diagnosis of skin tumours, treatment of low-risk skin (pre)malignancies, including field-directed treatment of AK and noninvasive treatment of BCC, and on prevention.

Introduction

Recent studies show a rapid increase in the incidence of skin cancer (SC)[1-3], which will lead to a burden on dermatologists' practices and healthcare costs.

Melanomas form the smallest, but most fatal, group of SCs. Non-melanoma skin cancer (NMSC) includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), and the premalignant lesions actinic keratosis (AK) and Bowen's disease (BD). Besides mortality, NMSC contributes to cosmetic and functional morbidity. Both early treatment and primary and secondary prevention are of great value to lowering SC-related mortality and morbidity. As in many countries, general practitioners (GPs) are the first to see a patients with SC. The present study aims to assess GPs' attitude towards their role in SC prevention, diagnostics and treatment, and information on their need for education.

Methods

This study was performed in 2010-12. Anonymous questionnaires were sent to 552 GPs in the region of Nijmegen, the Netherlands.

The questionnaire contained 17 dichotomous questions, 11 multiple-choice questions, four five-point Likert scales (range: never to always) and four essay questions. These were divided into the following. Section 1 containing questions concerning self-assessment of knowledge of AK, BD, BCC, SCC and melanoma (table 1). Sections 2-4 contained questions concerning diagnosis and treatment of AK, BCC and SCC, including diagnostics used, number of referrals, reason for referral, type of known and used treatments, follow-up, guideline use and total body examination (TBE). Section 5 contained questions concerning risk factors, prevention, and GPs' view on their future role in SC care.

Statistical analysis of the results was performed using SPSS for Windows (version 16.0; IBM, Armonk, NY, USA).

Results

In total 268 GPs returned the questionnaire (49% response rate).
An overview of GPs' need for knowledge and the possible influence of education on SC treatment is provided in table 1.

Actinic keratosis

Seventy-five percent of respondents believe that AK treatment is a task for GPs. Half of the respondents often/always treat patients with AK themselves. Only 3.7% would never refer a patient with AK to a dermatologist. The most common reason for referral was suspicion of SCC. Table 1 provides an overview of AK treatments used by GPs.

Table 1 General practitioners' need for knowledge, treatment skills for skin cancer, and knowledge and usage of actinic keratosis treatment.

Of which (pre) malignancy would you like to have more knowledge?	
Actinic keratosis	111 (41.4%)
Bowen's disease	213 (79.5%)
Basal cell carcinoma	121 (45.1%)
Squamous cell carcinoma	162 (60.4%)
Melanoma	149 (55.6%)
Which (pre) malignancy do you treat yourself?	
Actinic keratosis	239 (89.2%)
Bowen's disease	22 (8.2%)
Basal cell carcinoma	92 (34.3%)
Squamous cell carcinoma	18 (6.7%)
Melanoma	8 (3.0%)
Which (pre) malignancy would you treat if you had more knowledge of it?	
Actinic keratosis	151 (56.3%)
Bowen's disease	113 (42.2%)
Basal cell carcinoma	139 (51.9%)
Squamous cell carcinoma	53 (19.8%)
Melanoma	6 (2.2%)
Which treatment for actinic keratosis do you know?	
Cryotherapy	268 (100%)
Imiquimod	96 (35.8%)
5-FU cream	168 (62.7%)
Photodynamic therapy	76 (28.4%)
Other	10 (3.7%)
Which treatment for actinic keratosis do you use yourself?	
Cryotherapy	248 (92.5%)
Imiquimod	24 (9.0%)
5-FU cream	43 (16.0%)
Photodynamic therapy	0 (0.0%)
Other	10 (3.7%)

Data are *n* (%), based on responses from 268 general practitioners.

Basal cell carcinoma

Around 20% of GPs were of the opinion that treatment of BCC should be performed by a GP; 33.2% indicated that they would treat only low-risk BCCs. In case of suspicion of BCC, 73.0% would refer to a dermatologist, 9.7% would take a biopsy and refer afterwards, and 42.2% would excise the BCC. Thirty-four percent would perform TBE. Imiquimod and (referral for) photodynamic therapy are used by 9.3% of GPs. Twenty-seven percent are familiar with the BCC guidelines.

Squamous cell carcinoma

Only 3% of respondents were of the opinion that SCCs should be treated by a GP. In case of suspicion of an SCC 88.4% would refer to a dermatologist, 13.1% would take a biopsy and refer afterwards, and 13.1% would excise the SCC. One fifth would perform TBE, and 13.1% would palpate the lymph nodes.

Prevention and risk factors

Most GPs (93.7%) see SC as a health problem in which they should play a role, while 86% would like to play a larger role in SC care.

In total 93% of GPs indicated that they were familiar with the risk factors for SC development, whereas 70.5% would like to have more knowledge on risk factors. Only 1.3% never inform patients on risk factors.

Discussion

An overwhelming majority of GPs are willing to play a significant role in SC care; however, our results also demonstrate a high need for additional education and training.

Our survey demonstrates that after additional education, a larger number of GPs would treat BD, BCC and SCC. However, GPs remain reluctant to treat melanomas. This could be explained by the higher mortality rate caused by melanomas[4], and is in agreement with the Dutch melanoma guideline, which advices GPs to refer patients with suspicion of a melanoma to a dermatologist[5]. The number of GPs who would treat AK after education is lower than that 'before education'. This is probably because most GPs already treat AKs.

Only 3.7% of GPs would never refer a patient with AK to a dermatologist. Most GPs use only cryotherapy, which is suitable mainly for solitary AK[6]. As 75.4% of GPs agree that AK treatment is a task for the GP, field treatment for AKs would be a point of interest for education.

As the majority of GPs participating in this study were not widely familiar with the usage of guidelines, with the treatment options for low-risk tumours, or with the performance of diagnostic biopsies, education in BCCs should focus on these aspects.

Because of the metastatic potential of SCCs we agree that education on SCC should focus mainly on diagnostics, so GPs can play a role in early detection and referral[7]. At present there is no Dutch guideline describing whether GPs should treat BCC or SCC in primary care.

The finding that TBE or palpation of lymph nodes is performed in only a few patients is worrisome. It is well known that SC also occurs on parts of the skin that are not frequently exposed to ultraviolet (UV) radiation[8]. Lack of time could be an important reason for GPs not to perform TBE[9]. Most GPs inform patients about risk factors. This is important because it has been proven that UV protection advice given by a GP improves sun protection in patients[10].

A potential limitation of this study is that GPs were not asked about their years of experience or special interest. With a response rate of 49%, data on half of the selected GPs are missing. Although our data were collected in one specific region, it consisted of rural areas and large cities, and thus may provide a proper representation of the rest of the Netherlands.

Our results have implications for clinical practice. It is of great value that most GPs would like to contribute to SC care; however, more education is needed. Training in recognition of the most common (pre)malignancies might promote early detection, which may be useful in secondary prevention. Furthermore, the use of a diagnostic biopsy may support the diagnostic process. With respect to treatment, progress could be made by teaching GPs about field-treatment in patients with AK. Additionally, GPs may be educated in the use of different treatment modalities for low-risk BCC and guideline use. Furthermore, GPs are of great importance in primary SC prevention, which is easy to learn and easy to perform.

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3.2

Referrals by general practitioners for suspicious skin lesions: the urgency of training

M.C.J van Rijsingen
S.C.A. Hanssen
J.M.M. Groenewoud
G.J. van der Wilt
M.J.P. Gerritsen

Acta Derm Venereol. 2014 Mar;94(2):138-41

Abstract

Skin cancer (SC) is common among white populations and rapid increases in incidence are being observed in many countries, leading to a large burden on healthcare systems. Unnecessary referrals from general practitioners (GPs) may contribute to this burden. The aim of this study was to analyse the quality of referrals from GPs of patients with skin tumours. Referral letters for 734 patients were collected. The proposed diagnoses were compared with definitive diagnosis made by dermatologists.

In 44.5%, lesions appeared to be benign. Malignant skin tumours were poorly recognized by GPs and seborrheic keratoses were often mistaken for naevi (33.6%). Furthermore, with total body examination, dermatologists found 111 additional malignant lesions. We discussed several recommendations to minimize unnecessary referrals as well as the future role of GPs in SC care.

Introduction

Skin cancer (SC) is a public health problem of increasing magnitude among fair-skinned populations worldwide, and it is responsible for an increasing contribution to health care costs[1,2]. The occurrence of SC at young age[3,4] and the development of multiple tumours in many SC patients contributes to this problem[5]. A recent study showed that almost one in 5 persons will develop SC[6].

Basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and the premalignancies Bowen's disease (BD) and actinic keratosis (AK) belong to the group of non-melanoma skin cancers (NMSC). In these skin malignancies, the mortality rate is low; however, morbidity and disfigurement may be caused by excision of large tumours in functional and visible areas. The incidence of melanoma is much lower[4,7], but these tumours are responsible for the highest mortality rate. Treatment of BD and high risk AKs, especially in those with multiple lesions (e.g. field cancerisation), is recommended to eliminate the risk of evolution into invasive SCC[8]. Early detection may lower SC associated morbidity and mortality.

Most skin cancer presents in primary care, and an important determinant of outcome may be initial recognition and management of the lesion. Previous studies have shown that general practitioners (GPs) have difficulties in diagnosing various types of skin diseases, including SC[9-11]. A study performed in the U.K. showed that 81% of malignancies sent for pathological analysis, was treated by dermatologists and 2% by GPs, the others were treated by other hospital physicians[12]. The latter may indicate that GPs refer high numbers of patients to dermatologists. The aim of our study was to investigate the necessity and quality of referrals made by GPs in a population of patients with skin tumours.

Methods

Study population

We collected all referral letters sent by GPs of patients who were referred with the diagnosis of a possible skin tumour to the department of Dermatology of the Radboud University Nijmegen Medical Centre (RUNMC) in the period from January 2008 to November 2010. Selection was based on the final diagnosis of a malignant or benign tumour in the hospital's registration system. This computerised system is able to perform a patient selection based on a patient's final diagnosis. Only few patients who were incorrectly diagnosed may be missed in our inclusion. Of all patients, referral letters, dermatological charts (filled out by the dermatologist or dermatology resident (DR)), and pathological results (when available) were collected.

The following data were recorded:
(1) socio-demographic data including gender and age,
(2) description of the lesion,
(3) the number of diagnostic biopsies,
(4) the referral diagnosis,
(5) listed number; and
(6) location of (additional) lesions found by dermatologist or DR.

The diagnoses at referral were compared with the pathological diagnoses. If no additional pathological analysis was performed, the clinical diagnosis made by the dermatologist or DR was used as the final diagnosis. If necessary, mainly in case of a pigmented lesion or BCC, dermatologists or DRs made use of a dermatoscope. Since the RUNMC is a training hospital, many clinical diagnoses of DRs were confirmed by a supervising dermatologist. In case a differential diagnosis was proposed, the first diagnosis mentioned was used in the analysis.

A diagnosis was defined as 'correct' when the diagnosis of the GP was in line with the diagnosis of the dermatologist and DR, or (if available) with the pathologic results. The differential diagnoses of the dermatologists and DRs were defined as 'correct' when they were in line with the pathological diagnosis. Therefore, the dermatologists' and DRs' diagnoses could only be verified in case a pathologic result was available; mainly in malignancies and some premalignancies.

Data analysis

Statistic analysis was performed using the Statistical Package for Social Sciences (SPSS®) for Windows (version 20.0). Only descriptive statistics were used.

Results

A total of 734 referral letters were collected from patients referred by GPs to the department of Dermatology at the RUNMC. The population consisted of 325 men (44.3%) and 409 women (55.7%), with a mean age of 58.3 years.

Location and number of lesions

Over 90% of patients were referred by their GP with one suspicious lesion. In < 10% the GP discovered > 1 lesion. Of all lesions, 61.0% was located on the face or scalp, 29.3% on the trunk or extremities and 5.9% on multiple body parts. In 3.8% the lesion location was not mentioned in the referral letter.

By performing total body examination, dermatologists and DRs diagnosed 234 additional premalignant and malignant lesions, including AKs, BD, dysplastic naevi, BCCs, SCCs, melanomas, and atypical fibroxanthoma (table 1).

Table 1 Additional lesions found by dermatology resident or dermatologist after referral by general practitioner. Total of 146 patients with additional lesions (min. 1 and max. 20 per patient).

	Head/neck	Limbs	Trunk	*Total number of lesions*
Premalignancies				
Actinic keratosis	75	14	15	*104*
Dysplastic naevus	0	0	5	*5*
Bowen's disease	9	3	2	*14*
Total				*123*
Malignancies				
Basal cell carcinoma	36	12	48	*96*
Squamous cell carcinoma	6	0	2	*8*
Melanoma	1	0	4	*5*
Atypical fibroxanthoma	2	0	0	*2*
Total				*111*

Diagnostics

Overall, 327 (44.5%) of the lesions, which were reason for referral appeared to be benign, 204 (27.8%) were malignant, and 204 (27.8%) premalignant. Of the 255 lesions referred as malignant, 22.4% was diagnosed as premalignant and 25.1% as benign. Of all lesions referred as benign, 63.9% was diagnosed as benign. A cross tabulation of GPs' diagnosis at referral and the final diagnosis presents an overview of the most occurring diagnostic errors made in these referrals (table 2). Additionally, positive predictive values (PPV) for GPs' diagnosis at referral were calculated (table 3).

In 18.3% of the referrals a diagnosis was missing, the correct diagnosis was mentioned in 39.8% of letters. In 1.2% a diagnostic biopsy was taken by the GP prior to referral.

Non-melanoma skin cancer

GPs referred 188 patients with the possible diagnosis of a BCC. Ninety-one of these were finally diagnosed with a BCC, 11 with SCC, 34 with AK, one with BD, one melanoma, and 45 with benign lesions. Of 153 patients who were ultimately diagnosed with BCC, 29 were referred without a diagnosis, and 16 with the question 'malignant'. Out of 38 SCCs, 6 were referred as SCC. None of the 13 BD was referred with this diagnosis.

As compared to the pathologic diagnosis, dermatologists and DRs mentioned the correct diagnosis of a BCC in 95.4%, a SCC in 55.3%, and a BD in 30.8%. Additional PPVs were calculated (table 3).

Table 2 Overview of referral diagnosis of general practitioner (GP) and the final diagnosis.

	Final diagnosis										
Diagnosis made by GP	**BCC**	**SCC**	**AK**	**BD**	**Melanoma**	**Other benign**	**Other malignant**	**SK**	**Naevus/ lentigo**	**Dysplastic naevus**	**Total**
Basal cell carcinoma (BCC)	**91**	11	34	6	1	26	0	11	8	0	188
Squamous cell carcinoma (SCC)	3	**6**	4	1	0	5	0	0	0	0	19
Actinic keratosis (AK)	7	4	**72**	1	0	8	0	4	2	0	98
Bowen's disease (BD)	0	1	0	**0**	0	0	0	0	0	0	1
Melanoma	0	0	0	0	**2**	0	0	0	1	0	3
Other benign	4	5	14	1	1	**34**	2	6	5	0	72
Other malignant/'Malignant?'	16	2	12	0	0	2	**1**	10	1	0	44
Seborrheic keratosis (SK)	1	1	0	0	1	3	0	**32**	1	0	39
Naevus/lentigo	2	0	3	0	1	5	0	33	**62**	1	107
Diagnosis missing	29	8	48	4	0	16	1	20	8	0	134
Dysplastic naevus	0	0	3	0	2	1	0	9	14	**0**	29
Total	153	38	190	13	8	100	4	125	102	1	734

Bold figures represents number of correct diagnosis by GPs

Table 3 Positive predictive values of general practitioners' (GPs) diagnosis as mentioned in the referral letter and of dermatologists and dermatology residents (DR) prior to pathologic results.

	Positive predictive values	
Diagnosis	**GP, %**	**dermatologist and DR, %**
Basal cell carcinoma	48.4	72.6
Squamous cell carcinoma	31.6	65.6
Actinic keratosis	73.5	Not applicable
Bowen's disease	0.0	28.6
Melanoma	66.7	100.0
Seborrheic keratosis	82.1	Not applicable
Naevus/lentigo	57.9	Not applicable
Dysplastic naevus	0.0	20.0

Pigmented lesions

Forty-two of 125 of the finally diagnosed seborrheic keratosis were referred as (atypical) naevi. Furthermore, in 2 out of 8 melanomas and of 62 out of 102 benign naevi the correct diagnosis was mentioned in the referral letter.

As compared to the pathological diagnosis, dermatologists and DRs mentioned the correct diagnosis of a melanoma in 62.5% and a dysplastic naevus in 100%. Additional PPVs were calculated (table 3).

Lesion description

In 15.4% of the referrals, GPs added an adequate lesion description by using dermatological terminology. In 24.0%, a lesion description was missing, in 39.5% the word 'spot' was used as a description, in 5.3% the word 'lesion', and in 15.8% the description: 'looks like' was used.

Discussion

The present study provides insight in the quality of GPs' referrals of patients with skin tumours, and their ability to differentiate between malignant and benign skin lesions.

Forty-four percent of all referred patients had benign tumours. Therefore, the question arises whether these referrals were really necessary, and if these numbers might be reduced in the future.

With respect to NMSC, we found that GPs made the diagnosis of BCC in 188 of 734 referrals (PPV 48.4%); 45 of these lesions were diagnosed as benign. The fact that the referral diagnosis of BCC was commonly used for other tumours may be explained by the fact that BCCs are more common than other malignancies[4,7,13] and therefore BCC might be the first diagnosis a GP thinks of in these cases. Furthermore, it was also found that dermatologists and DRs were also less accurate in the diagnosis of SCC and BD, meaning that these tumours are probably more difficult to recognise[14].

Almost 1/3 of SCCs was referred with the diagnosis of BCC. Given the fact that BCCs do not metastasise, whereas SCCs have the potential to do so, this may have the effect that patients with a SCC are not seen by a dermatologist with the urgency needed. In this study, only a few GPs provided an adequate lesion description (15.4%) or performed a biopsy (1.2%). In case of a misdiagnosis (e.g. SCC referred as BCC), an adequate lesion description may help the dermatologist to triage the correct level of priority for a hospital appointment. The encouragement of biopsy use in primary care may be worthwhile since it may lower the number of unnecessary referrals and contribute to the decision of the urgency of a referral. Furthermore, the performance of a biopsy may provide immediate reflection on their differential diagnosis, which could be of educational value. On the other hand, in case of a suspicious lesion, a dermatologist might perform an excision without previous biopsy, in which case referral without biopsy would save pathological costs.

In pigmented lesions GPs only recognized 25.6% of seborrheic keratosis (SK), although they are very common. Thirty-four percent of these SK were diagnosed as (atypical) naevi, a misdiagnosis which is often made[15,16]. Furthermore, only 2 out of 8 melanomas and 62 out of 102 benign naevi were correctly diagnosed. This might indicate that GPs have difficulty in differentiating between pigmented lesions. There are some studies which indicate that dermatoscopy would be of additional value for GP[17,18]. This may suggest that dermatoscopy may help GPs in differentiating SK form other pigmented lesions, which might reduce unnecessary referrals. However, appropriate training and frequent use are necessary for adequate dermatoscopy performance and the question may arise whether GPs would make sufficient use of dermatoscopy to gain its additional value.

The number of additional lesions found in these patients is alarming, and proves the fact that many SC patients develop more than one lesion. The distribution of SC over the body surface has been described in several studies, showing that SC not only appears on the chronically sun-exposed areas of the skin[4,19,20], which pleads for total body examination. In a study of Terril et al.[21], additional (treatment requiring) skin lesions were detected in 67% out of 100 referred patients, 34 of the additional lesions were localized on sites covered by clothing. Therefore, we conclude that total body examination is not performed on a large scale, although it would lead to early SC detection. An explanation of the fact that GPs do not perform full body examination in all cases, could be unawareness of the lesion distribution over the body surface or lack of time.

A possible limitation of our study may be that, in case of a differential diagnosis, only the diagnosis listed first was included in our analysis. Therefore, in some cases the GP or dermatologist and DR could have mentioned the correct diagnosis, but not first in line. Additionally, it should be noted that GPs do not always have a diagnosis for a skin lesion, and sometimes only refer suspicious lesions with the question 'malignant?', or without a question or diagnosis, therefore, 'malignant?' and 'diagnosis missing' were also added to our cross tabulation. We also included benign tumours to establish a complete overview of (unnecessary) referrals made in the full array of skin tumours.

On the basis of our study, we conclude that referrals of patients with skin tumours could be optimized. With the increasing incidence of SC, it is worthwhile to reduce the number of unnecessary referrals, to gain more capacity for patients in need of specialist care, e.g. reducing the number of referrals of benign lesions may lead to a decrease of almost 50% of patients referred with skin tumours.

