Disease Management for Chronic Skin Cancer

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Disease management voor chronische huidkanker

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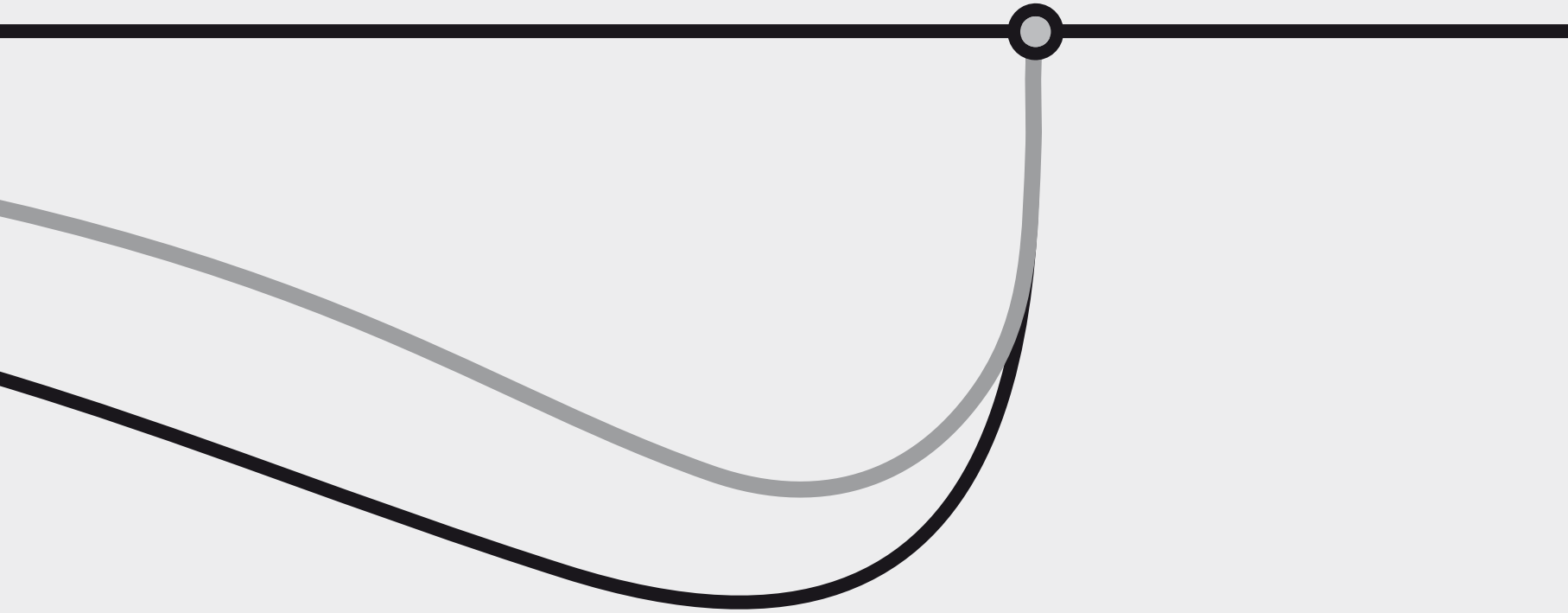
List of abbreviations

AK	Actinic keratosis
BCC	Basal cell carcinoma
ECR	Eindhoven Cancer Registry
FN	False-negative
FP	False-positive
GP	General practitioner
MMS	Mohs' micrographic surgery
NA	Not available
NBCCS	Nevoid basal cell carcinoma syndrome
NMSC	Non-melanoma skin cancer
PDT	Photodynamic therapy
SCC	Squamous cell carcinoma
SE	Standard excision
TN	True-negative
TP	True-positive

1 General introduction



The worldwide incidence of non-melanoma skin cancer (NMSC) has risen dramatically over the last decades. Basal cell carcinoma (BCC) is by far the most common type of skin cancer.[1,2] NMSC needs to be regarded as a chronic disease that has enormous implications for health care systems, as will be outlined in this thesis. Physicians will need to take these implications, including costs, into account.

Estimates show that one in five persons will be diagnosed with skin cancer in their life time.[1] This is an underestimate because adequate registration of NMSC is often lacking in many countries, as is the case in The Netherlands.[2] Traditionally, the incidence is highest in the elderly (> 65 years), 438 per 100,000 person-years.[3] The group of elderly patients is growing due to the fact that the population is aging. In elderly patients, the incidence of squamous cell carcinoma (SCC) is rising more rapidly than the incidence of BCC.[4,5] This is an alarming fact, since SCC has a risk to metastasize. For low-risk SCC, this risk is <5%, for high-risk; SCC, however, this risk has increased to 10-20%.[6] In Australia 137,600 new cases and 410 deaths from SCC each year are estimated.[7] The group of patients aging in a couple of years will have had more UV-exposure compared to the present aging group, therefore the problem will continue to rise.

A growing group of patients who develop multiple NMSC lesions consists of organ transplant patients. Since the improvement of graft survival has resulted in increased survival for transplant patients, the number of survivors has increased accordingly. This phenomenon is paired with a longer duration of immune suppressive medication, resulting in more skin malignancies.[8] Nearly 50% of all renal transplant patients develop skin cancers within 20 years after transplantation.[9]

Another patient group with increasing NMSC incidence is the younger adult population (15-34 years). For this group, it was predicted that skin cancer incidence would double from 322 incident cases in 2000 to 676 incident cases in 2015.[3] The numbers were based on incidence rates available from the Eindhoven Cancer Registry (ECR), which is part of the Netherlands Cancer Registry that keeps the most complete registry on NMSC in the country. A recent study, based on the ECR, has shown that the observed BCC incidence is even higher than expected. The total number of patients diagnosed with a first BCC in 2005 is 21% higher than predicted. Estimated incidences for 2010, 2015, and 2020 show continuous increases among all age groups in both sexes, and no signs of reaching a plateau are seen up to 2020.[10]

The figures used in these studies are still an underestimation of the actual problem, due to registration rules of the ECR that are being used for NMSC (Appendix 1). No reliable data on multiple NMSC exist. Approximately one-third of BCC patients develop multiple BCCs.[11] From a meta-analysis, a risk of 44% was found for BCC patients to develop a new BCC.[12] Additionally, almost all skin cancer patients have premalignant lesions, which mainly consist of actinic keratosis (AK) and extend to large skin areas of so-called field cancerisation. These premalignancies increase the risk for new invasive malignancies and are an extra burden on the skin cancer healt care system.[13,14,15]

One of the main risk factors for NMSC is UV exposure. Especially patients with Fitzpatrick skin types I and II, who easily burn, are at increased risk.[4,16] The increase in sun exposure during vacations in childhood and the use of solariums, in combination with an aging population, contribute to the enormous increase of skin cancer incidence.[3]