Therefore, adequate training in clinical tumour characteristics of most common SC, and more frequent use of additional diagnostic techniques are worthwhile to gain appropriate competency in GPs. With the rising numbers of SC the question arises whether more specialised SC care performed by dermatologists is needed in primary care. Another solution might be the training of GPs with a special focus on dermatology to contribute to low key dermatological care. In Australia this concept is already in use, as SC is a major health problem in the fair-skin population of this country, thereby leaving more capacity for dermatologists to treat severely affected patients.

At present, GPs could contribute to optimise their referrals by adding appropriate dermatological lesion descriptions in their referral letters and by total body examination in patients with suspicious lesions.

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3.3

Skin tumour surgery in primary care: do general practitioners need to improve their surgical skills?

M.C.J. van Rijsingen
R. Vossen
B.E.W.L. van Huystee
W.J.M.J. Gorgels
M.J.P. Gerritsen

Dermatology. 2015;230(4):318-23

Abstract

Background
Due to rapid increase in the incidence of skin cancer, it seems inevitable that general practitioners (GPs) will play a larger role in skin cancer care.

Objectives
To assess surgical procedures used by GPs in skin tumour management.

Methods
We performed a retrospective study of 1898 pathology reports of skin tumours excised by GPs in 2009.

Results
In 22.9% no diagnosis was provided on the application form. Mostly, once-off excisions (no preceding biopsy) were performed, 7% of excised lesions were malignant, 35% of excisions were incomplete. Excisions in the face and neck region were incomplete in 65.4%; 22% of melanomas were biopsied or shaved.

Conclusion
This study underlines the difficulties in skin tumour management in primary care. To stimulate adequate resource use, the number of excisions of benign lesions could be lowered, and pretreatment biopsy in non-melanoma skin cancer management should be encouraged. GPs should be aware of their limitations and consider referral of high-risk malignancies.

Introduction

The incidence of skin cancer is increasing in the fair-skinned population worldwide and increasing the burden on health care delivery systems[1-3].

The most common types of skin cancer are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. BCCs and SCCs, together with the premalignant actinic keratosis (AK) and Bowen's disease (BD), comprise the group of non-melanoma skin cancer (NMSC). NMSC has the highest incidence. Melanomas are responsible for the highest skin cancer related mortality[4].

For the treatment of AK, BD, and BCC (depending on the subtype), topical agents can be used, depending on the diagnosis; this can be imiquimod, 5-fluorouracil cream or ingenol mebutate. Another possibility are destructive procedures such as cryotherapy. Treatment modalities for NMSC are many (e.g. photodynamic therapy, radiotherapy, topical treatments, curettage), but excisional surgery is the mainstay of skin cancer management[5].

In many countries skin cancer patients initially present themselves in primary care settings. However, in many countries the majority of skin malignancies are treated by dermatologists[6]. In case general practitioners (GPs) excise skin cancer, it was found that the rate of complete excisions was lower as compared to dermatologists[7], and there were low rates of previous biopsies performed[8]. In Australia, where skin cancer is a significant health issue, GPs already excise the majority of skin cancers[9]. With the rising incidence of skin cancer it is likely that its management will increasingly fall into the realm of general practice. Therefore, it is necessary to gain insight into the quality and necessity of surgical approaches used by GPs at present. This study aims to describe the spectrum and quality of surgical procedures used by GPs in patients with skin tumours.

Material and methods

Population
A retrospective study on pathology reports of skin tumours excised by GPs during the year 2009 was performed. These specimens were investigated by the histopathology department of the Rijnstate Hospital in Arnhem, the Netherlands. In 2009, this region comprised a total of 161 GPs. We only included reports with a malignant or benign tumour in the (differential) diagnosis. Reports of non-tumour material (e.g. eczema, psoriasis) were excluded.

The surgical procedures used by GPs included:

1) excision: wide local excision which includes excision of a lesion along with an area of healthy skin (used for treatment or diagnosis)
2) punch biopsy: diagnostic procedure, performed with a small circular blade
3) re-excision/excision recurrence: excision of a lesion that was not excised completely in a previous excision, or excision of a recurrence after previous treatment
4) shave procedure: horizontal cut with a scalpel to excise the protruding and/or in depth fragment of a tumour
5) curettage: removing a protruding tumour more fragile than the rest of the skin with the use of a sharp ring or spoon curette
6) excisional biopsy: performed with a circular blade (punch biopsy) to completely excise a lesion.

The recorded data included the tumour location, the diagnosis of the GP written on the histopathology form, the final histological diagnosis, the procedure used and the completeness of the excision in case the lesion was (pre)malignant.

The histopathology form used by GPs was a standard form, containing open questions on tumour description and differential diagnosis. In case more than one differential diagnosis was provided, the first was considered to be the main clinical consideration. Personal data on the GPs were not available to the researchers in order to create an anonymous database; therefore GPs could not be contacted in case of missing data.

Statistics

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS®) for Windows (version 20.0). Descriptive statistics and crosstabs were used to calculate the different numbers and percentages.

Results

A total of 2527 reports concerning skin-related material provided by GPs were collected by the pathology department. After selection, 1898 reports were included in the study. Excluded reports were those of non-tumorous lesions, e.g. eczema or psoriasis.

The specimens comprised once-off excisions (excision without preceding biopsy) (58.4%), diagnostic punch biopsies (17.9%), shave procedures/curettages (22.3%), excision biopsies (0.3%), re-excisions (0.4%), excision following a punch biopsy (0.1%) and excision of a recurrence (0.1%). In 0.5% the type of procedure was unknown.

Table 1 provides an overview of histopathological diagnoses and lesion locations. Of all lesions 6.74% were malignant, 89.52% were benign, and 3.74% were pre-malignant.

In the present study a mean of 11.7 lesions were excised per GP over one year, including a total of 159 NMSCs (BCC, SCC, BD, AK and other malignant) excised by all 161 GPs (<1 per GP); furthermore a total of 23 melanomas were excised by all GPs (1 melanoma for every 7 GPs).

Table 1 Overview of lesion location and histopathological diagnosis of all material collected by GPs.

	n	%
Histopathological diagnosis		
Malignant		
Basal cell carcinoma	88	4.6%
Squamous cell carcinoma	16	0.8%
Melanoma	23	1.2%
Other malignant*	1	0.1%
Premalignant		
Bowen's disease	12	0.6%
Dysplastic naevus	17	0.9%
Actinic keratosis	42	2.2%
Benign		
Seborrhoeic keratosis	518	27.3%
Keratoacanthoma	46	2.4%
Naevus	881	46.4%
Lentigo simplex	2	0.1%
Dermatofibroma	188	9.9%
Fibroma	33	1.7%
Other benign	31	1.8%
Location of lesion		
Head and neck	427	22.5%
Trunk	878	46.3%
Extremities	523	27.5%
Unknown	70	3.7%
Total	**1898**	

* Metastatic breast cancer

Histopathology form use

In 22.9% (434/1898) GPs did not add any diagnosis to the histopathology form; of these lesions 21.2% (92/434) were (pre)malignant on histology. In 25.0% (32/128) in the subgroup of histologically diagnosed malignant lesions, GPs also considered a malignancy, whereas 72.9% (1239/1699) of benign lesions were considered as benign. In 8.5% (6/71) in the subgroup of histologically diagnosed premalignant lesions were considered premalignant. The accuracy of defining (pre)malignancies by GPs corresponds with a sensitivity of 25.1% (50/199) and specificity of 72.9% (1239/1699) when all samples are counted. When excluding application forms without a clinical consideration, the sensitivity rises to 42.7% (50/117) and the specificity to 92.0% (1239/1347). The GPs identified 21.6% (19/88) of BCCs, 0% (0/16) of SCCs, and 8.7% (2/23) of melanomas on their histopathology form. In case of SCC, the consideration of BCC was mentioned in 56.3% (9/16).

Type of surgical procedure

In 7.1% (79/1108) of all once-off excisions performed by GPs, histological results reported a malignancy, whereas in 6.5% (22/340) of the punch biopsies a malignancy was demonstrated. The surgical procedures used by GPs in case of (pre)malignancy, are shown in table 2 (based on the differential diagnoses of GPs) and table 3 (based on the final diagnoses of the pathologists). Of lesions excised under consideration of BCC, 22.4% appeared to be a BCC.

Table 2 Procedures used when general practitioners (GP) considered a malignant or premalignant lesion (absolute numbers).

GP's consideration	Excision	Punch biopsy	Re-excision/ excision recurrence	Shave	Excisional biopsy	Unknown	Total
Basal cell carcinoma	51	25	1	12	2	3	94
Squamous cell carcinoma	2	2	-	1	-	-	5
Melanoma	10	-	1	1	-	-	12
Bowen's disease	3	1	-	-	-	1	5
Dysplastic nevus	20	8	-	3	-	-	31
Actinic keratosis	2	4	-	3	-	-	9

Table 3 Procedures used by general practitioners in case of (pre)malignant histopathologic results (absolute numbers).

Histopathological diagnosis	Excision	Punch biopsy	Re-excision/ excision recurrence	Shave	Excisional biopsy	Unknown	Total
Basal cell carcinoma	49	16	3	17	-	3	88
Squamous cell carcinoma	13	1	-	-	2	-	16
Melanoma	17	4	1	1	-	-	23
Bowen's disease	4	4	1	2	1	-	12
Dysplastic nevus	17	-	-	-	-	-	17
Actinic keratosis	8	15	-	19	-	-	42

Table 4 Completeness of excisions in case of (pre)malignant histopathologic diagnosis. *n(%)*

	Incomplete	Complete	Doubtful/ unknown	Total
Basal cell carcinoma	25 (51.0%)	22 (44.9%)	2 (4.1%)	49
Squamous cell carcinoma	5 (38.5%)	8 (61.5%)	0 (0.0%)	13
Melanoma	1 (5.9%)	15 (88.2%)	1 (5.9%)	17
Bowen's disease	1 (25.0%)	3 (75.0%)	0 (0.0%)	4
Dysplastic nevus	3 (17.6%)	10 (58.8%)	4 (23.5%)	17
Total	35 (35.0%)	58 (58.0%)	7 (7.0%)	100

Completeness of excisions

The completeness of excisions was only assessed in (pre)malignant lesions, since in these lesions this is of clinical relevance; only once-off excisions were included. An overview of the completeness of excisions is shown in table 4. A total of 17 melanomas were excised, including 3 in situ melanomas (one of these included the one with 'unknown completeness'), 7 melanomas with a Breslow < 1 and 6 melanomas with a Breslow > 1 (including one 'not completely excised'). The thickness of one melanoma was unknown. Of (pre)malignant lesions located in the face and neck region 65.4% were incompletely excised, as compared to 29.5% on the trunk and 10.7% on the extremities.

Discussion

The present study provides insight into surgical procedures performed by GPs in the management of skin tumours. The chosen procedure types were related to GPs' differential diagnosis and the pathological outcome.

A potential limitation of our study may be that findings are based on a retrospective study in a regional population, and that the numbers in some individual tumour groups are low. Data analysis was only performed on a group level, not on an individual level. Therefore it should be stressed that our results represent the average diagnostic and surgery skills of this group of GPs; individual practitioners may have far better (or worse) results. Additionally, it should be noted that GPs may provide samples for histological evaluation to exclude a malignancy (rather than to confirm a diagnosis), which might influence the choice of diagnosis on the histopathology form. However, the present study does reflect real life practice in primary care with respect to the surgical procedures used in patients with skin tumours.

Histopathology form use

In 22.9% of cases GPs did not propose a diagnosis on their histopathology form; therefore it remains unclear which consideration the GP had that led to the procedure. Delaney *et al.*[10] also noted that most histopathology forms of GPs and hospital specialists did not include a presumptive diagnosis. It may be concluded that many physicians are not aware of the fact that a diagnosis/consideration on the histopathology form may be of help for the pathologist in establishing the diagnosis.

Incidence and management of benign lesions

The majority of excised skin lesions in this study was diagnosed as benign. In a study performed by Buis *et al.*[11] high numbers of benign lesions were submitted for pathological evaluation by GPs as well, with only 4.7% being (pre)malignant. The higher percentage of (pre)malignancies observed in the present study may be due to the increase in skin cancer incidence in the last 10 years, or may reflect regional differences.

Most benign lesions in the present study were also clinically considered to be benign. The intentional excision of a benign lesion may be due to the patient's request[12] or to diagnostic doubt of the GP. However, in many cases a less invasive method, e.g. a shave procedure or curettage, may have been more appropriate.

Surgical procedures in clinically suspected (pre)malignancies

In the case of suspicion on SCC or AK, biopsy procedures were more likely than excisions. Of lesions excised under suspicion of BCC, this diagnosis was only correct in 22.4%. Therefore, in case of diagnostic doubt a punch biopsy would be preferred above once-off excision, since a biopsy is less invasive (more patient-friendly), less time consuming and

may be less expensive. Furthermore, a pathological diagnosis obtained through biopsy is of value in the treatment choice, since the diagnosis determines the margins used in excision. Additionally, in case of a superficial lesion (AK, BD, superficial BCC), a non-invasive treatment may be preferred. In this case a diagnostic biopsy could also prevent an unnecessary excision. However GPs should be aware of the fact that there are mixed type BCCs and that there may be a sampling error when performing a biopsy[13].

If GPs considered SCC or AK as a diagnosis, the number of excisions performed was almost equal or lower to the number of other types of procedures chosen (e.g. biopsy). Since AK can usually be diagnosed clinically and non-invasive treatment is advised, it is encouraging to notice that less extensive procedures are used in the diagnosis of AK.

In almost all patients in whom GPs considered a melanoma, a diagnostic excision was performed. However, in case of clinical suspicion of a dysplastic naevus (with melanoma as an important differential diagnosis), GPs performed a biopsy or shave procedure in 11 (35.5%) patients. According to the Dutch and British melanoma guidelines it is advised to perform a diagnostic excision with a 2-mm margin in case of suspicion for melanoma[14,15]. Furthermore, both guidelines advice GPs to refer patients with lesions suspicious for melanoma[14,15]. Therefore, the question arises whether all GPs in our study were sufficiently aware of the directives provided by guidelines for skin cancer. Furthermore it was found that the number of in situ melanomas excised was small in this study. This might indicate that these were not detected by GPs, or they might have been referred to dermatologists.

Surgical procedures in pathologically proven (pre)malignancies

While 92% of lesions suspected of being melanoma were managed by excision only 74% of pathologically diagnosed melanomas were managed this way, the remainder being managed by biopsy or shave.This may indicate that GPs are aware of the fact that when a melanoma is suspected, apart from referral, no less than an excision is needed. However, the recognition of a melanoma appears to be more difficult. In case of a shave procedure of a melanoma, the GP was mostly in the assumption of treating a benign nevus. A dermatoscope may be a useful tool to help the GP differentiate between melanomas and benign lesions, however adequate experience is necessary[16,17].

Completeness of excisions

The highest percentage of complete excisions was observed in the group of melanomas. Bakhai *et al.*[18] found a complete excision rate of 83.8% in melanomas excised by consultants as compared to 62.3% in those excised by GPs in the UK. Consultants' excision margins were compliant with the guideline in 70.5%, those of GPs in 29.8%. According to the guidelines, diagnostic excision of a melanoma is performed with a 2 mm margin[14,15]. Since not all GPs may be aware of this directive, this may lead to the use of a wider margin and therefore a higher number of complete excisions. It should be noted that the number of melanomas excised by GPs in this study is small.

In NMSC, diagnostic difficulties could contribute to incomplete once-off excisions. Moreover, demarcation of the border of these tumours may be difficult in some cases. Due to the retrospective study design, specific tumour characteristics, surgical experience of GPs and excision margins could not be taken into account. Therefore, we are not able to draw conclusions on margins used in excision, only on the completeness of the excisions.

With respect to tumour location, tumours excised in the head and neck region had the highest percentage of incompleteness, but also excisions of malignancies on the trunk or extremities were often incomplete. In previous studies it was also reported that in the head and neck region more incomplete excisions were performed[8,19]. To lower the number of unnecessary excisions and re-excisions, GPs are advised to perform a representative biopsy of suspicious non-melanoma tumours. If thereafter excision is needed, the GP should preferably refer to a hospital specialist (e.g. dermatologist). BCCs in the head and neck area with poorly defined borders, which are considered high-risk BCCs[20], require wider surgical margins and these patients should preferably be referred to a hospital specialist (e.g. dermatologist). Furthermore, in areas in which the incidence of skin cancer is much higher as compared to Western Europe, GPs are often capable of and used to perform excisions of these tumour types themselves. However, our data show that in countries in which skin cancer training is limited, GPs often have difficulties in excising high-risk skin cancers in the face.

Implications for practice

GPs' capacity in the diagnosis and treatment of skin tumours could be improved. The following might be essential in the training of GPs:

1) With respect to benign lesions, GPs may consider whether excision is necessary.
2) In NMSC, where the diagnosis of the specific tumor (sub)type is in doubt, a preliminary biopsy is the diagnostic method of choice because the pathological results may prevent an excision which may be unnecessary or performed with wrong margins in case of misdiagnosis. The performance of a diagnostic biopsy also provides feedback for GPs on their differential diagnosis and may be of educational value.
3) To provide insight into appropriate margins for the individual tumour types, guideline use should be encouraged .
4) In melanocytic lesions a diagnostic excision should be performed, however in case of suspicion of a melanoma, patients should also be treated as stated in guidelines; in most countries this means referral to a dermatologist.
5) GPs are also advised to be aware of their limitations and consider referral of (high-risk) BCCs (depending on their clinical experience) as well as SCCs (for their metastatic potential) to a dermatologist.
6) Finally, to support the pathologist, it is advised to add a clinical consideration to the histopathology form for pathological investigation.

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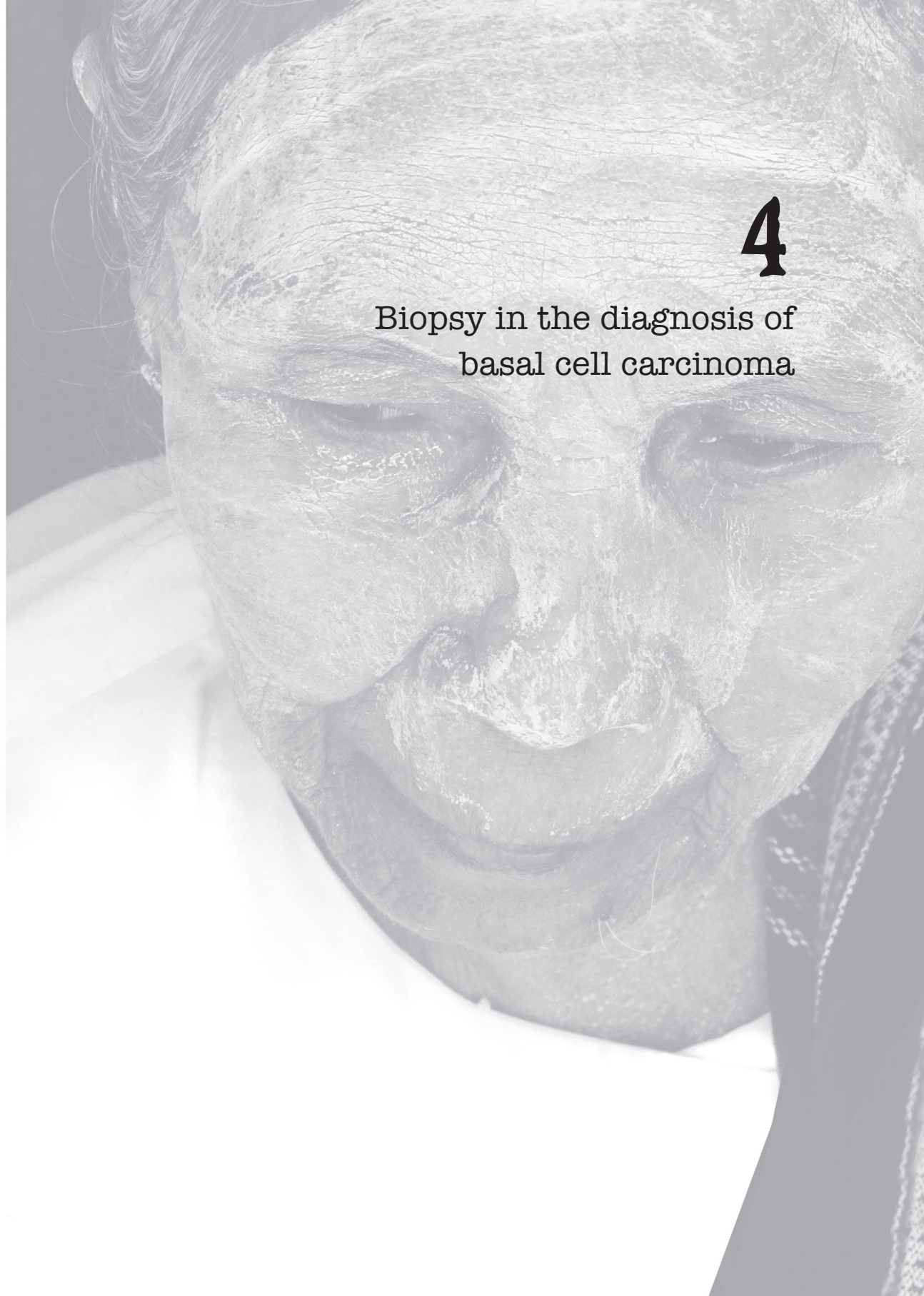

4

Biopsy in the diagnosis of basal cell carcinoma

4.1

The relevance of a diagnostic biopsy in the diagnosis and treatment of basal cell carcinoma

M.C.J van Rijsingen
S. de Mare
R. Vossen
J.P.C. Grutters
J.M.M. Groenewoud
M.J.P. Gerritsen

(submitted)

Abstract

Background
Basal cell carcinoma (BCC) is the most occurring cancer in Caucasians. Many BCCs are diagnosed by punch biopsy, however, these are costly and time-consuming. Therefore, the question rises whether once-off excision (without previous biopsy) is more efficient.

Objectives
To compare once-off excised BCCs with BCCs excised after biopsy, with respect to completeness and efficiency.

Methods
A retrospective study was performed on pathology specimens from 2009, of lesions with a differential- and/or histological diagnosis of BCC. Completeness was analysed in histologically proven BCCs. Efficiency was defined as time spent on biopsy and/or excision in lesions suspicious for BCC. Two-way sensitivity analysis was performed to prove the most time-efficient strategy.

Results
In total 844 once-off excisions and 357 excisions after biopsy were included. In once-off excisions the diagnosis BCC was correct in 84.2%. Overall, no significant difference in completeness between excision types was found. For nodular BCCs, excision after biopsy was significantly more often complete. In biopsies taken prior to excision of infiltrative BCCs, significantly more sampling errors were present in the 'incomplete excision group'. Based on sensitivity analysis, with a mean excision time of 13 minutes, once-off excision was found more efficient if biopsy takes >1.94 minutes.

Conclusion
Diagnostic biopsy in nodular BCC may contribute to completeness of excision, however, overall (all BCC types) no significant difference in completeness was found. Furthermore, sampling errors in biopsies of mixed type BCCs, may affect the excisions' completeness. However, to be more conclusive in omitting diagnostic biopsies, prospective research is essential.

Introduction

Basal cell carcinoma (BCC) is the most frequently diagnosed cancer in Caucasians, with a rapid increasing incidence[1]. As a consequence, the financial burden for our healthcare system will expand further[1]. Therefore, it is relevant to critically evaluate diagnostic and treatment protocols.

BCCs represent the largest group of non-melanoma skin cancer (NMSC). Although they have a low metastatic potential, treatment is necessary to prevent (further) invasion and destruction of the skin and underlying tissues. Topical and surgical treatments are available, however surgical excision is performed in the majority of cases[2,3]. Generally, prior to excision, a diagnostic biopsy is performed to verify the diagnosis and to identify the BCC's histological subtype. Treatment choice and surgical margins are based on the most aggressive subtype. However, the accuracy of a diagnostic biopsy for BCCs is limited and the most aggressive subtype may be missed[4,5]. Furthermore, international guidelines are not uniform in the urge for a biopsy prior to treatment[6-8]. While, the Dutch guideline recommends to perform a diagnostic biopsy prior to treatment choice[9], many dermatologists perform once-off excisions (without previous biopsy) of lesions that are clinically suspected for BCC.

Since punch biopsies and their pathological examination are costly and time-consuming, the question rises whether it is more efficient to excise all clinically suspected lesions by once-off excision. The aim of this study was to compare once-off excised BCCs with BCCs excised after biopsy, with respect to completeness and efficiency.

Materials and method

A retrospective study was performed on specimens processed by the pathology department of the Rijnstate hospital in Arnhem, the Netherlands, over the year 2009. Selected specimens comprised only those provided by dermatologists. In 2009, seven dermatologists were working at the Rijnstate hospital, their working experience as a dermatologist ranged between one to 27 years.

Specimens investigated met the following inclusion criteria: differential diagnosis and/or histological diagnosis of BCC, and treatment by a once-off excision or excision after diagnostic biopsy. Punch biopsies, excisions of recurrences, or re-excisions were excluded.

The following data were obtained from the included reports: differential diagnosis (the first mentioned), histological diagnosis, BCC subtype, location of the tumour, completeness of the excision, excision type, and the occurrence of a recurrence.

Completeness of excision

Completeness of the excision was defined by the pathologist. An excision was complete in case no tumour was involved in surgical margins. An additional analysis took place of all BCCs diagnosed with an infiltrative subtype after excision. Of these BCCs the diagnostic punch biopsies performed prior to excision were also collected and analysed.

Efficiency of excision

The level of efficiency was defined as the time the dermatologist had spent on performing a biopsy and/or excision. Time spent on patients who had a once-off excised lesion was compared to time spent on those who underwent a biopsy prior to excision. To define dermatologists' diagnostic accuracy in diagnosing a BCC prior to biopsy, a sample selection was carried out in patients with lesions suspicious for BCC who were biopsied in 2009.

To estimate the mean excision time, dermatologists working at the Rijnstate hospital collected data on the duration of 40 excisions of skin tumours on the body, face, or neck region. It should be noted that although patients and materials were often prepared by a nurse, the nurse's time was not included in our analysis.

Data analysis

Statistic analysis was performed using the Statistical Package for Social Sciences (SPSS®) for Windows (version 20.0). Descriptive statistics and crosstabs were used to calculate percentages. All bivariate relations were studied in crosstabs with a Chi-square test or a Fisher exact test (in case of low expected numbers). To correct for possible confounding and to be able to detect interaction between excision type and BCC subtype, logistic regression was performed, with completeness of excision as dependent variable. The relations as found in the logistic regression model were comparable with the crude relation (no confounding). Therefore, only cross tables are presented. A p-value of <0.05 was considered significant.

TreeAge Pro 2014 was used for a decision model, to compare time spend on a once-off excision to the time spend on a biopsy followed by excision in patients suspected of BCC. Since excision time and biopsy time may vary per lesion a two way sensitivity analysis was performed to provide insight in the most time-efficient strategy, dependent on the values of these two parameters.

Results

A total of 1201 specimens remained after selection, including 357 excisions after biopsy and 844 once-off excisions. Six hundred eighty-one lesions were located in the head and neck region, 360 on the trunk, and 150 on the extremities. Of 10 lesions, the location was unknown. A total of 1073 (89.3%) of all lesions appeared to be BCCs, of which 151 were superficial, 805 nodular, 107 infiltrative, nine basosquamous, and of one lesion the subtype was unknown.

The group of once-off excised lesions comprised 716 (84.8%) BCCs, 13 (1.6%) squamous cell carcinomas, 5 (0.6%) melanomas, 3 (0.4%) dysplastic naevi, 15 (1.8%) Bowen's disease, 29 (3.6%) actinic keratoses, and 63 (7.8%) benign lesions.

In 812 of all once-off excised lesions, the differential diagnosis of a BCC was mentioned. Within these 812 lesions the diagnosis BCC was histologically confirmed in 84.2%. Out of a random sample of 149 diagnostic biopsies performed in 2009 under suspicion of a BCC, the diagnosis BCC was histologically confirmed in 123 (82.6%) lesions.

Completeness of excisions

In total 11.4% of all BCCs were incompletely excised. BCCs located in the face/neck region (table 1) and the ones with an infiltrative subtype were significantly more often incompletely excised (P < .001).

Table 1 Completeness of all excisions based on location. *(n(%))*

Location	Incomplete	Complete	Total	P-value
Face and neck	97 (15.9%)	514 (84.1%)	611 (100%)	
Trunk	21 (6.5%)	304 (93.5%)	325 (100%)	
Extremities	3 (2.3%)	125 (97.7%)	128 (100%)	.000

Superficial BCCs were more often located on the trunk (61.3%), while nodular and infiltrative BCCs were more often located in the face and neck region (resp. 62.7% and 78.3%). BCC subtypes were equally divided between the two excision groups (P = 0.501). Overall, we found no significant difference in completeness between BCCs excised following a biopsy or once-off excised BCCs (resp. 9.5% and 12.3%, P = 0 .179).

By performing an analysis per BCC subtype, a difference in completeness between excision types was found for nodular BCCs. In nodular BCCs, excision after biopsy was significantly more often complete (table 2). In superficial and infiltrative BCC, no significant differences were found between excision types (table 2).

Table 2 Comparison of completeness of once-off excisions as compared to excisions after biopsy per basal cell carcinoma (BCC) subtype. *(n(%))*

BCC subtype		Incomplete	Complete	Total	P-value
Superficial	Once-off excision	7 (7.3%)	89 (92.7%)	96 (100%)	.748
	Excision after biopsy	3 (5.5%)	52 (94.5%)	55 (100%)	
Nodular	Once-off excision	59 (11.0%)	476 (89.0%)	535 (100%)	.047
	Excision after biopsy	18 (6.7%)	252 (93.3%)	269 (100%)	
Infiltrative	Once-off excision	22 (28.6%)	55 (71.4%)	77 (100%)	.144
	Excision after biopsy	13 (43.3%)	17 (56.7%)	32 (100%)	
Baso-sqamous	Once-off excision	-	7 (100.0%)	7 (100%)	-
	Excision after biopsy	-	2 (100.0%)	2 (100%)	

Analysis of the diagnostic biopsies taken prior to excision of infiltrative BCCs, showed that the diagnosis of an infiltrative BCC was significantly more often missed (sampling error) in the 'incomplete excision group' (table 3). In patients in the 'incomplete excision group', the biopsy only mentioned a nodular or superficial BCC in eight patients (61.5%). In patients with a completely excised BCC, a nodular BCC was found in 4 (23.5%) of the biopsies performed prior to excision.

Table 3 Pathologic results of diagnostic biopsies as compared to the results after excision within the group of infiltrative basal cell carcinomas (iBCC)

	Biopsy nodular/ superficial	Biopsy infiltrative	Total	P-value
Incomplete excised iBCC	8 (61.5%)	5 (38.5%)	13 (100%)	.035
Complete excised iBCC	4 (23.5%)	13 (76.5%)	17 (100%)	

When examining the influence of the body location on the completeness of the excision no significant differences were found between the two excision groups, (face and neck region P = 0.473, trunk P = 0.081, extremities P = 1.000).

During follow up, recurrences occurred in 9 (1.5%) patients with a once-off excised BCC and in 6 (2%) patients with excision after biopsy. There was no significant difference between these groups (P = .586).

Efficiency of excisions

Out of 40 excisions performed by dermatologists, a mean excision time of 13 minutes (range 5-22, SD 3.9) was calculated. A model was performed using a chance of 84.2% on a BCC after once-off excision or biopsy in case of suspicion on a BCC (figure 1). This percentage was chosen since it was based on the highest number of reports and was almost equal to the percentage of correctly diagnosed BCCs prior to biopsy. Based on this model, with a mean excision time of 13 minutes, it appears to be more time efficient to perform a once-off excision in case it would take more than 1.94 minutes to perform a biopsy (figure 2).

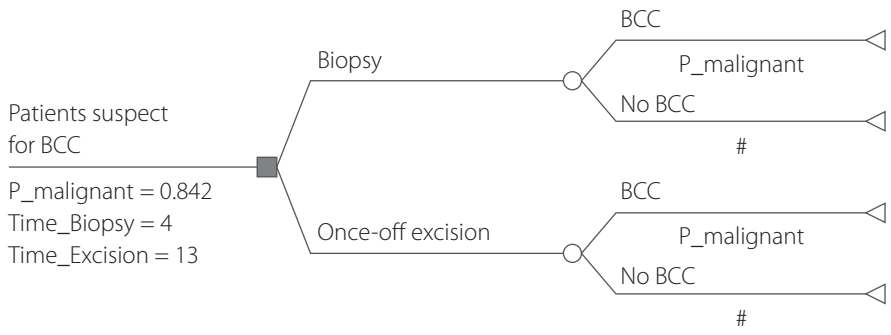

Figure 1 Tree age model to compare the strategies 'Biopsy' (in case of BCC followed by excision) and 'Once-off excision'. Chance on a BCC equals 0.842 (P_malignant), mean biopsy time equals 4 minutes (Time_Biopsy) and mean excision time equals 13 minutes (Time_Excision). Outcome measure is the mean time used to treat a patient in a given strategy.

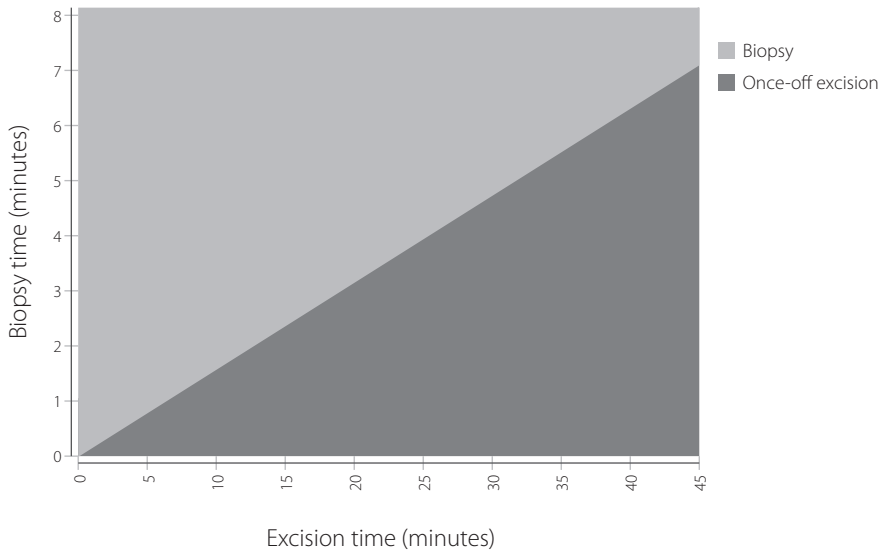

Figure 2 Result of a two way sensitivity analysis with 'Excision time' and 'Biopsy time' as independent variables. A point in the red plane denotes a combination of 'Excision time' and 'Biopsy time' for which the strategy 'Once-off excision' is the most time efficient. A point in the blue plane denotes excision with a previous biopsy as most time efficient.

Discussion

Overall, we found no significant difference in completeness of excisions between excision after biopsy and once-off excision. In a subgroup analysis per BCC subtype, only a significant difference in completeness of the excisions in the group of nodular BCCs was found. In this subgroup once-off excision led to more incomplete excisions. This is surprising since the margin for excision of a nodular BCC according to the Dutch guideline is 3 mm[9] (unless the tumour is > 1 cm), which is the smallest margin advised in BCC. An explanation for this difference might be that only biopsies were performed in those BCCs in which other factors may have had an influence on completeness, e.g. tumours on high risk sites, that are poorly defined, or have a larger diameter[7]. As a consequence, these tumours may have been excised with greater caution than the nodular BCCs that were not biopsied. The nodular BCCs that were not biopsied may have been smaller, more straightforward, and easier to excise. Therefore, smaller margins than 3 mm could have been used. In a study performed by Borgonjen et al.[10] it was found that only 63% of dermatologists use excision margins for low risk BCC (3 mm) as mentioned in the guideline.

In the group of infiltrative BCCs, no significant difference with respect to the completeness of excisions was found. This is surprising, since the surgical margin used for an infiltrative BCC needs to be wider than the margin used for the other subtypes. An explanation for this finding could be the fact that in the incompletely excised infiltrative BCCs, in 61.5% of the biopsies prior to excision, different BCC subtypes (superficial and nodular) were found, leading to smaller margins during excision. Betti et al. also found that margin involvement was more frequent in mixed type BCCs[11].

With respect to efficiency, it was found that based on a mean excision time of 13 minutes, a once-off excision would be more efficient if the time to perform a biopsy would be more than 1.94 minutes. This is a very short time frame, therefore it may be considered to chose for biopsy only in case more time is needed for an excision.

What should be considered is that in some hospital settings biopsies are performed by nurses, which saves doctors time. Also, from patient's perspective, it would be more convenient to perform a biopsy instead of an excision that could have been prevented. Furthermore, the performance of a biopsy could differentiate between different types of malignancies in case of diagnostic doubt and contribute to the urgency of the excision. In case of a superficial BCC a non-invasive treatment could be used. However, as compared to once-off excision, a biopsy costs time to perform, time to inform the patient, and extra costs are spent on materials and pathology analyses. Furthermore, it may delay the time to the actual excision.

Since this study was retrospective, it was not clear what made the dermatologist decide to perform a biopsy or a once-off excision, tumour characteristics and excision margins were unknown. To make recommendations on omitting incisional punch biopsies in specific cases, further prospective research has to be performed.

Conclusion

As far as we know, this is the first study to investigate the efficiency of diagnostic biopsies and the effect of these biopsies on completeness of excisions in BCC. It was found that performance of a diagnostic biopsy in nodular BCC may contribute to the completeness of the excision, however in general a biopsy does not influence the chance on surgical completeness. On the other hand sampling errors in biopsies may mislead the dermatologist in treatment and margin selection. A prospective study to investigate tumour characteristics, excision margins and reasons to chose for an incision biopsy or a once-off excision, may contribute to an evidence based differentiation of cases in which a diagnostic biopsy may be indicated.

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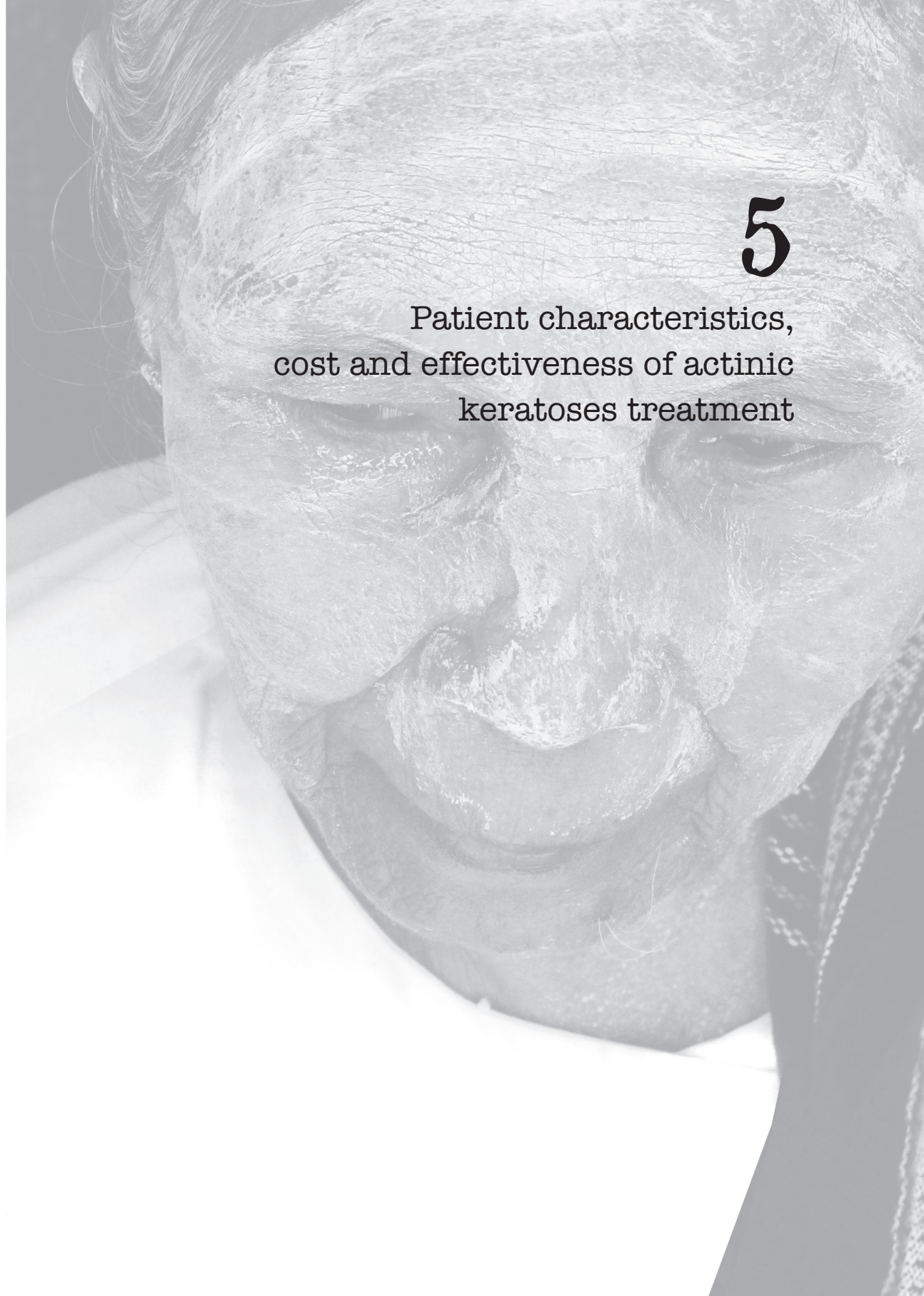

5

Patient characteristics, cost and effectiveness of actinic keratoses treatment

5.1

Real-life data on patient characteristics, cost and effectiveness of field-directed treatment for actinic keratoses: an observational study

M.C.J van Rijsingen
I. Seubring
J.P.C. Grutters
M.B. Maessen-Visch
J.A.C. Alkemade
R. van Doorn
J.M.M. Groenewoud
P.C.M. van de Kerkhof
G.J. van der Wilt
M.J.P. Gerritsen

Acta Derm Venereol. 2015 Aug 17. [Epub ahead of print]

Abstract

Actinic keratoses (AK) occur frequently; however, real-life clinical data on personalized treatment choice and costs are scarce. This multicentre one-year observational study investigated patient-characteristics, cost and effectiveness of methylaminolaevulinate photodynamic therapy (MAL-PDT), imiquimod (IMI), and 5-fluorouracil (5-FU) in patients with AKs on the face/scalp. A total of 104 patients preferred MAL-PDT, 106 preferred IMI and 110 preferred 5-FU. At baseline, significant differences between treatment groups were found; most patients were severely affected (mean 32.5 AK in PDT-group, 20.2 in IMI-group, 22.8 in 5-FU-group). A mean reduction in lesions of 81% after MAL-PDT, 82% after IMI, and 88% after 5-FU was found after one year. Annual costs were €1,950 for MAL-PDT, €877 for IMI and €738 for 5-FU.