An evaluation of the diagnosis-treatment codes at a large outpatient dermatology clinic at the CatharinaHospital Eindhoven in the Netherlands has shown that over 50% of dermatologists' time is spent on skin cancer and skin (pre-) malignancies (non-published data). The increased workload is reported by other colleagues as well.[10,17]

With an increasing number of patients and the development of multiple tumours during a lifetime, skin cancer can be regarded as a chronic disease; a disease of long duration and generally slow progression, as defined by the World Health Organization.[18]

NMSC has been considered to be a relatively mild health problem because of the low mortality rate. For a long time, the focus has been on melanoma. However, morbidity and the burden on the healt care system caused by NMSC are high, as are the costs related to skin cancer.[19] In the U.S.A. skin cancer has taken fifth position with respect to cancer costs, behind prostate-, lung- and bronchus-, colon- and rectum-, and breast carcinomas.[20] To manage the future costs and quality of care for skin cancer patients, a revised health strategy is needed. Physicians need to be engaged in cost control as well. Dermatologists, other healt care providers, health insurance companies, and the government need to become aware that the organisation of dermatological care needs to be reformed. With the present number of dermatologists and the provided dermatologic care, it will be impossible to deal with this expanding disease. It is necessary to focus on alternative pathways for treatment of NMSC and to think out of the box, to adjust hospital logistics and information systems for example.

A possibility is the use of a disease management system for chronic skin cancer. A disease management system that organises health care for one well-documented healt care problem uses a systematic approach. This includes prevention, education, multidisciplinary care, information technology, and management.[21] Several organisational models of management of chronic diseases have been proposed and implemented internationally.[22] The World Health Organisation recently discussed how to operate these programmes across care settings and providers.[18] There is increasing evidence that these disease management systems provide more efficient, high quality, and cost-effective care. There is also a clear and immediate opportunity to evaluate these benefits as part of a renewed health strategy for effective chronic care in our aging society. For chronic diseases, like diabetes mellitus and heart failure, these systems are already in place and demonstrate significant improvement of disease control and a reduction of complications.[23,24,25,26]

A revised strategy should start with prevention of chronic skin cancer.[21] The population needs to be educated so that people become aware of the risk factors for skin cancer; the use of

sunscreen, clothes, and hats is essential and should become a habit. Prevention campaigns need to be launched and repeated regularly. Children and their parents or caregivers form an important target group for interventions focusing on primary prevention of skin cancer.[27]

The impact of primary prevention initiatives appears, however, to be minimal. Behaviour change regarding skin cancer prevention seems to be difficult to achieve in the short term. Teenage behaviour in the sun is hard to change, and fashion dictates adult and adolescent behaviour in the sun.[28] The use of solariums creates extra risks for the development of skin cancer. Hirst et al. investigated that by implementing solarium regulations 250 serious skin cancers could be avoided over the lifetime of 100,000 persons in Australia, and 31 years of life could be gained through avoided melanoma deaths.[29]

Sunscreens have been proven to be an effective approach to non-melanoma skin cancer prevention, and cost-effective.[5,30] The skin cancer prevention initiative Sunsmart in Australia was estimated to yield a $2.32 saving in return for every dollar spent on the program.[31]

Next to primary prevention, secondary prevention also plays an important part. Early detection of skin cancer has multiple advantages: it leads to the diagnosis of smaller skin cancers, for which treatment is less difficult. When primary skin cancers are diagnosed and treated correctly, this leads to fewer recurrences, which are generally more difficult to treat and involve a higher risk of recurring, and that at higher costs.[32,33,34]

Secondary prevention includes the treatment of premalignancies as well. Photodynamic therapy, ablative lasertherapy, and oral retinoids have the potential to diminish the number of new premalignancies and skin cancers.[35,36,37,38,39,40,41,42]

Since secondary prevention will have a limited effect and it will take years before the effects of primary prevention become measurable, dermatologists and other partners in the healt care system will be confronted with the increased burden of skin cancer for many years. Adjustments in healt care processes can be made on various levels. Logistic processes concerning diagnosis, treatment and follow-up could be improved and could be supported by pro-active information technology systems. Existing skin cancer treatments could be optimized and a new delegation of tasks could be considered. In this thesis we will describe a new strategy for the management of chronic skin cancer and we will examine some of the above mentioned possible adjustments.

The aim of this thesis is to give insight into the actual burden of NMSC in dermatology. True insight into the number of NMSC is necessary to answer the question whether NMSC is underestimated in epidemiologic data and whether it meets the criteria of a chronic disease. In this thesis we want to answer these questions.

Secondly, we investigate whether a disease management strategy commonly used for chronic diseases could contribute to the reduction of the burden for NMSC patients, dermatology clinics, and healt care economics in general. We performed studies on innovations in treatment and treatment processes to see whether they contribute to the reduction of the

burden of NMSC. We wonder whether a one-stop-shop concept is feasible for NMSC and whether a combination of existing treatments would contribute to improved outcomes and efficiency at the dermatology department. In addition we investigate if non-dermatologists can effectively screen lesions suspect for NMSC in chronic skin cancer patients.

Appendix 1. Rules Non-Melanoma Skin Cancer Registration of the Eindhoven Cancer Registry

Registration of all skin cancers (except melanoma***), with incidence dates starting from 1-1-1999.
Registration of localisation takes place according to the ICD-10 code.

Per patient more than one primary skin tumour with the same morphology can be registered according to the following rules:

- In the case of multiple tumours at the same time* on the same sub-localisation**: registration of one primary tumour with the remark "multifocal".
- In the case of multiple tumours at the same time* on different sub-localisations**: registration of a new primary tumour per sub-localisation.
- In the case of a "new" skin tumour at the same sub-localisation** as former skin tumour: regard this tumour as a recurrent tumour, register only the last date of contact and hospital or practice where the tumour was diagnosed.
- In the case of a "new" skin tumour on another sub-localisation** than the former skin tumour: registration as a new primary tumour.

* At the same time means: incidence dates are within 3 months of each other.
** Same sub-localisation means: Fourth digit of the ICD-10 code AND lateralization are identical.
*** Melanomas are registered according to the rules of the national Dutch Cancer Registration.

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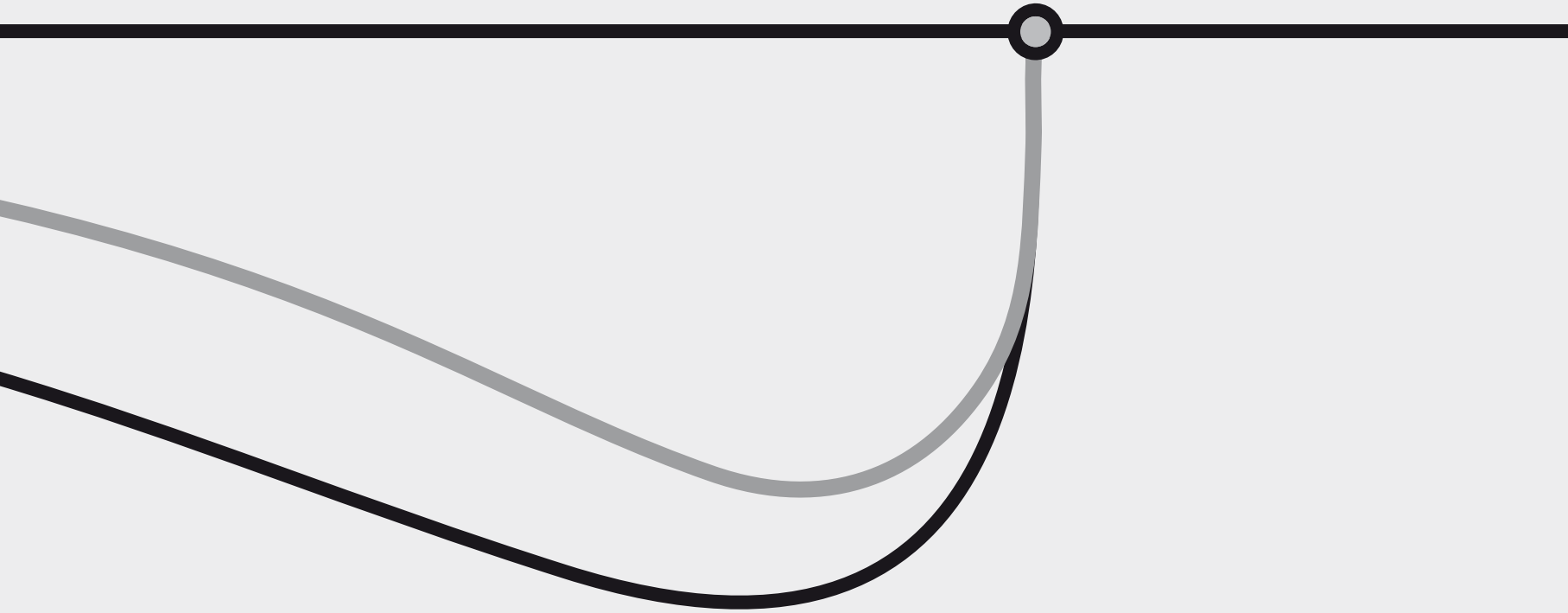
2 The burden of non-melanoma skin cancer



2.1

The burden of skin cancer in dermatology

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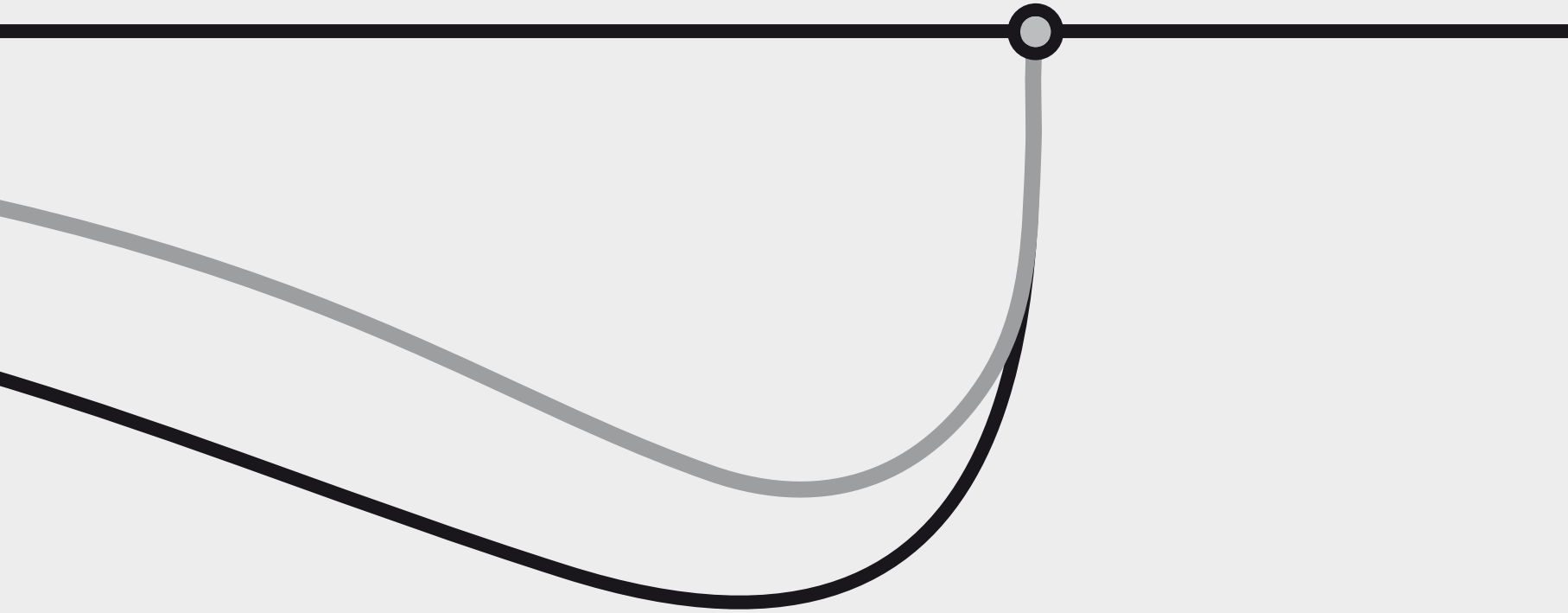
Submitted.

3

Nevoid basal cell carcinoma syndrome patient; a model for chronic skin cancer patients



3.1

Review: Treatment of basal cell carcinomas in patients with nevoid basal cell carcinoma syndrome

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J Eur Acad Dermatol Venereol. 2009 Mar;23(3):308-13.

Abstract

Background: Nevoid basal cell carcinoma syndrome (NBCCS) is characterized by the development of multiple basal cell carcinomas (BCCs). A major problem for these patients is the enormous amount of BCCs which can invade in the deepunderlying structures, especially in the face. Different treatment modalities are used in these patients; surgical excision,Mohs' micrographic surgery, cryotherapy, photodynamic therapy, ablative laser therapy and topical 5% imiquimod. Thereis no evidence based advice how to treat a NBCCS patient.