These results show that, compared with clinical trials, in the real-life clinical setting AK patients are usually more severely affected and treatment costs are much higher. Furthermore, patient characteristics are important factors in treatment choice.

Introduction

Actinic keratoses (AKs) are chronically recurrent premalignant lesions that occur mainly on chronically sun-exposed skin in Caucasians. In a recent study conducted in the Netherlands, a prevalence of AKs of 49% in men and 28% in women was found in a cohort of the general population aged 45 years or above[1]. Studies performed in other countries also show that AK frequently occurs in the elderly population[2,3]. Because of the potential of AK to develop into squamous cell carcinoma (SCC), treatment is recommended. Given the high incidence of AKs and their predominant occurrence in the head and neck region, a cost-effective therapy with good cosmetic results is needed.

Treatment can be directed at individual lesions, and cryotherapy is the most common treatment used. For patients with multiple AKs and in field cancerization, a field-directed approach is considered more appropriate, e.g. photodynamic therapy (PDT), imiquimod cream (IMI) or 5-fluorouracil cream (5-FU)[4]. Within the group of field-directed treatments no specific patient characteristics to guide treatment choice have been defined.

Although personalized medicine and costs are nowadays of great importance in treatment choice, only a few studies on the cost of field-directed treatments have been published[5-7]. Most of these studies are based on the results of randomized controlled trials (RCTs), in which selected patients with few AKs are treated and treatment choice is based on randomization. It is also known that patients in RCTs do not provide an adequate reflection of real-life clinical practice[8]. The present study aimed to investigate whether patient characteristics play a directive in treatment choice in methylaminolaevulinate (MAL)-PDT, IMI and 5-FU in real-life practice in patients with AKs on the face and/or scalp. Furthermore, data on the cost and effectiveness of these treatment modalities were collected.

Materials and methods

Study design

Multicentre, 1-year observational study, conducted in 2 general and 2 university hospitals in the Netherlands.

Patients

Patients of 18 years and older, with a clinical diagnosis of AKs on the face and/or scalp region, suitable for field-directed treatment (AK in close proximity from each other), were included in the period October 2009 to June 2011. Patients were excluded in case of pregnancy, breast-feeding or contra-indications to field therapy. The study was approved

by the local ethics committee of all participating institutions. All patients gave written consent to participate in the study.

Treatment modalities

Treatment choice between MAL-PDT, IMI and 5-FU was based on patients' preference (after explanation on the treatment options) in combination with the clinical appearance of AKs. The use of treatment was standardized in the participating hospitals.

PDT. During one week prior to PDT, patients were pre-treated with a keratolytic ointment (10% salicylic acid in petrolatum) to remove hyperkeratosis. On the PDT day (at the day-care centre), remaining hyperkeratoses were carefully removed by curettage and the skin was wiped with alcohol. In addition, a thin layer (approximately 1 mm) MAL cream (Metvix®; Galderma) was applied on the treatment area, and covered with an occlusive dressing and tinfoil to prevent influence of light. After 3 hours the dressing and cream were removed and the skin was illuminated with a red light (632 nm, 37J/cm^2) from a light-emitting diode light source (Aktilite®). Three months after PDT, clearance of AKs was assessed. In case of remaining AKs, additional treatment could be performed.

Imiquimod. IMI (Aldara®, MEDA) was used at home 3 times per week (Monday, Wednesday and Friday) for 4 consecutive weeks. Cream was applied prior to normal sleeping hours, and removed in the morning, after approximately 8 hours. Sufficient cream was applied to cover the treatment area (never more than 1 sachet). In case of an intense local reaction, treatment was interrupted and continued after recovery. Four weeks after finishing treatment, clearance of AKs was assessed. In case of remaining AKs, additional treatment could be performed.

5-FU cream. A sufficient amount of 5-FU cream was applied at home, twice daily, to cover the treatment area, until erosions, redness and crusting occurred (duration 2 - 4 weeks). After 3 months, in case of remaining AKs, additional treatment could be performed.

Subsequent and concomitant treatment. In case of AKs remaining after finishing the initial treatment of choice, patients received subsequent treatment, which could be a treatment other than the initial treatment. Depending on the number of AKs and the patient's preference, this could be lesion-directed (cryotherapy) or field-directed therapy. In case side-effects occurred (e.g. itching, infections) patients received concomitant treatment, e.g. topical corticosteroids or antibiotics.

Design

All patients were included and followed by the same 2 investigators. Patients were included at baseline (M0), prior to the start of the treatment. Follow-up evaluation was

scheduled at 3 months (M3) and at 12 months (M12) after treatment start. If necessary, extra appointments were made at the outpatient clinic (e.g. in case of subsequent treatment). Patients treated with IMI were also seen at 8 weeks after treatment start to evaluate the effect of the treatment. Effectiveness of the treatment for study purpose was evaluated only at M3 and M12.

At baseline, the following data were collected: age, sex, race and Fitzpatrick skin type of the patient; location, number and severity of AKs (according to the Olsen classification), number of diagnostic biopsies, previous AK treatments, patients' medical history and medication use. Presence of hypopigmentation, hyperpigmentation, atrophy, erythema, induration, scar formation, hyperkeratosis, and desquamation of the treatment area were scored.

Outcomes

Subjects were evaluated at M3 and M12. The following information was recorded:

Effectiveness of treatment

- *Lesion response:* the total number of AKs was evaluated by inspection, palpation and photography of the treatment area. Lesion response was registered as complete in case of 100% clearance.
- *Cosmetic results:* cosmetic score was classified as excellent when there was no scarring, atrophy, or induration and no or slight occurrence of erythema or change in pigmentation.

Consumption of care and associated costs. All costs related to the treatment of AK in the face/scalp during one year were collected. Total costs were calculated by multiplying every item with the unit costs. Standard unit costs as established by the National Healthcare Insurance Board of the Netherlands were used where possible, otherwise costs were gathered from the hospital administration, and converted to the 2011 price level[9]. Where relevant, different costs were used for general hospitals and university hospitals (general hospital €66 for a consultation, university hospital €134)[10]. MAL-PDT costs were based on the costs for day-care admission (€251)[10], costs for grams of MAL used (tube 2 gram €272, weighed before and after treatment), standard materials used (e.g. occlusive dressing, light source), and the costs for personnel. IMI was prescribed per treatment cycle, including 12 sachets (€60). For 5-FU one tube for the whole treatment area could be used (€41). The cost of a diagnostic biopsy was €150, including costs for pathologic evaluation.

Mean costs per patient were calculated over a one-year period for each treatment group. In addition, mean costs per individual AK lesion were calculated.

Analysis

Study size determination. A sample size calculation was performed in order to obtain a sufficiently precise estimate of the proportion of patients in remission at 1-year follow-up. This was based on the following assumptions: an overall remission percentage of 70% (86% for IMI, 57% for 5-FU, and 88-89% for PDT) [11,12] and a 2-sided 95% confidence interval with a maximum of 60-80%. This resulted in a sample size of 81 patients (α= 0.05) per treatment group. To control for possible loss to follow-up (LTFU), a minimum of 100 patients per treatment group was included.

Statistical methods. Data were collected in a web application (Trial Registry Information and Administration System). For further analysis, data were entered into Statistical Package for Social Science (SPSS 20.0, IBM Corp, Armonk, NY, USA). Descriptive statistics and crosstabs (χ^2, Fisher's exact test) were performed to analyse the differences between the study groups at baseline. *p*-values <0.05 were considered statistically significant in the comparison between baseline characteristics. Based on the observational design of the study, and the fact that our goal was to describe real-life data rather than comparing effectiveness between groups, follow-up results were only described per treatment group. All patients were analysed according to the intention-to-treat (ITT) principle.

Results

Study population

As this study had an observational design, most patients with field AK were willing to participate, thus the out-patient clinic population was well represented. Treatment choice was based on the patient's preference and the clinical appearance of the AK; no randomization was performed. A total of 320 patients was included in the study: 104 patients were initially treated with MAL-PDT, 106 with IMI, and 110 with 5-FU (figure 1). In one of the general hospitals no PDT was performed.

Five patients withdrew from the study directly after inclusion. Ninety-three patients who were treated with MAL-PDT, 101 patients who were treated with IMI, and 98 who were treated with 5-FU attended the M3 visit (figure 1). At M12, 17 more patients were LTFU (PDT 3, IMI 5 and 5-FU 9 patients).

As may be expected in case of a naturalistic study, statistically significant differences were found between the baseline characteristics of the treatment groups (table 1). Patients treated with MAL-PDT had significantly more AKs, a larger affected area (face in addition to scalp), and more previous AK treatments. Those treated with IMI were the youngest and had the lowest number of AKs. Patients treated with 5-FU had the worst baseline cosmetic scores.

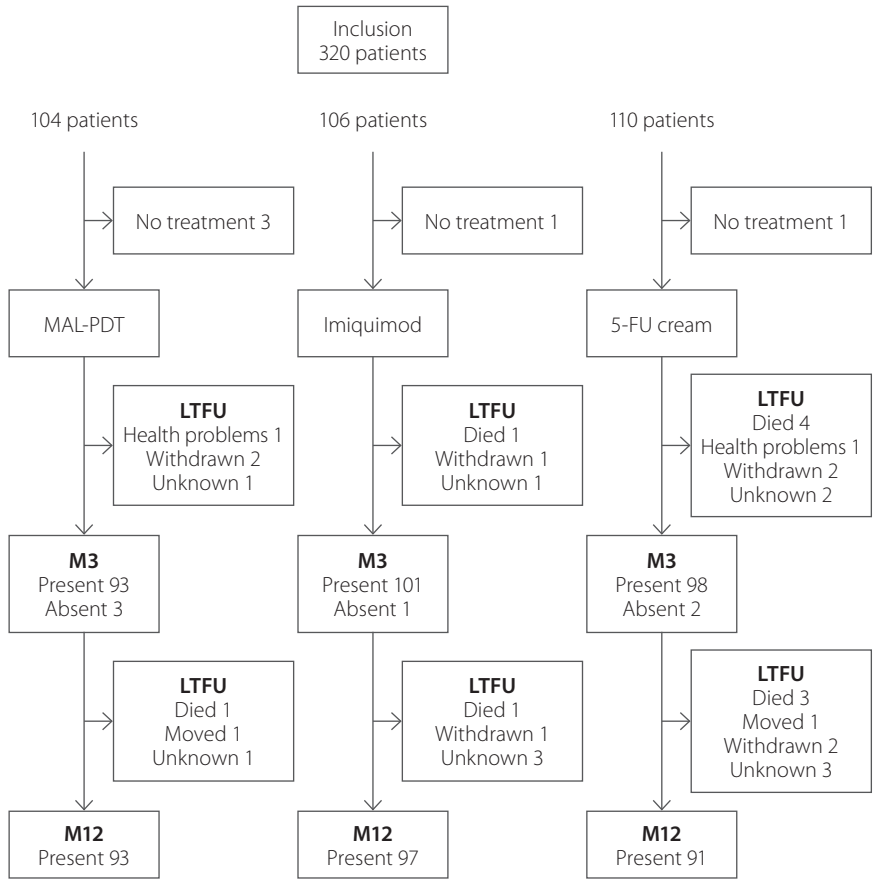

Figure 1 Included patients, patients lost-to follow-up (LTFU) prior to (no treatment) and after treatment (LTFU), and those who missed a visit (absent) at M3 (3 months after treatment) and M12 (12 months after treatment).

Table 1 Baseline characteristics of patients treated with methylaminolaevulinate photodynamic therapy (MAL-PDT), imiquimod cream (IMI), and 5-fluorouracil cream (5-FU) *(n(%))*

	MAL-PDT (n=104)	IMI (n=106)	5-FU (n=110)	*p*-value
Sex (male)	74 (71.2%)	72 (67.9%)	92 (83.6%)	.020
Age[$]	70.4 ± 8.1	68.5 ± 9.2	73.2 ± 8.1	.000
Skin type (Fitzpatrick)				.004
Type 1	35 (34%)	27 (25.7%)	13 (11.8%)	
Type 2	62 (60.2%)	69 (65.7%)	87 (79.1%)	
Type 3	6 (5.8%)	9 (8.6%)	10 (9.1%)	
History				
Bowen's disease				
- 1 or more	23 (22.1%)	7 (6.6%)	18 (16.4%)	.006
Basal cell carcinoma				
- 1 or more	39 (37.5%)	25 (23.6%)	34 (30.9%)	.091
Squamous cell carcinoma				
- 1 or more	15 (14.4%)	9 (8.5%)	24 (21.8%)	.023
AK - Olsen (grade)				.079
1	71 (68.3%)	60 (56.6%)	64 (58.2%)	
2	31 (29.8%)	40 (37.7%)	35 (31.8%)	
3	2 (1.9%)	6 (5.7%)	11 (10.0%)	
AK Location				.000
Scalp	22 (21.2%)	36 (34.0%)	48 (43.6%)	
Face	54 (51.9%)	63 (59.4%)	56 (50.9%)	
Face & scalp	28 (26.9%)	7 (6.6%)	6 (5.5%)	
AK				
Number of lesions[$]	32.48 ± 18.38	20.22± 16.00	22.78± 15.67	.000
Number lesions/size area (mm)[$]	0.15 ± 0.06	0.14 ± 0.10	0.11 ± 0.06	.000
Previous treatment	62 (59.6%)	45 (42.5%)	61 (55.5%)	.034
Cosmetic score[$]	4.47 ± 2.64	4.29 ± 2.24	5.37 ± 2.74	.005
Co-morbidity	2.21 ± 1.81	1.76 ± 1.56	1.70 ± 1.44	.097

[$] mean and standard deviation

Lesion response

The mean percentage of lesion reduction, absolute number of lesion reduction, and total number of full responders after 3 months (M3) and 12 months (M12) are shown in table 2. Patients treated with MAL-PDT showed the highest absolute number of lesion reduction. Patients treated with 5-FU demonstrated the highest percentage of lesion reduction and the highest number of full responders at both M3 and M12.

Cosmetic results

At M12, 65.6% of patients treated with MAL-PDT, 64.9% of patients treated with IMI, and 54.9% of patients treated with 5-FU had an excellent cosmetic outcome.

Table 2 Lesion reduction of actinic keratoses in patients treated with methylaminolaevulinate photodynamic therapy (MAL-PDT), imiquimod cream (IMI) and 5-fluorouracil cream (5-FU)

	MAL-PDT	IMI	5-FU
Number of lesion reduction at:			
M3 *(absolute numbers (SD))*	23.90 (14.6)	15.70 (13.0)	19.66 (13.8)
M12 *(absolute numbers (SD))*	25.81 (16.3)	15.14 (11.9)	19.34 (13.6)
Mean percentage of lesion reduction at:			
M3 *(% (SD))*	79.39 (22.3)	80.00 (24.7)	89.53 (18.9)
M12 *(%(SD))*	81.12 (22.4)	81.65 (23.4)	88.45 (15.8)
Total number of full responders at:			
M3 *(n (%))*	24 (25.8)	34 (34.0)	52 (54.2)
M12 *(n (%))*	19 (20.7)	35 (36.1)	37 (41.1)

SD = standard deviation, M3 = 3 months after treatment, M12 = 12 months after treatment

Consumption of care and costs

An overview of subsequent treatments is shown in table 3. Patients initially treated with MAL-PDT had the highest number of subsequent treatments. In only a few patients was a second cycle with PDT or IMI, as prescribed in the treatment protocol, performed. Since most often only a few isolated AK lesions remained, patients were almost always subsequently treated with cryotherapy. Two patients (MAL-PDT and IMI group) were subsequently treated with CO_2 laser (not mentioned in the table).

An overview of treatment costs per patient is shown in table 4. The mean cost per individual AK lesion was €87 (range €9.9 - 698.3) for MAL-PDT, €71 (range €16.0 – 527.5) for IMI and €55 (range €11.2-380.0) for treatment with 5-FU.

Table 3 Number of subsequent treatments during 1-year follow-up *(n(%))*

	MAL-PDT n=91	IMI n=96	5-FU n=92
Cryotherapy*	71 (78.0)	68 (70.8)	55 (59.8)
5-FU*	8 (8.8)	3 (3.1)	12 (13.0)
IMI*	5 (5.5)	13 (13.5)	2 (2.2)
MAL-PDT*	11 (12.1)	2 (2.1)	1 (1.1)
Total *	75 (82.4)	71 (74.0)	61 (66.3)

*** % per treatment group**
MAL- PDT = methylaminolaevulinate photodynamic therapy, IMI = imiquimod cream, 5-FU = 5-fluorouracil cream

Table 4 Costs (€) per treatment group; methylaminolaevulinate photodynamic therapy (MAL-PDT), imiquimod cream (IMI) and 5-fluorouracil cream (5-FU). (mean ± SD)

	MAL-PDT	IMI	5-FU
Outpatient clinic visits	754.31 ± 275.58 (198.99 – 1604.40)	627.55 ± 26.36 (265.32 – 1203.30)	590.74 ± 27.54 (198.99 – 1337.0)
Biopsies	22.80 ± 9.54 (0.0 – 781.7)	12.26 ± 6.04 (0.0 – 469.02)	21.67 ± 6.97 (0.0 – 312.68)
Treatment	984.11 ± 56.60 (0.0 – 2704.41)	99.50 ± 4.50 (59.59 – 238.36)	41.14 ± 0.0 (41.14 – 41.14)
Concomitant treatment	4.73 ± 1.13 (0.0 – 47.69)	2.34 ± 0.51 (0.0 – 24.40)	2.55 ± 0.43 (0.0 – 24.50)
Subsequent treatment	180.83 ± 25.30 (0.0 – 1432.38)	130.48 ± 22.60 (0.0 – 1550.25)	79.98 ± 10.03 (0.0 – 538.58)
Total	1949.90 ± 75.52 (534.34 – 4127.83)	877.17 ± 43.49 (329.98 – 3332.72)	738.41 ± 34.29 (306.46 – 1875.20)

Discussion

The present study demonstrates which treatment patients with multiple AKs currently receive in real-life clinical situations, how these patients fare in terms of lesion load and cosmetic outcome, and what costs are incurred.

Differences were found in patient characteristics between the treatment groups. Patients who were much more severely affected with number of AKs, who had had more previous treatments, and a higher overall number of previous skin tumours, were more often treated with MAL-PDT. We also noted more co-morbidities in this patient group. The youngest patients, who were least severely affected by AKs and previous treatments were more frequently treated with IMI. Male patients, those of older age, with more previous SCCs, and worse cosmetic scores at M0, were most often treated with 5-FU.