Objective: To give a review of the literature about the possible treatment modalities for the multiple BCCs in NBCCS patients.

Results: Literature consists mainly of case reports; no evidence based advice how to treat a NBCCS patient exists. Multiple treatments are available (surgical and non-surgical), and a lot of them can be combined. Treatment in a megasession is an option to diminish the medical and social inconvenience for the patient

Introduction

Nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin-Goltz syndrome is an autosomal dominant inherited disease, exhibiting high penetrance and variable expression. The prevalence is estimated at 1 in 56,000.[1] The disease is linked to chromosome 9q22.3-q31. Inherited or spontaneous mutations in the human homologue of a Drosophila gene, patched (PTCH1), underlie this syndrome. Its inactivation in combination with a second hit mutation leads to tumour formation; this is often a mutation in p53 due to UV-exposure[2]

NBCCS is characterized by the development of multiple basal cell carcinomas (BCCs), odontogenickeratocysts, palmar and plantar pits and abnormalities of the face (frontal bossing, hypertelorism). Other less frequently seen characteristics are; spine and rib abnormalities, and calcification of the falxcerebri. It is also associated with other malignancies.[3] The diagnosis can be made in the presence of 2 major criteria or 1 major and 2 minor criteria (Table 1).

A major problem for these patients is the enormous amount of BCCs which can invade in the deep underlying structures, especially in the face.[1] Different treatment modalities are used in these patients; surgical excision, Mohs' micrographic surgery (MMS), cryotherapy, photodynamic therapy (PDT), ablative laser therapy and topical 5% imiquimod.[4,5,6] One of the great advantages of the non-surgical therapies is preservation of the skin and these therapies provide good cosmetic results. Aggressive, large BCCs however, need to be radically excised to prevent invasion in deep structures, metastasising and possible death by local invasion.[7,8] The different treatments will be discussed.

Table 1. Diagnostic criteria NBCCS[3]

Major Criteria	Minor Criteria
> 2 BCC or 1 BCC and < 20 years	Macrocephaly
Odontogenickeratocysts	Congenital malformations: cleft lip or palate, frontal bossing, 'course' face, moderate or severe hypertelorism
3 or more palmar/ plantar pits	Other skeletal abnormalities: sprengel deformity, pectus deformity, syndactyly of the digits
Bilamellar calcification of the falxcerebri	Radiological abnormalities: bridging sellaturcica, vertebral anomalies (hemivertebrae, fusion or elongation of vertebral bodies), modelling defects hands or feet, flame shaped lucencies of hands or feet
Bifid, fused or markedly splayed ribs	Ovarian fibroma
First degree relative with NBCCS	Medulloblastoma

Prevention

While the development of BCCs is due to a second hit mutation, effort should be made to prevent the second hit by UV-radiation for example. Therefore sunscreens are necessary for NBCCS patients.[9] Other treatments are suggested to prevent the rapid development of BCCs; oral retinoids and PDT. These options will be discussed later.

Surgical excision

Surgical excision is the standard treatment of basal cell carcinomas, with histological examination of the surgical margins, however, less than 1 % of the surgical margins are examined with this procedure.[10] Recurrence rates for primary and recurrent BCCs are resp. 10 and 17%.[8,11] Smeets et al demonstrated that 25% of the primary and 30% of the recurrent aggressive BCCs were incompletely excised with a 3 mm margin. After incomplete excision, a re-excision will have to take place, which will leave a larger scar.[12] In patients with extensive skin cancers, like NBCCS patients, this could cause problems for cosmetic and functional outcomes, especially in the face.

No specific literature exists about surgical excision of BCCs in NBCCS patients. Many case-reports mention the use of standard surgical excision in these patients, but no data exist about total clearance or recurrence rates.

Mohs' micrographic surgery (MMS)

MMS is an advanced method of excising non-melanoma skin cancers. It is mainly used for high-risk basal cell carcinomas in the face; infiltrative or micronodular growth pattern for example. 100% of the surgical margins are examined per-operatively in frozen horizontal sections. It provides the highest cure rates and lowest recurrence rates compared to other treatments. For primary BCCs the recurrence rate ranges between 1 and 3%, for recurrent BCCs this is 5-7%.[8,11,13,14] With MMS, healthy skin can be preserved, and the aggressive component can be eradicated to prevent tumour invasion in the deeper underlying structures. This was already described in 1980, when Mohs used MMS in 30 NBCCS patients.[15]

Ablative laser treatment

CO2 or Erbium-Yag laser treatment is used for skin resurfacing. Ablation takes place with minimal destruction of normal surrounding tissue. Potential side effects include transient erythema, post inflammatory hyperpigmentation, infection, haemorrhage and hypertrophic scarring.[5] The use of ablative CO2 laser for widespread superficial BCCs in NBCCS patients is described in case-reports.[5,16,17] A NBCCS patient with a large BCC on the abdomen was treated by Krunic et al.[16] MMS was used to treat the central thick portion of the tumour; this was followed by CO2 laser treatment for the superficial part of the lesion. At 15 months follow-up, no recurrence was seen. Nouri et al. treated 3 patients with multiple BCCs on the face, trunk and extremities. In one patient over a hundred BCCs (2-5 mm in diameter) were treated on the trunk. The lesions healed within 2 weeks and scarring was minimal. MMS verified complete histological clearance.[5] Doctoroff et al describe a patient with 45 facial BCCs whom they treated with full-face CO2 laser resurfacing.

She healed well postoperatively and developed 6 facial BCCs during the 10 month follow-up. The possibility to treat all BCCs in one single session was a great advantage, this minimized the inconvenience of repeated surgical procedures.[17] Postoperative pain after ablative laser treatment is little and scarring is minimal.[5]

Photodynamic therapy (PDT)

PDT is a well-known treatment of BCCs. Total clearance rates for superficial BCCs range from 68%-100% and it provides cosmetically excellent results. For solid BCCs total clearance rate is about 50%.[18] The main complication of PDT is a burning pain during treatment.[6,19]

One of the advantages is that large fields of BCCs can be treated in one session.[20] In patients with NBCCS excellent outcomes are achieved with PDT, it is well tolerated and gives good cosmetic and functional results.[6,21] It further may have a positive effect on subclinical areas of (pre-) malignancies. Three NBCCS patients were treated by Oseroff et al for multiple BCCs on the trunk, with a clearance rate of 85-98%. In respectively 5 and 6 years follow-up, two patients did not develop any new BCCs.[6] Chapas et al report about a NBCCS patient whom they treated with PDT for multiple BCCs on his face and chest. He underwent treatments every 2-3 months, in total, 4 treatments were given. This resulted in a reduction of the size and number of the existing BCCs, scars from previous excisions improved and the rate of tumour developing decreased.[22] Similar results are seen by Itkin et al.[23] They treated two patients with multiple superficial and nodular BCCs on the face and extremities. A total clearance of 67-89% was observed for superficial BCCs and 31% for nodular BCCs. The remaining 21 lesions showed partial clinical resolution. In 8 months follow-up, no new BCCs were found in the treated areas. Cosmetic outcome was excellent and old surgical scars were less prominent.