MAL-PDT is registered for AK treatment when other treatments are considered less appropriate. Therefore, it is not surprising that patients in the PDT group were more severely affected and had had more previous treatments. Compared with patients treated with IMI, the number of AKs was 60% higher in the PDT group, compared with patients treated with 5-FU, the number of AKs was 43% higher in the PDT group. It is well known that these AK fields (field cancerization) are more difficult to treat and have a higher potential for recurrence, and that multiple initial treatments are recommended in these patients[13-15]. The higher number of previous treatments in the PDT patient group may thus be a consequence of rapid recurrences and/or therapy-resistant AK.

Another difference between PDT and the other treatments is that PDT is an in-hospital treatment. Patients who are unwilling or unable to treat themselves with IMI or 5-FU will choose PDT. This may explain the larger treatment area and the higher number of co-morbidities in the MAL-PDT group, since these might be patients who prefer more assistance with their treatment.

With respect to consumption of care, it was found that patients treated with MAL-PDT had more pre-treatment consultations. This may be because one of the university hospitals planned a standard pre-PDT visit for instructions. This is not standard in other hospitals. Furthermore, treatment costs for MAL-PDT were the highest. This is mainly due to the high costs of MAL cream and costs related to day-care admission. In patients with large treatment areas, multiple appointments were necessary to treat all lesions.

The number of full responders in the present study is lower than in previous clinical trials[11,16]. This may be because there is a striking difference in the number of AKs at baseline (approximately 7 in previous studies, compared with approximately 25 in the present study). An earlier study from our group, in which patients with AK were treated with MAL-PDT, showed that patients in whom therapy failed, had significantly higher numbers of AK at baseline[13]. This may have an important influence on overall efficacy.

Furthermore, the follow-up period and treatment regimen were different from previous trials. The official treatment protocol for 5-FU prescribes a single treatment session, whereas for MAL-PDT and IMI an additional session after evaluation may be part of the initial treatment session. In our study it was found that, in clinical practice, cryotherapy is more often used as a subsequent treatment instead of an additional cycle of MAL-PDT or IMI.

Compared with previous studies of field-treatment for AK, different costs were found. In a study by Annemans *et al.* [5] cost per AK lesion after 6 months' follow-up and treatment with MAL-PDT was €58. Other studies performed were based on a decision analytical approach or assumptions on the number of treatments[6,7]. Except for Gold's study, in which a standard second treatment cycle was calculated, treatment costs in the literature were lower than the costs found in our study. Although the published studies were performed in other countries, additional factors may explain the differences in costs. Only one of these studies is observational, with a follow-up of only 6 months[5]. In addition, a smaller spectrum of costs was included (e.g. no subsequent treatment, no treatment of recurrences). Moreover, patients in the present study were more severely affected.

The aim of our study was to assess the costs and effectiveness of the various treatment modalities as used in clinical practice for patients with multiple AK. The appropriate design for such a study is an observational longitudinal study, monitoring treatment effects and costs as they arise in practice. The disadvantage of such a design is that many patients received additional treatment for their AK, as AK is a chronic and recurrent disease, therefore the reduction in lesion number at M12 was influenced by subsequent treatments. However, our aim was not to demonstrate the efficacy of a single treatment modality alone.

Another limitation may be the fact that the number of AKs assessed at M3 and M12 were all AKs present in the treatment area, including new lesions. Other study designs mainly assessed the response and recurrences of specific lesions. However, to calculate the costs for field-directed treatment in patients with multiple lesions, it is more appropriate to include all lesions appearing in the treatment area, since they all need treatment.

Conclusion

The present observational study shows that, in real-life clinical practice, patients with AK are more severely affected than patients in clinical trials and that the costs of field-directed treatment are much higher. This is caused mainly by the high number of AKs and the wider range of costs included in our study. New developments, e.g. daylight PDT for individual cases, may reduce these costs in the future.

Since all treatments appeared to be effective in the different treatment groups, patient characteristics and costs could play an important part in treatment choice. Since, at present, MAL-PDT is regarded as a costly treatment, this therapy is preferred for specific cases, e.g. patients with extensive or therapy-resistant field cancerization, or who are not compliant or able to perform treatment at home. Otherwise, 5-FU appears to be the least costly treatment that is effective in cases of multiple AK.

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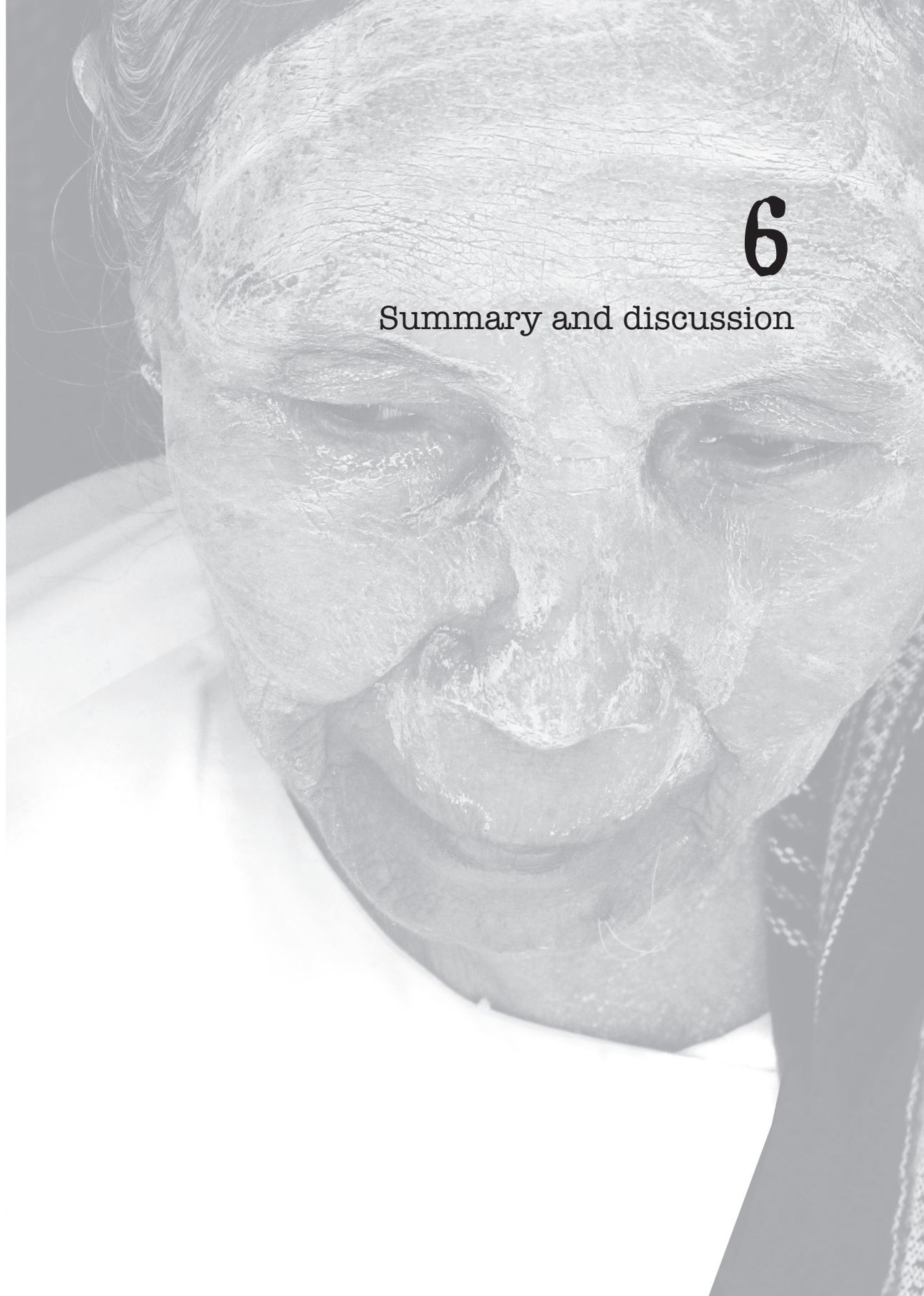
6

Summary and discussion



Summary and discussion

In this thesis outcomes of (observational) studies on skin cancer (SC) practice in primary, secondary and tertiary care in the Netherlands have been described. Data of studies performed in primary care were obtained from a questionnaire, referral letters and pathology reports. To provide insight in SC practice in secondary and tertiary care, real-life patient data were collected and pathology reports were analysed. In this chapter a summary of the main conclusions is written, based on the aims provided in chapter 1, followed by a discussion.

1. To investigate the tumour characteristics of NMSC populations in different hospital settings

Most studies on the incidence and prevalence of non-melanoma skin cancer (NMSC) report the number of patients with a skin tumour. Studies on the number and types of skin cancer per patient are rare. We studied a patient population with field actinic keratosis (AK) in the face and scalp region (population described in **chapter 5**) or with nodular or superficial basal cell carcinomas (BCCs). These patients could have presented themselves with a skin tumour for the first time, or may have had a history of previous skin tumours. Combining the complete number of tumours that developed during a two-year follow-up (FU) with those from the patients' history, we found that 47.1% of our population had more than one malignancy. Furthermore, 59.9% had more than one type of (pre-)malignancy. In another Dutch study, 2106 tumours were diagnosed in 876 patients between 2004 and 2010[1]. Two or more tumours occurred in 406 (46%) patients. The second tumour developed within a median FU of 5 months. In this, as well as in our study, it was found that half of the 'in-hospital SC population' did develop at least a second skin cancer, mainly BCC. From these numbers it may be concluded that SC should be regarded as a chronic disease. Furthermore, the question arises how FU should be performed in the near future. The present Dutch BCC guideline does not advise FU for patients with a single BCC, except if it concerns a high risk BCC[2]. Therefore, patients who are discharged from FU should be advised in self testing of their skin and be aware that additional tumours could occur. Additionally, in the near future, general practitioners (GPs) could play a role in the FU of low-risk SC patients.

As mentioned in **chapter 2**, patients included in our study are only a selection of the total SC population. Therefore, to provide a complete overview of the burden of SC in hospital patients, or in primary care as well, complete registration of all (pre-)malignant tumours should be performed. Attempts to register NMSC in a database have been performed in Denmark[3]. Their conclusion was that the NMSC database had the potential to become a resource for epidemiological research of NMSC, however improvement was necessary, since registration was not complete.

A complete registration of (pre-)malignancies of the skin could also be useful in the financial compensation of SC care. At present, an established maximum is paid for the diagnosis and FU of SC patients. This may be sufficient in case of 'regular' SC patients with a few skin tumours. However, as described in **chapter 2**, we found that 10.8% of patients included in university hospitals had > 10 malignancies. In clinical practice it is noticed that some of these patients may present themselves with high numbers of tumours at once. For this selected patient population the question arises whether the current compensation rate is sufficient for diagnostics, treatment, and FU needed for these patients.

2a. To investigate the present role and skills of GPs in skin cancer care

GPs perform a gatekeeper role in Dutch healthcare. From this position they are the first to see a patient with SC. Therefore adequate recognition of SC, appropriate treatment and/or adequate referral is important. Additionally, GPs could play a significant role in both primary and secondary prevention by means of sun protection advice and total body inspection of patients with sun damaged skin. Up till now, Dutch studies to assess the present role and skills of GPs in SC care are scarce. In **chapter 3**, three paragraphs are devoted to this theme.

As stated in **chapter 3.1**, GPs do request additional SC training, mainly with respect to diagnosing Bowen's disease (BD), squamous cell carcinoma (SCC) and melanoma. However, it was also found that only 3% of GPs believed that SCC treatment should actually be carried out in primary care. Furthermore, in case of a melanoma, the Dutch guideline recommends GPs to refer patients to a dermatologist[4].

With respect to AK, 75%, and with respect to BCC, 20% of the GPs believe that treatment should be performed by GPs. An additional 33.2% would treat low-risk BCC themselves.

When evaluating current practice in primary care, the most commonly used AK treatment is cryotherapy, followed by 5-fluorouracil (5-FU) cream (16%) and imiquimod (IMI) (9%). In case of suspicion of BCC 9.7% would perform a biopsy; 42.2% would perform an excision; IMI and (referral for) photodynamic therapy (PDT) in case of BCC are used by 9.3%. These low numbers indicate that GPs are not familiar with topical treatments for AK and low risk BCC. Our findings are in line with data from a previous study performed in seven different countries[5]. In this study, 31% of primary care physicians would treat BCC, 80% would refer these patients to a dermatologist. The first choice for BCC treatment was surgical therapy, the first choice for AK treatment was cryotherapy. In the same study, more than 80% of dermatologists and primary care physicians reported that the main factors affecting treatment choice for BCC and AK were personal skill level, efficacy, recurrence rate, and cosmetic results. Therefore, low frequency of topical therapy use in primary care for AK and BCC treatment may be caused by a lack of knowledge and experience. Training of GPs would thus be necessary, since it is known that topical treatments are (cost-)effective and have excellent cosmetic results[6-9].

In **chapter 3.2** the results of an analysis of 734 referral letters of GPs are described. In only 1.2% of these referrals, a biopsy was performed. A much lower percentage as compared to the percentages indicated in the questionnaires. This low number may be explained by the fact that the referrals did not only include NMSC and that referred patients might form another population than those treated in primary care. Furthermore, in the population of referred patients, letters of all referring GPs were included, in the questionnaire there may have been a selection of GPs responding who have a special interest in dermatology and therefore take biopsies more often.

With respect to the clinical diagnostics of skin tumours, we found a correct diagnosis mentioned in 39.8% of referral letters. In an evaluation of 1898 analysed pathology reports in **chapter 3.3,** GPs correctly diagnosed 21.6% of BCC, 0% of SCC, and 8.7% of melanomas. Although SCC and melanoma are preferably not treated in primary care, GPs should be able to recognise these tumours to refer them to dermatologists. With respect to the quality of referrals we found that out of 38 confirmed SCCs, only six were referred as SCC. In only 15.4% of referral letters, an adequate lesion description by using dermatological terminology was performed. The latter is an important finding, since adequate lesion description helps the dermatologist to triage referred patients, especially in cases where correct referral diagnoses are missing.

A limitation of the analysis of referral letters is that it does not provide a complete picture of the SC management as it is performed in primary care. Therefore, also pathology reports of skin tumour material collected by GPs were analysed (**chapter 3.3**). The most common used methods were: once-off excision (excision without previous biopsy) (58.4%), shave/curettage (22.3%), and diagnostic biopsies (17.9%). After pathological investigation, almost 90% of these tumours were diagnosed as benign, indicating that GPs excise high numbers of benign lesions using once-off excision. On the other hand, GPs did not excise SC very often; in total159 NMSC (mainly BCC, SCC, BD, and AK) (< 1 per GP) and 1 melanoma for every 7 GPs. This could also be an explanation for the fact that the rate of incomplete excisions was substantial: 65.4% located in the face and neck region, 29.5% on the trunk, and 10.7% on the extremities. The fact that GPs have difficulties with complete excisions of skin malignancies has been confirmed by previous foreign studies as well. In a British study, margin involvement with tumour was present in 68% (15/22) of excision biopsies performed by GPs in melanoma, BCC and dysplastic naevus[10]. Unfortunately lesion location was not mentioned. In a Scottish study, it was found that GPs excise smaller lesions as compared to dermatologists, perform less diagnostic procedures, and have an incomplete excision rate for skin cancer of 23.1%, with the highest for melanomas (34.6%)[11].

With regard to the current screening and FU skills of GPs, in our questionnaire it was found that total body (TB) examination is performed by 34% of GPs in case of BCC and by 19% in case of SCC. Twenty-seven percent of GPs is familiar with the FU guidelines for BCC. With regard to the fact that many patients develop multiple (pre-)malignancies, as

described in **chapter 2**, and the fact that SC also occurs on infrequently UV exposed skin[12] it could be seen as an inaccurateness that not all these patients are screened by means of TB examination, especially in those who are not referred to a specialist. Failure to perform total body examination could result in one in three of melanomas being missed[13]. The lack of performance of TB examination on a large scale is also discussed in **chapter 3.2** in which the finding of 234 additional premalignant and malignant lesions by dermatologists after referral are reported. Most of these patients were referred with a single lesion on the face or scalp; tumours that can be seen without the patient being undressed.

An encouraging finding was the fact that risk factors for development of SC were known by 93% of GPs. However, additional knowledge on risk factors is requested by 70.5%. If education results in an increase in UV protection advice, this is very worthwhile, since it has been proven that, if mediated personally by a GP, sun protection advice can lead to an improvement in sun protection over a prolonged time period[14].

A limitation of the study on the skills of GPs in SC care is the fact that these data are based on patients in which action was taken. The numbers described in **chapter 3.2** and **3.3** are those collected from patients that have been referred or from whom material was collected for pathological investigation. Missing data are those of patients in whom no action was undertaken, patients who were incorrectly diagnosed or in case no pathological investigation was performed after excision. To provide complete insight in their current skills and role in SC care, GPs should be followed prospectively during their practices. This type of research is difficult to perform.

2b. To explore the future role of GPs in SC care

When speculating on the future role of GPs in SC care, data on GPs current role (as discussed at aim 1a) should be considered. Furthermore, additional data as described in **chapter 3** will be summarised below.

In a questionnaire assessing the future role of GPs in SC care (**chapter 3.1**) 93.7% indicated that they judge SC as a health problem in which GPs should play a role, 86.0% would like to play a larger role themselves. This is very encouraging since the cornerstone of the extension of GPs future role in SC care is based on their willingness to participate.

As mentioned previously, 89.2% of GPs treat AK themselves already. This number does not seem to increase after additional education, most likely, because for GPs who treat AK already, additional education would not make a difference. However, most GPs treat AKs only with cryotherapy, whereas in case of multiple AKs, topical (field) treatment is more appropriate.

The number of GPs that would treat BCC after additional education is 51.9%, for BD this is 42.2%. The percentage of GPs that would treat SCC or melanoma after education remains, as can be expected, low (resp. 19.8% and 2.2%).

In order to improve treatment skills in primary care, diagnostic skills should be improved as well, to make sure GPs are aware of the type of tumour they are confronted with. The data presented in **chapter 3** point out that GPs have difficulty with clinical diagnosing (pre-)malignancies of the skin. By analyzing referral letters it was also found that half of the referrals included benign lesions and only half of the patients referred under suspicion of a BCC actually had a BCC. Additionally, out of 125 seborrhoeic keratoses diagnosed by the dermatologists, 42 were referred as atypical naevi. These findings are supported by previous studies, which also demonstrated the difficulties of GPs with diagnosing skin cancer[15-18].

Furthermore, GPs do not use diagnostic tools on a large scale[19]. Performing biopsies in NMSC has educational value, as the results will give adequate feedback on the clinical diagnosis. Furthermore, it lowers the number of unnecessary referrals and excisions of benign lesions. Dermatoscopic investigation is another helpful tool, although primarily in trained hands. It helps to differentiate between pigmented lesions[20-22]. Training in dermoscopy for the most common lesions (nevi, seborrhoic keratoses, angioma) may lower the number of referrals of seborrhoeic keratoses mistaken for naevi and may also prevent unnecessary excisions of benign lesions.

With respect to treatment of skin tumours in primary care, improvement can be made with adjustment and education in a few areas. As discussed previously, GPs mainly excise benign lesions with primary excision. The number of these excisions could be reduced by increasing the use of shave or curettage. These treatments are less invasive, and in case of diagnostic doubt material for histological evaluation is available. The number of excisions may be further lowered by the use of topical agents in the treatment of superficial BCC (sBCC). In previous studies it has been shown that the use of topical creams is cost-effective [6,7]. More widespread use of topical agents for patients with multiple AKs in primary care lowers referrals to dermatologists and contributes to prevention of SCC. As described in **chapter 5**, both 5-FU and IMI are effective treatments that may be used by GPs in the treatment of field AK. Recently, also ingenol mebutate became available for topical treatment of AKs.

With respect to the surgical treatment of SC, GPs are advised to be aware of their own surgical abilities. As discussed in **chapter 3.3**, excisions performed by GPs are often incomplete, especially in the face. Data presented in this chapter is an average of 161 GPs. There may be differences between individual GPs. However, since the number of incomplete excisions in the face and neck region is very high, GPs are advised to refer tumours in this area to a dermatologist. Furthermore, for those who want to perform excisions in primary care, additional training with respect to surgical techniques and knowledge on guidelines (e.g. surgical margins) should become available.