Imiquimod 5% cream

Imiquimod 5% cream is described in randomized controlled trials for the treatment of superficial BCCs. Total clearance rates are about 81-100% for superficial BCCs and 50-76% for nodular BCCs.[24,25,26,27] Little data exist about recurrence rates. Small trials (n= 5-70) suggest 0-2,3% recurrence after 10-24 months.[28,29,30] Two larger studies (n= 182, n= 169) found recurrence rates of 21% respectively 18% after a follow-up period of 2 years.[31,32]

Successful treatment of BCCs in NBCCS patients is described for topical imiquimod 5% cream. Stockfletch et al described 3 patients. They all had multiple BCCs in the face, on the extremities and/ or on the trunk. The lesions were treated 3 times a week, during 6 to 8 weeks. 2 Weeks after treatment clinical and histological clearance was achieved. No recurrence was seen during a 12 month follow-up period.[4] Micali et al. treated 4 NBCCS patients with imiquimod 5% cream for multiple BCCs on the face and the trunk. The cream was applied 3-5

times a week, for 8-14 weeks. 13 Out of 17 BCCs completely cleared; this was confirmed by histological evaluation.[33]

Ferreres et al treated more than 300 superficial BCCs in one NBCCS patient. Treatment was performed in multiple areas. Each area was treated once daily, during 6 weeks. 9 Lesions did not respond; these were all pigmented BCCs. These lesions were excised. At 36 months follow-up no recurrent BCCs were seen and only 3 new lesions developed.[34] Total clinical and histological clearance of a solid BCC was obtained in a NBCCS patient by using imiquimod 6 days a week, during 3 months.[35]

Cryosurgery

Cryosurgery is used for the treatment of BCCs, often in combination with curettage. Recurrence rates vary from 8-18 %.[8,11,36] It is preferably used for well-defined, small, nodular or superficial BCCs.[37] Little data exist about the use of cryotherapy in NBCCS patients. Tsuji et al treated a NBCCS patient with topical 5-fluorouracil (5-FU) combined with cryosurgery. At 6 months follow-up, biopsy specimens did not show recurrence. They also used 5-Fu and cryosurgery alone, but thatappeared to be insufficient.[38]

Dixon describes a (non-NBCCS) patient with 17 BCCs on his trunk, half was treated with imiquimod 5% cream, the other half was treated with curettage and cryosurgery. All lesions resolved with histological clearance.[39]

5-Fluorouracil

Little information is found about 5-fluorouracil for the treatment of BCCs. Gross et al describe the use of 5% 5-fluorouracil cream in 29 patients with 31 superficial BCCs. It was used twice daily for 12 weeks. Histologic cure rate was 90%, no follow-up or recurrence rate was described.[40]

A child with NBCCS was treated with topical 5-FU and topical tretinoin, for a period of 10 years his condition was successfully managed.[41] As mentioned earlier, it is also combined with other therapies, like cryosurgery.[38] There are reports about 5-FU used in NBCCS patients with little satisfying results.[42]

Oral retinoid

Oral retinoids have shown to reduce the number of skin cancers and premalignant lesions in high risk patients like organ transplant patients and patients with numerous non-melanoma skin cancers.[43,44] The reduction of incidence of skin cancers is most effective for squamous cell carcinomas and for actinic keratosis. For BCCs, this treatment is less effective.[45]

It is used in the management of various genodermatoses, including NBCCS. It provides partial regression and inhibition of the development of new tumours is described. Oral

etretinate is also combined with surgical treatment.[46] Because of the regression of the BCCs, surgical excision was facilitated, and there was also a reduction in recurrence rate.

Radiotherapy

This treatment modality is mostly not recommended orcontra-indicated in NBCCS patients, therefore no data about total clearance rates or recurrence rates exist. Recurrence rates and incomplete clearance rates, concerning the treatment of BCCs in non-NBCCS patients, are significantly higher compared to surgery.[47] In addition, radiotherapy can induce the formation of new BCCs. PTCH1 +/- mice develop BCCs and other skin tumours more rapidly after UV exposure or ionizing radiation than wild-type control mice.[48] The induction of BCCs after radiotherapy is also described for healthy patients who have been treated with radiotherapy for other (skin) diseases.[49]

Discussion

No disease management system or protocol for the treatment of NBCCS patients exist. And although they present with multiple BCC's, these NBCCS-patients require a treatment approach with focus on long term preservation of healthy skin, combined with adequate treatment of invasive tumors. In fact more and more skin cancer patients resemble NBCCS patients in a way that premalignant skin combined with skin cancer is becoming a chronic disease. With all the above mentioned therapies (Table 2), dermatologists try to manage the extensive BCCs that arise in NBCCS patients. All treatments do have their own benefits and complications, therefore the combination of therapies could be an optimal treatment. Some treatments are already combined as described above, for example; MMS and ultra-pulse CO2 laser, or 5-FU and cryosurgery. In NBCCS patients wide areas are affected and the ideal approach is to treat large areas at once, with minimal inconvenience for the patient. Treatment of nodular or agressive BCCs on low-risk areas (like the extremities or trunk) can be treated fast and easily with a standard surgical excision. After a surgical excision there is always a risk of infection or bleeding and it will leave a scar.[12] Clearance of the aggressive tumours on high risk areas like the face, is of great importance, because they can invade in deeper underlying structures and result in a high morbidity. MMS is the preferred method to achieve complete clearance, because it has the highest cure rates and lowest recurrence rates.

A disadvantage of MMS is that it is a time-consuming therapy which requires a special training of the physician.[12]

Another important issue is to preserve skin, while these patients develop BCCs at a young age and they will develop more lesions during life. Superficial lesions could be treated with

Table 2: Treatment options for BCCs in the NBCCS patient

Treatment	Study design	Nr of patients	Nr of lesions	Efficacy	Follow-up	Recurrence	Reference
Excision	General statistics					10-17%	Rowe et al
Mohs	General statistics					1-7%	Rowe et al
Ablative laser	Case report	1	1	total clearance in combination with MMS total clearance	15 months	0	Krunic et al
	Case report	3	100	total clearance	2 weeks	0	Nouri et al
	Case report	1	45		10 monts	0, 6 new lesions	Doctoroff et al
PDT	Case report	3	Multiple	85-98% clearance reduction of size and number	5-6 years	No recurrence in 2/3 patients	Oseroff et al
	Case report	1	Multiple	31-89% clearance	?	?	Chapas et al
	Case report	2	Multiple		8	0	Itkin et al
Imiquimod	Case report	3	Multiple	Total clearance 76% clearance	12	0	Stockfletch et al Micali et al
	Case report	4	Multiple	97% clearance	?	?	Ferreres et al
	Case report	1	> 300	Total clearance	36 months	0, 3 new lesions ?	Vereecken et al
	Case report	1	1		?		
5-Fluorouracil (5-FU)	Case report	1	Multiple	Condition was managed in combination with topical tretinoine	10 years	?	Strange et al

Table 2: Treatment options for BCCs in the NBCCS patient

Treatment	Study design	Nr of patients	Nr of lesions	Efficacy	Follow-up	Recurrence	Reference
Cryosurgery	General statistics					8-13%	Rowe et al
	Case report	1	8-9	Total clearance	?	?	Dixon et al
	Case report in combination with 5-FU	1	?	Total clearance Cryosurgery alone was insufficient	6 months	0	Tsuji et al
Oral retinoids	General			Partial regression and inhibition of lesions and Regression of lesions			
	Case report	1	multiple		?	Reduction of recurrence rate	Sanchez et al

? = not given in the literature

non-invasive skin preserving techniques like PDT or imiquimod 5% cream.[50] These therapies can also be used as an adjuvant treatment to MMS or excision. [19,51]

The greatest advantage of PDT, imiquimod 5% cream and 5-fluorouracil cream is the preservation of skin. A disadvantage is the lack of histopathological examination on radicality. The treatments have some different advantages and disadvantages; PDT is performed only once or twice and large areas can be treated. Most patients experience a burning pain during treatment. The skin becomes erosive and then reepithelialisation will take place.[18] Imiquimod 5% and 5-fluorouracil creams however, are therapies with duration of 6 weeks or more. The skin becomes irritated, itchy and erosive, and then reepithelialisation will take place. Overall patients experience no pain.[24,25,40]

With ablative laser therapy, large areas can be treated in one single session, however without histopathological examination. Another disadvantage is that a large area becomes erosive with a risk of infection. Other possible complications are erythema, pigment changes and scarring.

Treatment with cryosurgery is performed in only a few minutes. Radicality cannot be examined histopathologically and there is a risk of hypopigmented scars. Recurrence rates are higher than for surgical excision (8-18% versus 10%).[8,11]

Radiotherapy is, as we mentioned, contraindicated for NBCCS patients, because of the high risk of the induction of new tumours.[47]

A special way to treat patients with multiple lesions is treatment in a megasession.

In a megasession; a patient is treated for multiple lesions in one single session. This diminishes the inconvenience of multiple excisions, the number of visits to the hospital and it decreases the downtime. In a megasession different treatment modalities can be combined as well.

The excision of numerous skin cancers in a single session has been described before.

Martinez et al described 10 patients with multiple skin cancers; one of them was a NBCCS patient. They were all treated under local anaesthesia and some oral sedation. All patients preferred the megasession above the standard procedures, reasons they reported were; less overall pain, less inconvenience, decreased travel, more efficient. Although more wounds are created in a megasession, the number of complications (bleeding, pain, infection) was not increased.[52]

Conclusion

The treatment of BCCs in the NBCCS patient remains challenging. Multiple treatments are available, surgical and non-surgical, and a lot of them can be combined. There is no evidence based advice how to treat a NBCCS patient. The aggressive lesions should be irradicated to prevent invasion, superficial lesions could be treated with non-surgical treatments to preserve skin. Treatment in a megasession is an option to diminish the medical and social inconvenience for the patient.

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3.2

Treatment of the Nevoid Basal Cell Carcinoma Syndrome patient in a megasession. A Case series.

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Abstract

Background: The nevoid basal cell carcinoma syndrome (NBCCS or Gorlin-Goltz syndrome) is an autosomal dominant inherited disease, characterized by the development of multiple basal cell carcinomas (BCCs) which start developing at a relatively young age. Surgical and non-surgical therapies are available for the treatment of BCCs.There is no evidence based advice for the treatment of the NBCCS patient.

Objective: To describe our experience in the management of the enormous amount of BCCs in NBCCS patients.

Methods: We describe 3 cases of NBCCS patients, whom we have treated with a combination of therapies in megasessions under general anaesthesia.

Results: The number of lesions treated surgically in one session varied from 3 to 15. In most cases different treatment modalities were combined; Mohs' micrographic surgery (MMS), surgical excision and photodynamic therapy (PDT). All patients experienced little post-operative pain and no complications, like bleeding or infection, were seen.

Conclusion: No evidence based advice exists for the treatment of NBCCS patients. Many treatment options are available, surgical and non-surgical. Most of them can be combined. We have positive experience with treatment in a megasession, this diminishes patient's burden of multiple visits and treatments in the hospital.

Introduction

The nevoid basal cell carcinoma syndrome (NBCCS or Gorlin-Goltz syndrome) is an autosomal dominant inherited disease, linked to chromosome 9q22.3-q31. Inherited or spontaneous mutations in the human homologue of a Drosophila gene, patched (PTCH1), underlie this syndrome. [1] The disease has a high penetrance and a variable expression, its prevalence is estimated at 1 in 56,000.[2]

NBCCS is characterized by the development of multiple basal cell carcinomas (BCCs) which start developing at a relatively young age. Other characteristics are odontogenickeratocysts, palmar and plantar pits and abnormalities of the face. The disease is also associated with other malignancies and there can be spine and rib abnormalities and calicification of the falx cerebri.[3]

The management of the multiple BCCs in these patients is challenging. NBCCS patients develop enormous amounts of BCCs at a young age and during life they will only develop more. One of the aims in the treatment is the prevention of tumor invasion in the deep underlying structures. On the other hand it is favourable to preserve as much skin as possible, while these patients will need to undergo multiple treatments and possible plastic reconstructions in the future. Surgical and non-surgical therapies are available for the treatment of BCCs. [4,5,6,7] There is no evidence based advice for the treatment of the NBCCS patient. In this article we describe our experience in the management of the enormous amount of BCCs in NBCCS patients.

Case series

We describe three male NBCCS patients, who were all diagnosed with NBCCS in childhood and have had multiple surgical and non-surgical treatments in the past years for BCCs in the head/ neck region, on the trunk and on the extremities. We treated them in megasessions under general anaesthesia plus some local lidocaine with adrenaline, for extensive solid and superficial BCCs and some aggressive BCCs in the face. The number of lesions treated surgically in one session varied from 3 to 15 (Table 1). The mean time patients were under anesthesia was about 7-8 hours per megasession.