As discussed in **chapter 2**, multiple (pre)malignancies per patient are found in more than half of hospital SC patients. The question arises whether the follow-up of all SC patients

should be performed in hospital settings. A future role of GPs in SC care may also include the FU of patients with low risk BCC and/or AK. However, in this case GPs should use guidelines and perform total body examination.

3. To investigate the value of a diagnostic incision biopsy in BCC

To diagnose BCCs, a diagnostic biopsy is recommended. Previous studies have been performed to investigate the concordance between the BCC subtype diagnosed in biopsy specimen as compared to the subsequent excision[23-25]. These studies show an agreement of 60.9%-72.3%, due to sampling error in which the most aggressive subtype is missed. In **chapter 4** an overview is presented of the completeness and efficiency (in time) of excised BCCs with and without previous biopsy, performed by dermatologists. A total of 357 excisions after biopsy and 844 once-off (without previous biopsy) excised BCCs were evaluated. In 84.2% of all lesions excised under suspicion of BCC, this diagnosis was pathologically confirmed.

With respect to the completeness of excisions no significant difference ($P = 0.179$) was found between BCCs excised after biopsy and once-off excised BCCs. When analysing subgroups, in nodular BCCs (nBCC) significantly ($P = 0.047$) more excisions after biopsy were complete. Due to the retrospective design of the study, there was no explanation found for this difference, since we could not obtain data on excision margins used, exact tumour location and tumour size. Furthermore, we were not able to provide insight in the considerations made by the dermatologists when choosing the used procedure.

In the group of incompletely excised infiltrative BCCs (iBCCs), a significant higher number of disagreement in BCC subtype was found between the biopsy and the excision. This could indicate that the performance of a biopsy with sampling error in this subgroup misled the dermatologist to use an incorrect margin which led to an incomplete excision.

With respect to the efficiency of a once-off excision it was found that, with a mean excision time of 13 minutes, a once-off excision is more efficient if performing a biopsy would take more than 1.94 minutes. Since excision time may differ per tumour, a two-way sensitivity analysis was performed to provide insight into the most efficient strategy, dependent on the excision and biopsy time (**chapter 4**). In this comparison only the doctors' time to perform a biopsy/excision was included. In clinical practice there are more factors to consider, e.g. the time of the nurse spend on the biopsy or excision, the additional time spend on a phone call or visit after biopsy, and the costs of the biopsy.

In some specific cases a diagnostic biopsy is relevant for treatment choice, e.g. in cases when topical treatment is considered in sBCC, or in case Mohs micrographic surgery or radiotherapy is considered in high risk or difficult to excise BCC. Especially since the diagnostic ability of a biopsy is still better than the clinical diagnosis of the dermatologist in sub-typing a BCC[26].

Based on our data it is difficult to decide whether or in which cases a diagnostic biopsy can be omitted in the future. To provide more insight in the effectiveness and efficiency of a diagnostic biopsy, a prospective study should be performed.

The discussion of the necessity of a biopsy prior to excision is mainly relevant in dermatological practice. Although not directly investigated, it seems justified to conclude that in case of suspicion of a BCC in primary care, as discussed in **chapter 3**, a biopsy is recommended since the accuracy of clinical diagnosis by GPs in much lower as compared to dermatologists.

4. To investigate patient characteristics, efficacy, and costs in patients with field AKs

Previous studies have been performed to provide insight in the costs and efficacy of field treatment for AK. However, most of these studies are based on randomised clinical trials in patients with few AKs, providing data which are not applicable in the real-life situation[27-30].

In **chapter 5** we provided an overview of real-life clinical data of 320 patients treated for field AK in an observational multicenter study. All patients included had AK on the face and/or scalp suitable for field directed treatment with methyl aminolevulinate photodynamic therapy (MAL-PDT), IMI or 5-FU.

With respect to patient characteristics documented at baseline, significant differences between the treatment groups were found. Patients in the MAL-PDT group had the highest number of previous treatments, highest percentage of both face and scalp affected, and significant higher numbers of AK lesions. Those treated with IMI were most often females, with the lowest age, and lowest number of AK lesions. The latter is not that surprising since IMI may only be performed in small fields. Patients in the 5-FU group were most often males, with the highest age, and the highest number of previous SCC. The treatment choice was made by both the dermatologist and the patient, based on the (dis)advantages of each treatment. This may explain some of these baseline differences. As PDT is registered for AK treatment when other treatment options are less appropriate, this treatment may have been chosen more often after insufficient efficacy of previous therapies, explaining the higher number of previous treatments in the MAL-PDT group. Furthermore, PDT is an in-hospital treatment and treatment is finished after one single visit. This might explain the fact that patients with higher AK numbers and larger affected areas chose PDT.

The mean number of AKs in the treatment groups was 32 for MAL-PDT, 20 for IMI, and 23 for 5-FU. These numbers also indicate, as mentioned in **chapter 2** as well, that in real life, the NMSC population is more severely affected as compared to patients treated in clinical trials.

As the purpose of our study was to collect real-life clinical data, we chose to perform an observational study. This led to significant differences between the baseline characteristics of the treatment groups, as described above. Therefore, data on effectiveness and cost

are described per group instead of being compared between groups. The mean percentage of lesion reduction after 3 months was 79.4% for MAL-PDT, 80.0% for IMI and 89.5% for 5-FU. After 12 months this was resp. 81.1%, 81.7%, and 88.5%. It should be noted that most patients received additional treatment if necessary and not all patients received a second cycle of the initial treatment in case of remaining AK. We found that in clinical practice, if only few AK had to be treated, cryo-therapy was the first choice of subsequent treatment. This deviates from PDT and IMI treatment protocols in which, in case of residual lesions, an additional cycle of treatment is advised. However, in real-life practice the choice for additional cryotherapy is cheaper and faster than an additional cycle of IMI or PDT.

With regard to the treatment and FU cost over one year, we found mean costs of €1949.90 for MAL-PDT, €877.17 for IMI, and €738.41 for 5-FU. Compared to a previous study performed in Belgium, total cost including 6 months FU were €381 for MAL-PDT[31]. However, in the Belgian study a shorter FU time with less additional treatment costs was performed, a mean of 7.1 AK per patient was found, and no cost for day-care admission were calculated.

Based on patient characteristics, efficacy of treatment and cost, we conclude that MAL-PDT should be used for a specific patient population, e.g. patients with extensive AK, in whom previous therapies have failed or who are not capable to use treatments at home.

Conclusion and future perspective

Skin cancer patients, when investigated in real-life clinical practice are more severely affected than those in clinical trials. Thus, results from clinical (randomised) studies may not be appropriate in real-life clinical practice. Observational studies performed in the real-life situation may contribute to this lack of information and personalized medicine.

Adequate registration of the complete number of (pre-)malignancies of the skin is necessary to create a realistic overview of the extensiveness of the SC problem.

Additional skin cancer training for GPs and GPs in training should precede the shift from low risk skin cancer care to the primary care setting. Although GPs are willing to play a more extensive role in SC care, their diagnostic ability and use of diagnostic tools should be extended. Furthermore, education on treatment regimes and accompanying protocols should be available in general practice.

In secondary and tertiary care further evaluation of the additional value of punch biopsies in the diagnosis of BCC could contribute to efficiency of care and reduction of cost. When choosing a field directed treatment in AK, patient characteristics should also be considered, leading to better cost-effectiveness.

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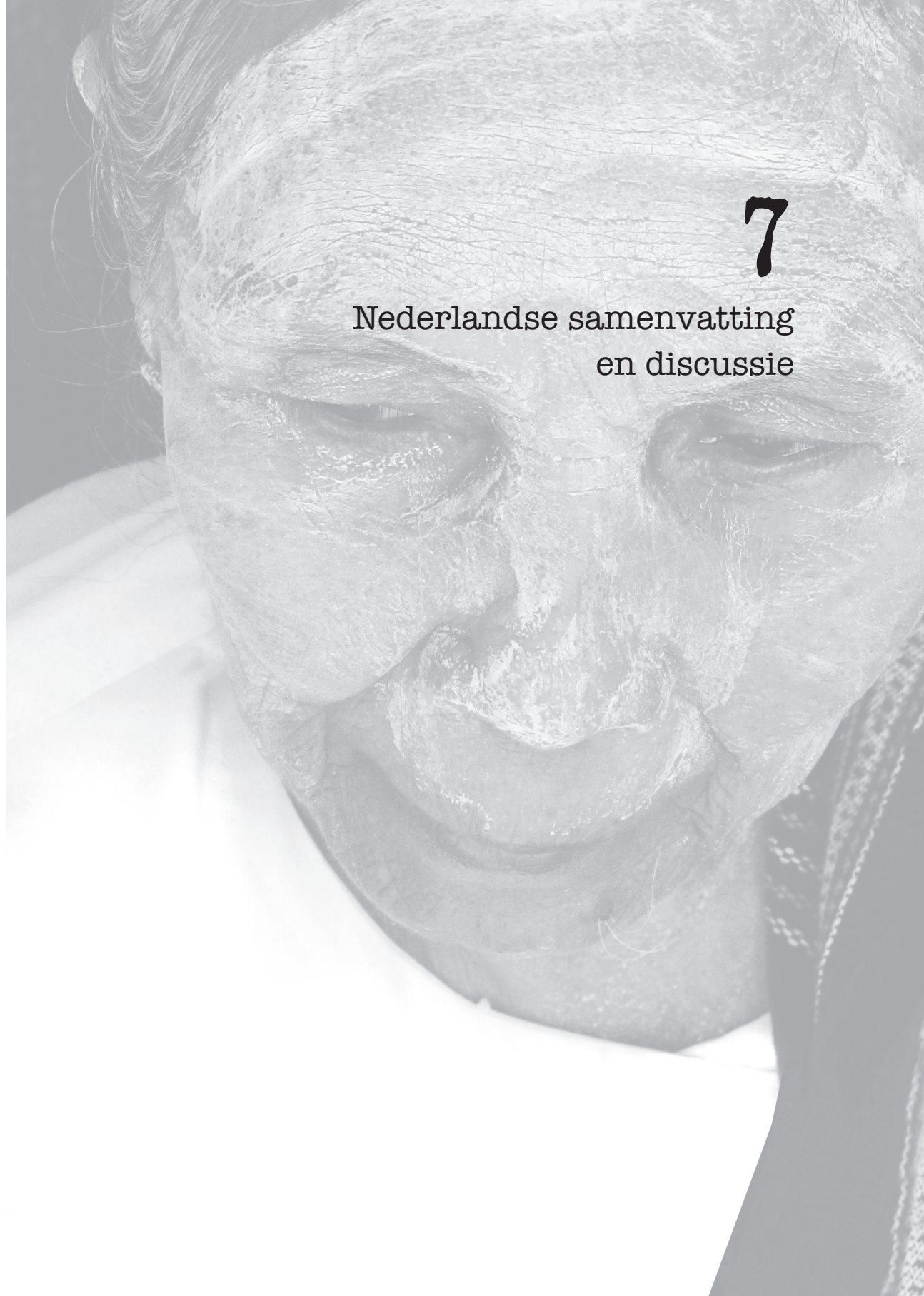

7

Nederlandse samenvatting en discussie

Nederlandse samenvatting en discussie

In dit proefschrift zijn de uitkomsten van (observationele) studies naar de huidkanker zorg in de eerste, tweede en derde lijn in Nederland beschreven. Data uit de eerste lijn werd verkregen door middel van analyse van vragenlijsten, verwijsbrieven en pathologie verslagen. Om inzicht in de huidkankerzorg in de tweede en derde lijn te verkrijgen werden patiëntgegevens en pathologieverslagen verzameld. In een groot deel van deze studies werd 'real-life clinical data' gebruikt, wat betekent dat de verzamelde data zoveel mogelijk een afspiegeling van de dagelijkse praktijk vormen. In dit hoofdstuk wordt een samenvatting van de belangrijkste uitkomsten van deze onderzoeken gegeven, gevolgd door een discussie. Het hoofdstuk is opgebouwd uit verschillende onderzoeksvragen welke wij hebben getracht te beantwoorden.

1. Het in kaart brengen van de tumorkarakteristieken van patiënten met NMSC in verschillende soorten ziekenhuizen.

De meeste studies die gedaan zijn naar de incidentie en prevalentie van niet-melanomen huidkanker (NMSC) vermelden het totaal aan patiënten dat huidkanker krijgt. Studies naar het aantal tumoren en de verschillende soorten tumoren per patiënt zijn minder beschikbaar. Wij hebben een populatie van patiënten bestudeerd die geïncludeerd waren in een studie vanwege aanwezigheid van multipele actinische keratosen (AK) (de populatie zoals beschreven in **hoofdstuk 5**) of een nodulair of superficieel basaalcel-carcinoom (BCC). Deze patiënten konden nieuwe patienten zijn, die zich voor de eerste keer met huidkanker presenteerden, of waren al jaren onder controle vanwege eerdere huidtumoren. Het aantal tumoren van deze patiënten, uit een twee jaar durende follow-up (FU), werd opgeteld bij de tumoren uit het verleden. Hierbij vonden we dat 47.1% van deze patiënten meer dan één maligniteit had ontwikkeld. Daarnaast had 59.9% meer dan één soort (pre-)maligniteiten ontwikkeld. In een andere Nederlandse studie werden 2106 tumoren gediagnosticeerd bij 876 patiënten tussen 2004 en 2010[1]. In 406 (46%) van deze patiënten werden twee of meer tumoren gevonden. De tweede tumor ontwikkelde zich met een mediane FU van 5 maanden. In deze studie, alsmede in onze eigen studie, werd gevonden dat van patiënten met huidkanker uit de ziekenhuispopula-tie de helft een tweede tumor ontwikkelt, meestal zijn dit BCCs. Hieruit kunnen we concluderen dat huidkanker als een chronische ziekte gezien kan worden.

Daarnaast is het de vraag hoe de vervolgcontroles van deze patiënten in de toekomst georganiseerd dienen te worden. In de huidige Nederlandse BCC richtlijn wordt geadviseerd om patiënten na een enkel BCC uit de controle te ontslaan, tenzij er sprake is van een hoog risico tumor[2]. Deze patiënten zouden geadviseerd kunnen worden om zelf onderzoek van de huid te doen en hen erop te wijzen dat er een reële kans is op het ontstaan van een tweede tumor. Daarnaast zouden huisartsen een rol kunnen spelen in de FU van patiënten met laag risico tumoren.

Zoals in **hoofdstuk 2** werd beschreven zijn de patiënten die in deze studie zijn geïncludeerd slechts een selectie van de totale huidkanker populatie. Daarom zou het, om een juiste inschatting te maken van de totale omvang van deze populatie, goed zijn om een complete registratie op te zetten waarin zowel premaligniteiten als maligniteiten van de huid worden geregistreerd. In Denemarken zijn pogingen gedaan om een soortgelijke database voor NMSC op te zetten[3]. Wat zij ontdekten was dat deze database zeker potentie had als bron voor epidemiologische studies naar NMSC. Er waren echter verbeteringen nodig om tot complete registratie van alle tumoren te komen.

Een volledige registratie van alle (pre)maligniteiten van de huid kan ook van toegevoegde waarde zijn voor het berekenen van de vergoeding voor deze populatie. Momenteel staat voor de behandeling en FU van patiënten met huidkanker een maximale vergoeding. Deze vergoeding is toereikend voor de 'normale' huidkanker patiënt. Echter, de vraag is of deze vergoeding ook voldoende is voor die 10.8% van de academische populatie (zoals beschreven in **hoofdstuk 2)** met >10 maligniteiten van de huid. Zeker wanneer deze patiënten zich met meerdere tumoren tegelijk presenteren, zoals in de praktijk vaker het geval blijkt te zijn.

2a. De rol en vaardigheden van huisartsen in de huidige huidkankerzorg in kaart brengen.

In het Nederlandse zorgsysteem hebben huisartsen een poortwachtersfunctie. Vanuit deze positie zijn zij vaak de eerste die de huidkankerpatiënt ziet. Daarom is de diagnostiek van huidkanker door de huisarts, gevolgd door een adequate behandeling en/of verwijzing, van groot belang. Tevens kunnen huisartsen een significante rol spelen in de primaire en secundaire preventie van huidkanker door het geven van zonprotectie advies en het verrichten van huidinspectie bij patiënten met een door de zon beschadigde huid (actinische schade). Tot op heden zijn slechts een klein aantal studies verricht naar de rol en kennis van huisartsen in de Nederlandse huidkankerzorg. In **hoofdstuk 3** van dit proefschrift zijn drie paragrafen gewijd aan dit onderwerp.

In **paragraaf 3.1** worden de resultaten uit een enquête beschreven waaruit blijkt dat huisartsen behoefte hebben aan nascholing op het gebied van huidkanker, voornamelijk wanneer het gaat om het diagnosticeren van Morbus Bowen (MB), plaveiselcelcarcinoom (PCC) en melanoom. We vonden ook dat slechts 3% van de huisartsen vindt dat de behandeling van PCC thuishoort in de eerste lijn. Daarnaast is het zo dat in het geval van een melanoom de Nederlandse richtlijn adviseert om de patiënt naar een dermatoloog te verwijzen[4]. Met betrekking tot AK vonden we dat 75% van de huisartsen vindt dat deze in de eerste lijn behandeld kunnen worden, in het geval van een BCC vindt 20% dit. Een additionele 33.2% zou enkel laagrisico BCCs behandelen.

Met betrekking tot de behandeling in de huisartsenpraktijk vonden we dat cryotherapie de meest gebruikte methode is in geval van AKs, gevolgd door 5-fluorouracil (5-FU) crème (16%) en imiquimod (IMI) (9%). In het geval van verdenking op een BCC zou 9.7% een biopt nemen en zou 42.2% een excisie verrichten. IMI en (verwijzing voor) fotodynamische therapie (PDT) zou door 9.3% van de huisartsen ingezet worden. Deze lage percentages laten zien dat huisartsen niet uitgebreid bekend zijn met het gebruik van topicale behandelingen voor AKs en laagrisico BCCs. Deze bevindingen worden ondersteund door data van een eerder verrichte studie in 7 verschillende landen[5]. Deze studie liet zien dat 31% van de huisartsen een BCC zou behandelen en 80% de patiënt naar de dermatoloog zou verwijzen. Hun voorkeursbehandeling voor BCC was excisie, voor AK was dit cryotherapie. In dezelfde studie werd door meer dan 80% van de dermatologen en huisartsen aangegeven dat de belangrijkste factoren in het maken van de behandelkeuze bij AK en BCC het volgende waren: niveau van persoonlijke vaardigheden, effectiviteit, recidiefkans en cosmetisch resultaat. Het lage aantal huisartsen dat AK en BCC met topicale therapie behandelt in onze studie zou daarom verklaard kunnen worden door een gebrek aan ervaring (en dus ook vaardigheden) met deze middelen. Training van huisartsen met topicale middelen wordt daarom geadviseerd, aangezien bekend is dat deze middelen (kosten)effectief zijn en cosmetisch goede resultaten geven[6-9].

In **paragraaf 3.2** worden de resultaten beschreven van een analyse van 734 verwijsbrieven van huisartsen aan de dermatoloog. Bij slechts 1.2% van de verwezen patiënten met huidtumoren was voorafgaand een biopt genomen. Dit is een lager percentage dan wat de huisartsen in de enquête hadden aangegeven. Een verklaring hiervoor kan zijn dat de verwezen patiënten niet alleen maar NMSC hadden en dat deze populatie anders van samenstelling is dan die van patiënten die in de eerste lijn worden behandeld. Daarnaast bestaat er een kans dat de huisartsen die de enquête hebben geretourneerd niet geheel representatief zijn voor de totale huisartsen-populatie. De respondenten in het enquête-onderzoek zouden huisartsen geweest kunnen zijn met een bijzondere interesse in de dermatologie, die daarom vaker een biopt afnemen.

Met betrekking tot de klinisch diagnostische vaardigheden van huidkanker vonden we dat in 39.8% van de verwijsbrieven een juiste diagnose vermeld stond. In een evaluatie van 1898 pathologieverslagen (**paragraaf 3.3**) vonden we een correcte diagnose in 21.6% van de BCCs, 0% van de PCCs en 8.7% van de melanomen. Hoewel behandeling van PCCs en melanomen in de eerste lijn niet de voorkeur heeft, moeten huisartsen wel in staat zijn deze maligniteiten te herkennen om ze tijdig door te kunnen verwijzen naar de dermatoloog.

In de analyse van de verwijsbrieven bleek dat van 38 histologisch bevestigde PCCs er slechts 6 onder de diagnose PCC verwezen waren. In 15.4% van de verwijsbrieven werd een adequate beschrijving van de laesie gegeven door middel van dermatologische

efflorescenties. Dit laatste is een belangrijke bevinding aangezien een goede laesiebeschrijving de dermatoloog kan helpen in de triage, zeker wanneer een correcte verwijsdiagnose ontbreekt.