In most cases different treatment modalities were combined. Mohs' micrographic surgery (MMS) was used for the aggressive (infiltrative, micronodular, sclerotic) BCCs in the face and surgical excision was performed to treat the lesions (agressive or nodular BCCs) on the trunk and extremities. For superficial BCCs and large areas affected with superficial or small nodular BCCs, we used photodynamic therapy (PDT). PDT was performed with the photosensitizer ALA-cream, this was covered with plastic foil and a light protecting foil (aluminium foil). The areas received light fractions of 20 and 80 J/cm^2 , 4 and 6 hours after a single application of

Table 1. Overview of megasessions.

	Patient 1	Patient 2	Patient 3
Age	51 y	34 y	47 y
Number megasessions	7	2	1
Mean number MMS (range)	5.3 (2-9)	5 (4-6)	4
Mean number MMS+excisons (range)	9 (3-15)	9 (7-11)	4
Description megasessions			
	2001: 2 MMS face 3 excisions scalp	2005: 4 MMS face 3 excision face PDT frontal, neck, chest, shoulders (about 20-25 BCCs)	2007: 4 MMS scalp Adjuvant PDT scalp (about 10-15 BCCs)
	2002: 3 MMS face	2006: 6 MMS face 5 surgical excisions chest, right leg PDT chest + Shoulders (about 15-20 BCCs) i.l. kenacort injections	
	2003: 8 MMS face 1 excision left arm PDT left + right temporal region (about 8-10 BCCs)		
	2005: 9 MMS face defects 4 surgical excision chest PDT scalp (about 10-15 BCCs)		
	2006: 6 MMS face 9 surgical excision chest end 2006: 4 MMS scalp 11 excisions trunk + extremities		
	2007: 11 excisions trunk + extremities PDT arms (about 20-30 BCCs)		

ALA, illumination took place during 4 respectively 16 minutes. During the 2 hour dark interval between light fractions, lesions were covered with a light protecting dressing. The illumination took place with a red light source of 633 nm (Omnilux, Waldmann, Tiel, The Netherlands). Before 2005 we treated the patients with a single illumination, 100 J/cm^2 . The number of lesions treated in one PDT session was about 10-15 per area.

Patient 1, a man of 51 years, underwent his first megasession in 2001, two BCC in the face were treated with MMS and 3 lesions on the scalp were excised. The following years the number of lesions treated in one session increased. The most extensive treatment consisted of 9 MMS procedures in the face, 4 standard surgical excisions on the chest plus PDT on the scalp. From 2001 till now, he has undergone 6 megasessions.

Patient 2, a man of 34 years, has had two megasessions, the first in 2005 and the other in 2006. In the first megasession 4 MMS procedures and 3 surgical excisions took place in the face. In addition, the frontal area of the scalp, the chest and shoulders were treated with PDT. In 2006 he was treated under general anaesthesia for the second time. In this session MMS was used for 6 lesions in the face and surgical excisions were performed for a total of 5 BCCs on the trunk and the right leg. PDT was given for BCCs on his chest and shoulders. Keloids in this area (which he had developed after excisions in the past) were treated with intralesionaltriamcinolonacetonide injections.

Patient 3, a man of 47 years of age, has had one megasession in 2007. MMS was performed for 4 aggressive BCCs on his scalp. The rest of his scalp was treated with PDT, the areas treated with MMS were not included in the PDT treatment, so that there was no difficulty in reading the Mohs tissue sections.

All patients experienced little post-operative pain, if needed they used paracetamol 1g 3 times a day. After the megasession patients stayed overnight for observation and no complications, like bleeding or infection, were seen.

Discussion

Treatment of the numerous BCCs in NBCCS patients remains challenging. They develop new BCCs at a high rate and often need to undergo many treatments in a relatively short period of time, which intervenes with their social lives. This burden can be diminished when multiple lesions are treated in one session, a megasession. There is no exact definition of a megasession; Martinez et al used the term megasession when 5 or more lesions were treated in one session. All our patients were employed, and had to stay home for only a couple of days after the megasession. After treatment with mainly PDT patients went back to work after 1 or 2 days. In-betweenmegasessions they seldom visited the hospital.