Een beperkende factor in de analyse van de verwijsbrieven is dat deze geen compleet beeld geeft van de totale huidkankerzorg zoals deze in de eerste lijn geleverd wordt. Om die reden zijn tevens pathologieverslagen, van materiaal dat door huisartsen is ingestuurd, geanalyseerd (**paragraaf 3.3**). De door huisartsen meest gebruikte methoden voor het verzamelen van materiaal van huidtumoren waren: primaire excisie (zonder voorafgaand biopt) (58.4%), shave/curettage (22.3%) en diagnostische biopten (17.9%). Na pathologisch onderzoek bleek bijna 90% van al het tumormateriaal benigne. Hieruit kan worden afgeleid dat huisartsen hoge aantallen benigne laesies excideren. Ook zagen we dat huisartsen maar zelden maligniteiten excideren: in totaal 159 NMSC voor alle huisartsen samen (< 1 per huisarts) en 1 melanoom per 7 huisartsen. Dit kan ook een verklaring zijn voor het hoge aantal niet-radicaal geëxcideerde laesies; 65.4% in het hoofd-hals gebied, 29.5% op de romp en 10.7% op de extremiteiten. Dat huisartsen moeite hebben met de radicale excisie van tumoren van de huid wordt door verschillende buitenlandse studies bevestigd. In een Britse studie bleek dat in 68% (15/22) van de excisie biopten die huisartsen uitvoerden in melanomen, BCCs en dysplatische naevi, de randen niet vrij waren van tumorweefsel[10]. Helaas was van deze tumoren de locatie niet vermeld. In een Schotse studie werd gevonden dat huisartsen kleinere laesies excideren dan dermatologen, minder gebruik maken van diagnostische methoden en dat 23.1% van de huidkanker niet radicaal werd geëxcideerd, met het hoogste percentage binnen de melanomen (34.6%)[11].

Met betrekking tot de screenings- en FU vaardigheden van huisartsen, bleek uit onze enquête dat huisartsen in geval van BCC een totale huidinspectie doen bij 34% van de patiënten en in geval van PCC bij 19%. Van alle ondervraagde huisartsen geeft 27% aan bekend te zijn met de FU richtlijn voor het BCC. Het is bekend dat patiënten multipele (pre)maligniteiten van de huid ontwikkelen (**hoofdstuk 2**) en dat huidkanker ook op de minder frequent aan ultraviolet (UV) licht blootgestelde delen van de huid voor kan komen[12]. Daarom kan het niet uitvoeren van totale huidinspecties bij huidkankerpatiënten als inaccuraat beschouwd worden, zeker bij die patiënten die niet naar de dermatoloog verwezen worden voor FU. Uit onderzoek is gebleken dat het niet uitvoeren van totale huidinspectie er toe kan leiden dat 1 op de 3 melanomen wordt gemist[13].

Het op grote schaal ontbreken van de uitvoering van totale huidinspectie wordt ook in **paragraaf 3.2** besproken. In deze paragraaf wordt beschreven dat bij patiënten, na verwijzing door de huisarts, nog 234 extra premaligne en maligne laesies werden gevonden. In de verwijsbrieven van deze patiënten stonden voornamelijk solitaire laesies in het gezicht beschreven, tumoren die zichtbaar zijn zonder dat de patiënt zich dient te ontkleden.

Een bemoedigende bevinding is dat de risicofactoren voor het ontwikkelen van huidkanker bekend zijn bij 93% van de huisartsen. Echter, 70.5% heeft behoefte aan scholing op het gebied van risicofactoren. Als het effect van nascholing over risicofactoren leidt tot een toename van zonprotectie-advies in de eerste lijn, dan is dit zeker de moeite waard. Het blijkt namelijk dat zonprotectie-advies, wanneer persoonlijk gegeven door een huisarts, leidt tot een verbetering in het zonbeschermingsgedrag over lange tijd[14].

Een beperking van de studies naar de vaardigheden van huisartsen in de huidkankerzorg is dat deze gebaseerd zijn op die patiënten waarbij actie ondernomen is. De data beschreven in **paragraaf 3.2** en **3.3** zijn van patiënten die dan wel verwezen zijn of waarbij materiaal voor pathologisch onderzoek is weggehaald. De data die ontbreken zijn die van patiënten waarbij de huidkanker niet als dusdanig is herkend en geen actie is ondernomen of het afgenomen materiaal niet naar de patholoog is gestuurd. Om ook inzicht in deze populatie te krijgen zou de huisarts gedurende zijn dagelijkse praktijk gevolgd moeten worden. Een dergelijk onderzoek is helaas moeilijk in de praktijk uit te voeren.

2b. Een beeld vormen van de toekomstige rol van de huisarts in de huidkankerzorg

Wanneer het gaat om de toekomstige rol van de huisarts in de huidkankerzorg, zijn de data omtrent de huidige rol zoals beschreven bij 2a. uiteraard van belang. Daarnaast zal hieronder aanvullende data, zoals beschreven in **hoofdstuk 3**, worden samengevat.

In een enquête, waarin huisartsen gevraagd werd naar hun rol in de huidkankerzorg, gaf 93.7% aan dat zij huidkanker zien als een gezondheidsprobleem waarin zij een rol dienen te spelen, 86.0% wil hierin zelf een grotere rol spelen. Dit zijn bemoedigende resultaten, aangezien de mogelijkheid tot gedeeltelijke verplaatsing van de huidkankerzorg naar de eerste lijn valt of staat bij de bereidheid van huisartsen om hierin deel te nemen.

Zoals eerder beschreven geeft 89.2% van de huisartsen aan AKs zelf te behandelen. Dit aantal neemt niet toe na nascholing, waarschijnlijk omdat het aantal huisartsen dat AK reeds behandeld al hoog is. Echter, wanneer naar de behandelmethode voor AK wordt gevraagd, blijkt dat de meeste huisartsen voornamelijk gebruik maken van cryotherapie en dat topicale (veld) behandeling amper gebruikt wordt.

Het aantal huisartsen dat BCC zou behandelen, na hierin geschoold te zijn, is 51.9%, voor MB is dit 42.2%. Het percentage huisartsen dat PCCs of melanomen zou behandelen blijft laag na aanvullende scholing, respectievelijk 19.8% en 2.2%.

Alvorens de behandelvaardigheden van huisartsen uit te breiden zullen ook de diagnostische vaardigheden aangescherpt moeten worden, zodat huisartsen zich bewust zijn van de aard van de tumor die zij behandelen. De data, zoals beschreven in **hoofdstuk 3**, laat zien dat huisartsen moeite hebben met het diagnosticeren van huidkanker. Uit een analyse van verwijsbrieven bleek dat de helft van de patiënten verwezen was met wat uiteindelijk benigne laesies bleken te zijn en dat slechts de helft

van de patiënten die onder verdenking van een BCC werd verwezen ook daadwerkelijk een BCC had. Daarnaast zijn van de 125 als verruca seborrhoica gediagnosticeerde laesies, 42 laesies verwezen onder verdenking van een atypische naevus. Deze bevindingen worden ondersteund door voorgaande studies waaruit blijkt dat huisartsen moeite hebben met het diagnosticeren van tumoren van de huid[15-18].

Daarnaast blijkt dat huisartsen slechts op kleine schaal gebruik maken van diagnostische hulpmiddelen[19]. Terwijl deze middelen juist van betekenis kunnen zijn in het optimaliseren van de huidkankerzorg. Het nemen van een biopt in geval van NMSC kan van educatieve waarde zijn omdat de huisarts op deze manier directe feedback krijgt op de klinische diagnose. Daarnaast kan dit het aantal onnodige excisies en verwijzingen van benigne laesies omlaag brengen. Een ander diagnostisch hulpmiddel is de dermatoscoop die, mits in getrainde handen, onder andere kan helpen in de differentiatie tussen verschillende gepigmenteerde laesies[20-22]. Trainen van huisartsen in het dermatoscopisch herkennen van de meest voorkomende laesies (naevi, verrucae seborrhoicae, angiomen) kan onnodige verwijzingen en excisies voorkomen.

Met betrekking tot de behandeling van huidtumoren in de eerste lijn zijn er een aantal zaken die aandacht behoeven in nascholingen. Zoals eerder besproken excideren huisartsen voornamelijk benigne laesies met primaire excisie. Het aantal van deze excisies kan verlaagd worden door gebruik van curretage of shave excisies. Deze behandelmethodes zijn minder invasief en in geval van twijfel over de diagnose leveren ze voldoende materiaal op voor pathologisch onderzoek. Het aantal excisies zou nog verder gereduceerd kunnen worden door toenemend gebruik te maken van topicale middelen in de behandeling van oppervlakkige BCCs (sBCC). Uit onderzoek is gebleken dat gebruik van deze middelen kosteneffectief is[6,7]. Het gebruik van topicale middelen voor patiënten met multipele AK in de eerste lijn kan bijdragen aan de reductie van verwijzingen uit deze populatie en kan bij dragen aan de preventie van PCCs. Zoals beschreven in **hoofdstuk 5**, zijn zowel IMI als 5-FU effectieve middelen die de huisarts kan gebruiken in de veldbehandeling van AK. Daarnaast is sinds kort ingenolmebutaat op de markt verschenen als nieuwe topicale methode voor AK.

Bij de chirurgische behandeling van huidkanker dienen huisartsen zich bewust te zijn van hun eigen chirurgische vaardigheden. Zoals in **paragraaf 3.3** is beschreven zijn excisies uitgevoerd door huisartsen vaak niet-radicaal, met name in het gezicht. De data uit deze paragraaf is een gemiddelde van data van 161 huisartsen, natuurlijk kunnen er op individueel niveau verschillen zijn. Echter, gezien het dusdanig grote aantal niet radicaal geëxcideerde tumoren in het gezicht, willen wij huisartsen adviseren deze tumoren door te verwijzen voor behandeling. Verder zal er voor huisartsen die zelf willen excideren onderwijs gericht op operatietechnieken en richtlijn gebruik (oa. excisie marges), georganiseerd moeten worden.

Zoals uiteengezet in **hoofdstuk 2**, zijn er in de ziekenhuispopulatie veel patiënten die meer dan één (pre)maligniteit van de huid ontwikkelen. Het is de vraag of al deze patiënten in het ziekenhuis vervolgd moeten worden. In hun toekomstige rol in de huidkankerzorg zouden huisartsen de FU van laag risico huidkankerpatiënten op zich kunnen nemen. Echter in dit geval moeten er richtlijnen voor de eerste lijn beschikbaar komen en dienen huisartsen totale huidinspectie te verrichten.

3. Inzicht krijgen in de toegevoegde waarde van het biopt in de diagnostiek van BCC

Bij het diagnosticeren van een BCC wordt aangeraden een biopt te nemen. Uit verschillende studies waarin de overeenkomst tussen het BCC subtype na biopt vergeleken is met de diagnose na de aanvullende excisie, bleek een overeenkomst van 60.9%-72.3%[23-25]. Een verklaring voor dit verschil is 'sampling error', waarbij het meest agressieve subtype wordt gemist.

In **hoofdstuk 4** wordt een overzicht gegeven van de radicaliteit en efficiëntie (in tijd) van BCCs geëxcideerd door de dermatoloog met en zonder voorafgaand biopt. Een totaal van 357 excisies na biopsie en 844 primaire excisies (zonder voorafgaand biopt) werden geëvalueerd. In 84.2% van alle laesies, geëxcideerd onder verdenking van een BCC, werd deze diagnose histologisch bevestigd. Met betrekking tot de radicaliteit van de excisies werd geen significant ($P = 0.179$) verschil gevonden tussen excisies na biopt en primaire excisies. Analyse van de verschillende BCC subtypen liet zien dat binnen de nodulaire BCCs (nBCC) significant ($P = 0.047$) meer excisies na biopt radicaal geëxcideerd waren.

Door de retrospectieve opzet van het onderzoek was het niet mogelijk een verklaring voor dit verschil te vinden omdat data over de gebruikte excisiemarges, tumorlokatie en -grootte ontbraken. Daarnaast was het niet mogelijk om inzicht te krijgen in de overwegingen die de dermatoloog ertoe hebben bewogen voor een bepaalde procedure te kiezen.

In de groep van de niet-radicaal geëxcideerde infiltratieve BCCs (iBCC) werd een significant hoger aantal afwijkende BCC subtypes in de biopten voorafgaand aan excisie gevonden. Dit zou er op kunnen wijzen dat het nemen van een biopt (met een ander BCC subtype als uitkomst) leidde tot kleinere excisie marges en daardoor een niet-radicale excisie.

Met betrekking tot de efficiëntie van de primaire excisies werd gevonden dat, bij een gemiddelde excisietijd van 13 minuten, een primaire excisie efficiënter is wanneer het nemen van een biopt langer duurt dan 1.94 minuten. Aangezien de excisietijd kan variëren per tumor, werd een 'two-way' sensitiviteitsanalyse uitgevoerd om een overzicht te maken van de meest efficiënte methode afhankelijk van de excisie en biopsietijd (**hoofdstuk 4**). In deze analyse werd alleen de tijd geïncludeerd die de arts kwijt was aan het uitvoeren van een exisie of biopt. In de dagelijkse praktijk zijn er meer factoren die een rol spelen, zoals de tijd van de verpleegkundige ondersteuning, additionele tijd voor telefonische consulten na een biopt en de kosten van het biopt. In sommige specifieke

gevallen is het uitvoeren van een biopsie belangrijk in het maken van de behandelkeuze, bv. bij topicale behandeling in geval van sBCC of wanneer Mohs chirurgie of bestraling geïndiceerd is bij een hoog risico BCC. Ook omdat de diagnostische kwaliteit van een biopt nog steeds groter is dan de klinische blik van de dermatoloog in het subtyperen van een BCC[26].

Op basis van onze data is het moeilijk om te bepalen of en in welke gevallen het diagnostisch biopt in de toekomst achterwege gelaten kan worden. Om meer inzicht te krijgen in de effectiviteit en efficiëntie van het biopt zal prospectief onderzoek uitgevoerd moeten worden.

De discussie over de noodzaak van het biopt is voornamelijk relevant voor de dermatologische praktijk. Hoewel dit niet direct in dit proefschrift is onderzocht, lijkt het gerechtvaardigd om in geval van verdenking op een BCC in de eerste lijn, zoals beschreven in **hoofdstuk 3**, het nemen van een biopt aan te bevelen, aangezien de diagnostische accuratesse van huisartsen een stuk lager ligt dan die van de dermatoloog.

4. Het in kaart brengen van patiëntkarakteristieken, effectiviteit en kosten bij behandeling van veld AK.

In het verleden zijn reeds studies verricht naar de kosten en effectiviteit van veldbehandeling bij AK. Echter, de meeste van deze studies zijn gebaseerd op gerandomiseerde trials met patiënten met slechts enkele AKs, waardoor deze data niet geheel van toepassing zijn op de dagelijkse klinische praktijk[27-30].

In **hoofdstuk 5** wordt een overzicht gegeven van klinische gegevens uit de dagelijkse praktijk van 320 patiënten die veldbehandeling kregen voor AKs in een observationele multicenter-studie. Alle geïncludeerde patiënten hadden AKs op het gezicht en/of scalp die geschikt waren voor behandeling met methylaminolevulinaat fotodynamische therapie (MAL-PDT), IMI of 5-FU.

Er bleken significante verschillen te zijn tussen de behandelgroepen in de op baseline gedocumenteerde patiëntkarakteristieken. Patiënten in de MAL-PDT groep hadden het hoogste aantal voorafgaande behandelingen, hoogste percentage van zowel gezicht als scalp aangedane huid en een significant hoger aantal AKs. Patiënten die met IMI werden behandeld waren vaker vrouwen, met een lagere leeftijd en het laagste aantal AKs. Dit laatste is niet verassend, aangezien IMI slechts voor een klein oppervlak gebruikt kan worden. Patiënten in de 5-FU groep waren vaker mannen, met de hoogste leeftijd en het hoogste aantal SCC in de voorgeschiedenis. De behandelkeuze werd door de arts in samenspraak met de patiënt gemaakt op basis van de voor- en nadelen van elke behandeling. Dit kan een aantal van de op baseline bestaande verschillen verklaren. Zo is PDT geregistreerd als behandeling voor therapieresistente AK, vandaar dat deze behandeling vaker gekozen zal worden als voorafgaande (andere) behandelingen niet effectief zijn gebleken. Dit kan een verklaring zijn voor het hoge aantal voorafgaande behandelingen in de MAL-PDT groep. Daarnaast is PDT een behandeling die in het

ziekenhuis wordt uitgevoerd en is de behandeling na één bezoek voltooid. Dit kan een verklaring zijn voor het hoge aantal AKs en het grotere oppervlak te behandelen huid in deze groep.

Het gemiddelde aantal AK was 32 in de MAL-PDT groep, 20 in de IMI groep en 23 in de 5-FU groep. Deze aantallen laten zien dat, zoals ook in **hoofdstuk 2** beschreven, patiënten in de dagelijkse praktijk veel ernstiger zijn aangedaan dan in klinische trials.

Aangezien het doel van deze studie, het verzamelen van data uit de dagelijkse praktijk was, is gekozen voor een observationele studie-opzet. Deze opzet heeft geleid tot significante verschillen op baseline tussen de behandelgroepen. Daarom zijn de data met betrekking tot de effectiviteit en kosten van de behandeling per groep beschreven en niet vergeleken tussen de groepen.

Het gemiddeld percentage laesie-reductie na 3 maanden was 79.4% voor MAL-PDT, 80.0% voor IMI en 89.5% voor 5-FU. Na 12 maanden was dit respectievelijk 81.1%, 81.7% en 88.5%. Hierbij moet in acht worden genomen dat de meeste patiënten aanvullende behandeling hebben gehad wanneer dit nodig was en dat niet alle patiënten een tweede cyclus van de initiële behandeling kregen bij resterende AK. In de dagelijkse praktijk blijkt dat wanneer slechts een klein aantal AK resteren, de voorkeur uit gaat naar cryotherapie als aanvullende behandeling. Dit wijkt af van de PDT en IMI richtlijnen waarin wordt geadviseerd een tweede cyclus van deze behandeling te geven bij onvoldoende effect na de eerste cyclus. Uiteindelijk is de keuze voor cryotherapie, zoals gemaakt in de dagelijkse praktijk, goedkoper en sneller dan een extra cyclus PDT of IMI.

Met betrekking tot de behandel- en FU kosten over 1 jaar vonden we gemiddelde kosten van €1949.90 voor MAL-PDT, €877.17 voor IMI en €738.41 voor 5-FU. In een eerder onderzoek uitgevoerd in België, met een FU van 6 maanden, werden totale kosten van €381 voor MAL-PDT gevonden[31]. Echter in deze studie is een kortere FU gebruikt, zijn minder additionele kosten geïncludeerd (zoals dagopname) en hadden patiënten een gemiddelde van 7.1 AK.

Gebaseerd op de patiëntkarakteristieken, effectiviteit en kosten kunnen we concluderen dat MAL-PDT gereserveerd dient te worden voor een specifieke patiëntenpopulatie, te weten patiënten met hardnekkige en uitgebreide AK die niet in staat zijn zelfstandig een thuisbehandeling toe te passen.

Conclusie en toekomst perspectief

Huidkankerpatiënten, onderzocht in de dagelijkse praktijk, blijken ernstiger aangedaan te zijn dan patiënten uit klinische trials. Hieruit kan geconcludeerd worden dat resultaten van (gerandomiseerde) trials niet altijd toepasbaar zijn op de dagelijkse praktijk. Observationele studies, die een duidelijker beeld geven van de alledaagse praktijk, kunnen bijdragen aan het invullen van het hiaat aan kennis dat nodig is voor het leveren van zorg op maat.

Zo kan registratie van het totale aantal van zowel premaligniteiten als maligniteiten van de huid een realistischer beeld geven van de omvang van het huidkanker probleem.

Met betrekking tot de eerste lijn werd gevonden dat aanvullende scholing over huidkanker voor huisartsen en huisartsen in opleiding nodig is, alvorens een deel van deze zorg naar de eerste lijn te verplaatsen. Hoewel huisartsen bereid zijn een grotere rol te spelen in de huidkanker zorg, zal hun diagnostisch vermogen en het gebruik van diagnostische hulpmiddelen verder uitgebreid moeten worden. Daarnaast moeten trainingen in huidkankerbehandeling en bijbehorende richtlijnen beschikbaar zijn voor de eerste lijn.

In de tweede en derde lijn zou verdere evaluatie van de toegevoegde waarde van het diagnostisch biopt bij BCC bij kunnen dragen in efficiëntere zorg en reductie van kosten. Wanneer voor veldbehandeling van AK een geschikte methode gekozen moet worden, zal het meenemen van patiënt karakteristieken kunnen leiden tot een betere kosteneffectiviteit.

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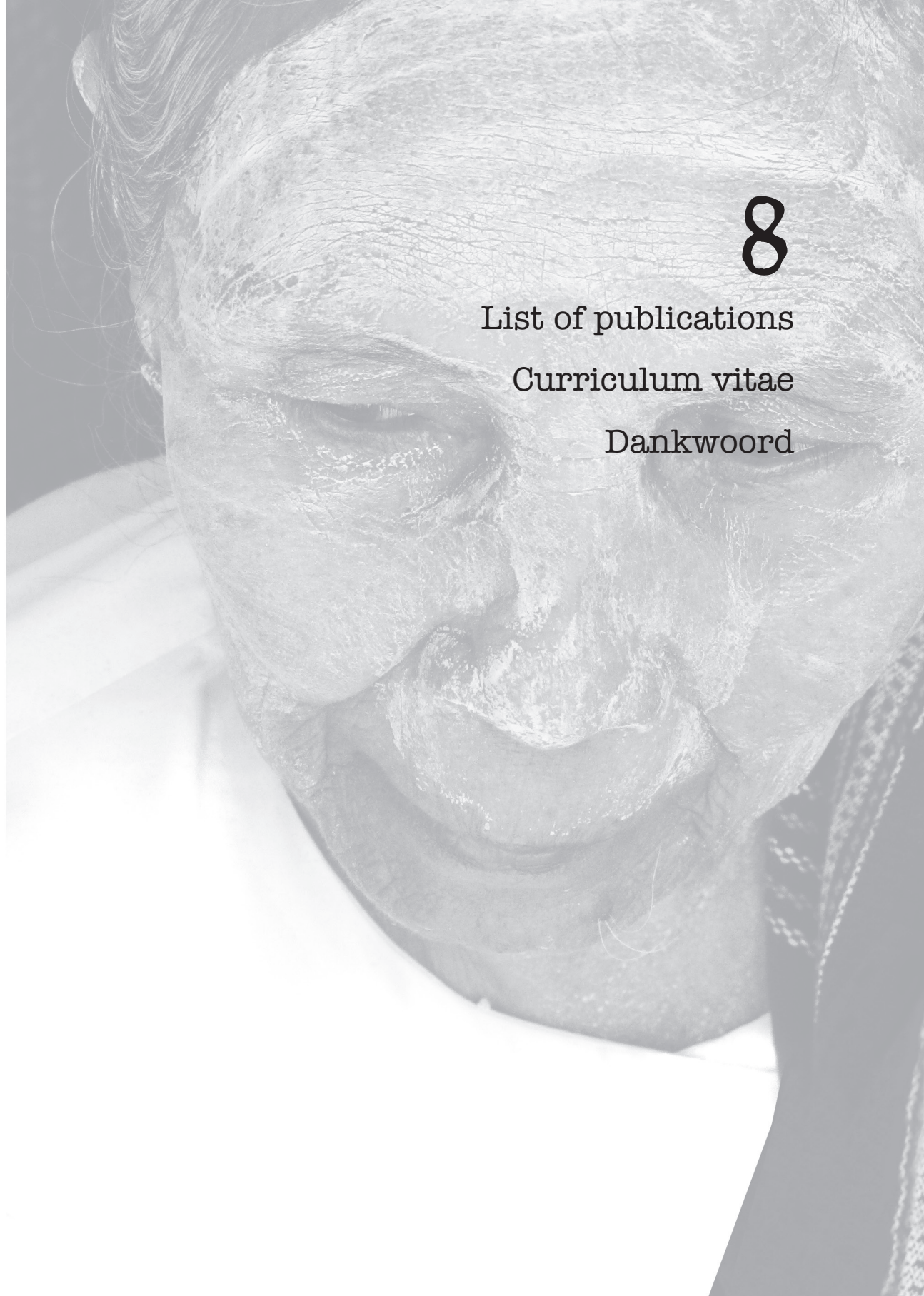

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List of publications

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Publications related to this thesis

van Rijsingen MCJ, de Mare S, Vossen R, Grutters JPC, Groenewoud JMM, Gerritsen MJP. The relevance of a diagnostic biopsy in the diagnosis and treatment of basal cell carcinoma. (submitted)

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Curriculum Vitae

Margit Catharina Johanna van Rijsingen werd geboren op 29 april 1983 in Eindhoven. Nadat zij in 2001 haar VWO diploma haalde aan het Bisschoppelijk College te Weert startte zij met de propedeuse psychologie aan de Universiteit Maastricht. In het jaar daarop volgend voltooide zij het eerste jaar van de bachelor gezondheidswetenschappen. In 2003 kon zij starten met de studie geneeskunde aan dezelfde universiteit. Gedurende haar doctoraal was zij tevens werkzaam voor de Universiteit Maastricht in zowel binnen- als buitenland en volgde zij extra-curriculair onderwijs in tropenziekten en medische ethiek. Enkele maanden van haar artsexamen bracht zij door in Zuid-Afrika voor haar co-schap gynaecologie. Ook ving zij in deze periode aan met een literatuurstudie naar huidafwijkingen bij cryoglobulinemie onder begeleiding van dr. P. Poblete-Gutiérrez op de afdeling dermatologie in het Maastricht UMC (toen nog Academisch Ziekenhuis Maastricht). Zowel haar klinische als wetenschapsstage in het 6de jaar van de opleiding volbracht zij op deze afdeling, waar zij onderzoek deed naar de immunodiagnostiek van bulleus pemfigoid. Een onderzoek dat deels plaatsvond op de afdeling medische immunologie. In november 2009 behaalde zij haar artsexamen, in diezelfde maand ging zij van start met haar promotietraject aan de afdeling dermatologie van het Radboudumc. Vanaf 2013 was zij in opleiding tot dermatoloog tot zij na 2 jaar besloot de opleiding te beëindigen. Heden is zij met veel plezier werkzaam als arts bij ArboNed. In de toekomst hoopt zij zich onder andere te specialiseren in de arbeidsdermatosen. Tevens wil zij doorgaan met het uitvoeren van wetenschappelijk onderzoek.

Dankwoord

En dan is het klaar en eindelijk tijd om iedereen te bedanken. En wat zijn er dan opeens veel mensen die je hebben geholpen. Allereerst wil ik alle 600 **patiënten** bedanken die ik al die tijd heb mogen vervolgen en tot in den treuren vragenlijsten hebben ingevuld. Uiteraard zou ik ook graag de leden van de manuscript commissie willen bedanken voor het beoordelen van mijn manuscript en voor hun aanwezigheid vandaag.

Daarnaast wil ik **alle medewerkers van de afdeling dermatologie van het Radboudumc** bedanken. 6 jaar lang heb ik op deze afdeling mogen werken en wat is er veel gebeurd in die tijd.. Ik had me geen betere plek met fijnere collega's kunnen wensen dan jullie tijdens alles wat er de laatste jaren is gebeurd. Bedankt voor het luisterend oor en alle liefs en begrip toen het even niet mee zat. Ik mis jullie nu al!

Verder zijn er een aantal mensen die een belangrijke rol hebben gespeeld tijdens mijn promotie traject en ik daarom hieronder speciaal wil benoemen:
Professor van de Kerkhof, bedankt voor alle gesprekken die we onder het genot van een 'kopske' koffie in uw kamer hebben gevoerd. Bedankt voor alle tijd die u voor mij heeft genomen en bemoedigende woorden die mij zowel privé als tijdens mijn onderzoeksperiode hebben gestimuleerd om door te zetten.

Professor van der Wilt, als we vastliepen met het onderzoek, of als ik de grote lijn even niet meer zag in de chaos van data, dan was u er om weer 'orde te scheppen'. Bedankt daarvoor en voor de theorie: '1 artikel, 1 boodschap' die ik nog steeds in mijn hoofd hoor als ik een artikel aan het schrijven ben.

Rianne Gerritsen, lieve Rianne, 6 jaar geleden solliciteerde ik bij jou voor de functie van OIO, niet wetende dat ik later nog heel vaak in diezelfde kamer zou zitten voor overleg. En wat hebben we veel overlegd, besproken en naar het computerscherm met data voor het CVZ rapport gestaard. Ik wil je bedanken voor de supervisie, de overlegmomenten, maar ook voor die keren dat ik bij jou en Peter-Paul mocht komen logeren als het spoor was dicht gesneeuwd en ik niet naar Utrecht kon. En niet te vergeten al die keren dat we samen met de voetjes van de vloer gingen op congres! Bedankt voor het luisteren en je interesse!

Ik ben voor mijn onderzoek in een aantal ziekenhuizen werkzaam geweest waar ik oncologie-poli's deed om patiënten te kunnen includeren en vervolgen. Hieronder wil ik deze afdelingen bedanken:

Uit het **Rijnstate in Velp** zou ik graag alle medewerkers willen bedanken voor de fantastische tijd die ik bij jullie heb gehad. Alle gezellige lunchmomenten (met Erna taartjes!), de dagjes uit, kerstborrels en natuurlijk de fantastische supervisie (al die keren

dat ik Jaap bij de laser heb weg gekaapt). Ik heb ontzettend veel geleerd in de jaren bij jullie en ontzettend veel patiënten geïncludeerd. Ik denk dat zeker de helft van mijn publicaties in samenwerking met jullie tot stand is gekomen (dank Barbara, Saskia en Birgitte). En niet te vergeten, administratiedames: bedankt voor het eindeloos verzetten van patiënten op onze spreekuren. Tevens dank aan de **afdeling pathologie** in het Rijnstate voor het aanleveren van alle data.

Uit het **LUMC** zou ik alle artsen willen bedanken voor de inclusie en supervisie op de poli, de verpleging voor de hulp als ik iets niet kon vinden. De administratie, en dan met name **Paula** (you're the best), heel erg veel dank voor het verzetten en bellen van patiënten!

Iedereen van de afdeling dermatologie in het **CWZ**: wat was het fijn dat wij, toen de inclusie vastliep, bij jullie mochten komen includeren. En toen ging het opeens snel met alle patiëntenlijstjes die dan weer klaar lagen op het bureau van Hans. Bedankt voor de supervisie en hulp met biopsie spullen zoeken. Maar natuurlijk ook voor alle leuke grappen en gezellige momenten.

En dan last but not least: mijn eigen afdeling in het **Radboud.** Om te beginnen alle arts-assistenten en dermatologen bedankt voor het verwijzen van patiënten naar de OncoZon poli, het overnemen van poli's en geven van supervisie als Rianne afwezig was. **Yvonne Leusink**… hoe vaak heb ik jou de centerfold in mijn boekje beloofd, ik denk wel 156 keer? Helaas geen foto, maar wel 1000 maal dank voor al je hulp op onze poli en met het nabellen van patiënten. O ja, en bedankt voor het leren delegeren... Anja en Jan, dank voor de enorme hoeveelheid foto's die jullie van onze patiënten hebben gemaakt. De verpleging bedankt voor alle ondersteunende hulp, inplannen van OK's en wegen van de Metvix. Tevens wil ik jullie bedanken voor jullie onuitputtelijke bron van grappen, interesse, lieve knuffels (met mijn vriendinnetje), troost stukjes chocola (M.), hilariteit bij de verpleegpost (you know who.. ☺), **Jan Boezeman** voor de hulp bij alle financiële vragen en **Piet van Erp** bedankt voor het DROBO beheer.

Hans Groenewoud, ik durf toch wel te zeggen dat als jij er niet was geweest, dit proefschrift er ook niet was geweest. Ik kan niet eens een schatting maken van het aantal uren dat we op jouw kamer en zelfs bij jou thuis hebben doorgebracht met het uitvoeren van analyses en brainstormen over BBCs, Imiquimop, of hoe heten die dingen ook alweer... Maar ik denk dat als je alle uren achter elkaar plakt je op een erg lange reis kan. O ja, en ook daar hebben we het veel over gehad. Nog plannen? Ook veel dank voor jouw bijna buurvrouw **Janneke Grutters**. Wat fijn dat jij bij ons onderzoek betrokken was met je expertise op het gebied van alles waar ik niks vanaf weet en heldere uitleg!

Ik heb niet alleen onderzoek naar huisartsen, maar ook met huisartsen gedaan: **Toine Lagro** en **Wim Gorgels**, bedankt voor jullie benadering vanuit de eerste lijn en kritische beoordeling van mijn artikelen. Wim, fijn dat we zo vaak konden overleggen/bellen/mailen als dat nodig was.

Voor mijn studie naar de huisartsen heb ik hulp gehad van stagiaires; **Brigitte van Bon** en **Sabine Hanssen**. Bedank en succes met jullie carrière. Student-assistent **Eline Spierings**, bedankt voor je hulp bij het soms monotone invoerwerk en de snelheid waarmee je alles oppakte. Ik ben benieuwd waar we elkaar binnenkort weer tegen komen. **Robin Vossen** bedankt voor het uitpluizen van alle pathologie verslagen.

Met de onderzoeksgroep van het ZonMw project hadden wij op regelmatige basis overleg over hoe nu verder en wat te doen met alle data die we hadden, **Helma Monteban**, **Patricia van Lith** en **Albert Riemens** dank voor jullie input hierin.

Inge Seubring, samen hebben wij de enorme klus geklaard van de inclusie en follow-up van 600 patiënten. Dit verliep niet altijd even soepel als we hadden gehoopt en wat hebben we uiteindelijk een uren gedraaid om dit toch voor elkaar te krijgen. Ik ben zo blij dat we dit samen hebben kunnen doen. Bedankt dat je mij hebt helpen relativeren als ik aan het stressen was, succes met je verdere carrière.

Alle 'bieb' collega's, na jaren onderzoek doen een hele rij: **Rieke, Michelle, Haike, Kim, Esther, Renee, Anne, Jeffrey, Lisa, Malou, Maartje, Inge** en **Jorre**. Bedankt voor alle gezelligheid, kopjes thee, taartjes en biertjes op vrijdag. **Paula**, wat een goeie tijd heb ik met jou in de vissenkom gehad, fijn om samen te spuien, maar ook om lief en leed te delen. **Tom Hillary** bedankt voor het overnemen van onze poli en meewerken aan ons onderzoek. **Marisol** en **Wilmy** dank voor alle lieve woorden bij zowel werk als privé gerelateerde tegenslagen. En Marisol.. misschien mag ik nu nog een extra knuffel..?

Toen ik naar Nijmegen verhuisde kende ik hier niemand. **Juul, Annet, Romy, Karlijn** en **Anke** wat hebben jullie mij hier een warm welkom gegeven samen met jullie mannen. Buiten het onderzoek en de cocom's hebben wij vrijgezellenfeestjes, bruiloften en vakanties gedeeld. Dank voor alle momenten van stoom afblazen op de racefiets of in de kroeg. En nog veel meer dank voor alle steun die ik de laatste jaren heb gekregen en het geduld dat jullie met mij hebben gehad (☺ xx). Zo fijn dat jullie er zijn!

Mijn oud-collega-AIOS, jullie staan hierboven al een keer vermeld, maar ook jullie wil ik bedanken voor de 2 fijne opleidingsjaren die ik met jullie heb gehad. **Paula, Esther, Haike** en **Rinke** bedankt voor jullie luisterend oor als roomies op C40, jullie weten wel waarom! **Satish**, heel erg veel dank voor alle brainstorm momenten, artikelen en hoofdstukken uit mijn boekje die je na hebt gekeken. We zijn een goed NMSC-team, leuk dat we dat kunnen delen, en dan gaan we in maart ook nog on-tour! En wat fijn dat we elkaar nog zo vaak zien en **Joris** dan lekker voor ons kookt ☺. Veel succes met je eigen boekje! **Elsemieke** bedankt voor alle peptalks en leuke etentjes.

Mijn kersverse **ArboNed collega's**: dank voor het aanhoren van al mijn proefschrift verhalen en gestress over de voorbereidingen voor de verdediging!

Lieve **Juultje**, met jou werd de vissenkom de vogelkooi vol met Queen en Brabantse grapskes. Buiten de mooie feestjes samen heb ik nog veel meer met je kunnen delen. Als ik niet lekker in mijn vel zat door werk, privé of een debakel op de IC in Lijiang dan was jij (samen met **Rick**) er altijd om mij te helpen. Door jou ben ik tot vele inzichten gekomen, dank voor je begrip altijd weer. Fijn dat je mijn paranimf wilt zijn, ik heb je vast nodig-nodig.

Paul Frerichs, de meeste jaren van mijn onderzoek waren wij samen, nu niet meer. Toch wil ik je bedanken voor al die jaren dat je mij hebt gesteund en in mij hebt geloofd toen ik van Utrecht naar Nijmegen moest en mijn eerste artikelen geschreven moesten worden. Ik ben je dankbaar voor alle avonturen die we hebben beleefd.

Tijdens mijn studententijd heb ik een veel lieve jaarclub en dispuutsgenootjes (en aanhang) gekregen die nu nog voor fijne goede momenten samen zorgen. In het bijzonder **Bob, Aron, Tim, Tom, Emiel, Jeroen, Sanne, Martijn, Jonas, Jessie, Carlijn, Roos** en **Eline**; bedankt voor alle borrel, zeil, feest en logeer partijtjes. En natuurlijk **Margot**; bedankt voor alle steunende telefoontjes en bezoekjes aan Nijmegen toen alles even stom was. Zo fijn! Je bent lief!

Ook uit Maastricht, mijn partner in crime op derma/onderzoeksgebied; lieve **Tjinta**, wat is het toch altijd fijn als ik je zie en we over onderzoek kunnen sparren en lachen om alle gekke dingen in het leven. En zijn er geen gekke dingen, dan maken we ze zelf. Ik ben zo trots op alles wat je doet!

Lieve **Mara, Nienke** en **Eefje**, wij kennen elkaar al 30 jaar, een bijzondere vriendschap. Bedankt voor jullie interesse en fijne borrels/thee-tjes. **Mara**, met jouw hulp is de kaft van dit boekje tot stand gekomen. Fijn dat je dat hebt willen doen. Via deze weg wil ik jou de woorden terug geven die jij ooit tegen mij sprak in Neustift: 'jij bent er altijd voor mij als dat nodig is'.

René, Marian, Rutger, Carla, Iris en **Colm**, jullie hebben het staartje van mijn onderzoekstijd meegemaakt. Bedankt voor jullie interesse in de voortgang. Carla and Colm thanks for supporting me in the family-in-law-team ☺.

Lieve **oma**, bedankt voor alle adviezen, lekkere taartjes en pannen met oma-soep.

Heel veel dank voor de beste zusjes van de wereld; **Ingrid, Sylvia** en **Astrid**. De afgelopen jaren heb ik mij meer en meer gerealiseerd hoe onvoorwaardelijk onze band is en hoe makkelijk we elkaar begrijpen. Ik ben zo kei trots op jullie. Ingrid, met jou deel ik het dokter zijn en de onderzoeksambities. Jouw nuchterheid heeft mij altijd erg geholpen als ik even wilde sparren over het werk. Fijn dat jij nu mijn paranimf wilt zijn.

Uiteraard wil ik de beste 'schoonbroers' van de wereld bedanken voor alle mooie grappen telkens als we elkaar zien, maar ook de goede gesprekken als dat nodig is. En de kleine **Alix** en **Norah**, mijn lieve nichtjes, als kleine tovenaars weten jullie altijd een glimlach op mijn gezicht te toveren.

Lieve **papa** en **mama**, misschien dat jullie het niet altijd merken, maar ik ben jullie dankbaar voor alle mogelijkheden die jullie mij gegeven hebben. Misschien met hier en daar wat druk, maar kijk waar ik nu sta. Een diploma, een promotie en een fijne baan. Bedankt voor alle steun, begrip en adviezen als dat nodig was!

Lieve lieve **Laurens**, wat zal jij, net als ik, blij zijn dat dit boekje af is. De laatste maanden heb ik je vaak lastig gevallen met de vraag of je toch weer eens een hoofdstuk door wilde lezen. Want ja, het is nou eenmaal fijn om alles ook nog een keer door een huisarts beoordeeld te hebben. Bedankt voor al die keren dat je dit zonder enige tegenzin voor me hebt gedaan, maar ook dank voor al die keren dat jij 's avonds 'huisvrouw' moest spelen terwijl ik achter mijn laptop zat. We hebben een wat roerige start gehad en ik kan niet wachter tot er (nog meer) rust komt en we samen fijn huisje-boompje-beestje kunnen spelen en fijne verre reizen kunnen maken. O en Lau, wanneer gaan we…? ♥ xx

Margit.