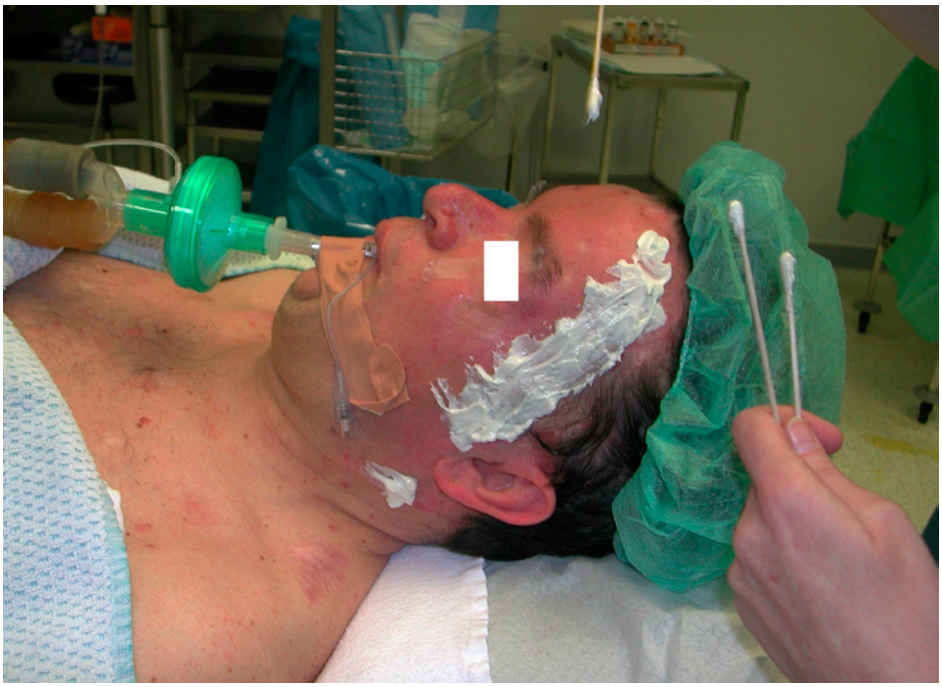

Figure 1. Applying ALA-cream

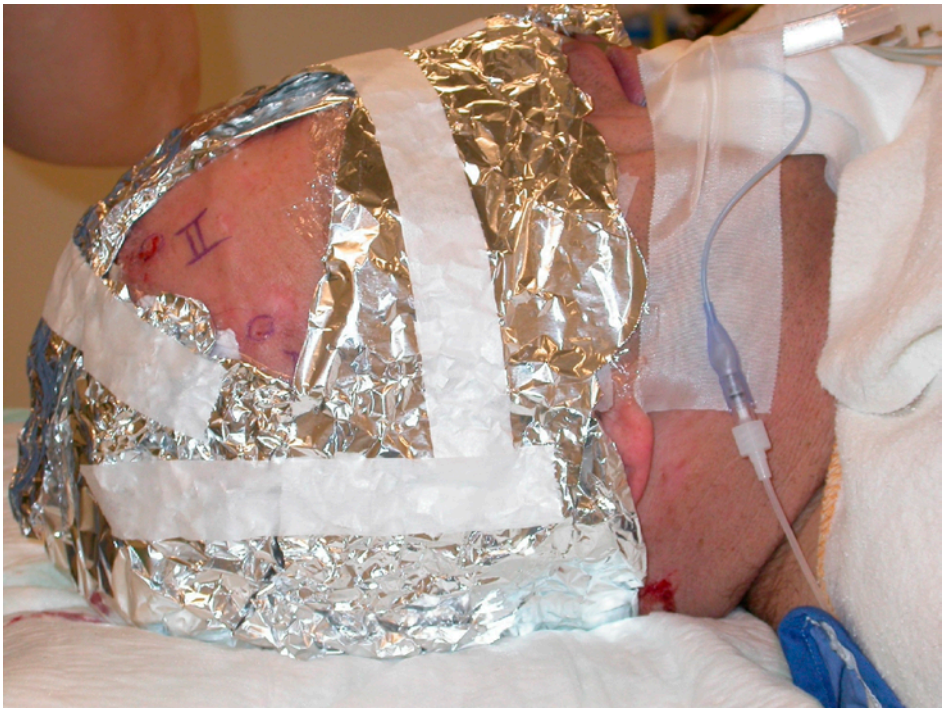

Figure 2. ALA-cream covered

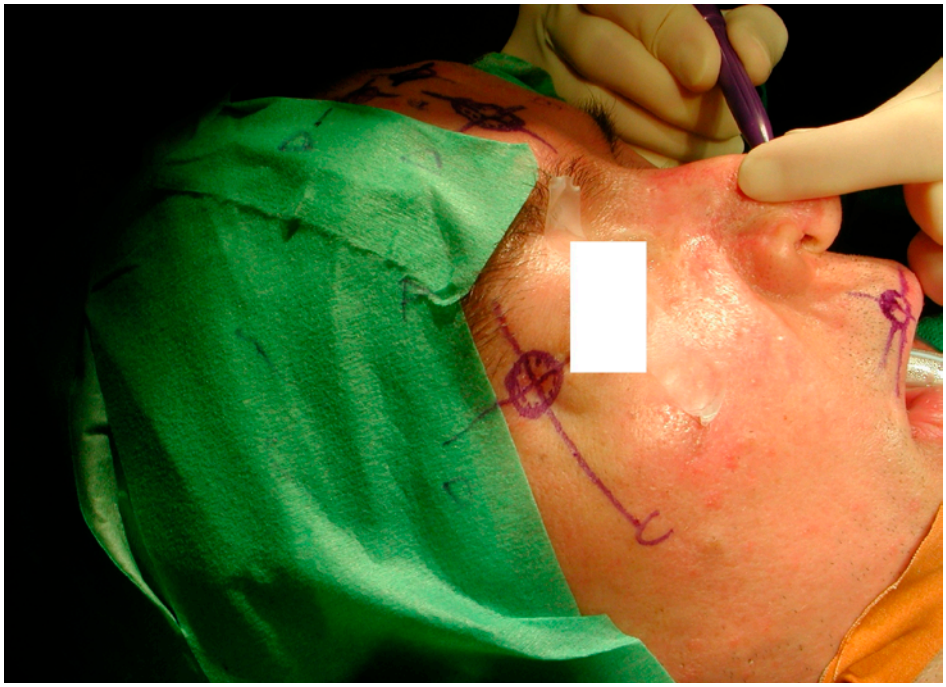

Figure 3. Mohs micrographic surgery

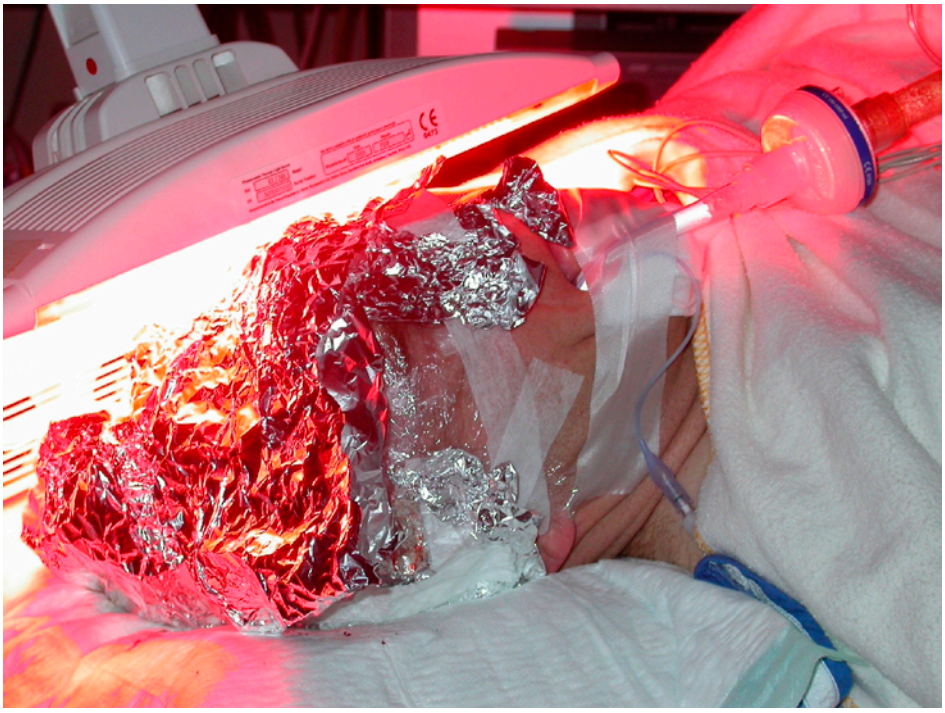

Figure 4. Illumination

Martinez et al treated 10 patients with multiple skin cancers in megasessions; one of them was a NBCCS patient.[8] They were all treated under local anaesthesia and some oral sedation. All patients preferred the megasession above the standard procedures, reasons they reported were; less overall pain, more convenience, decreased travel, more efficient. Our patients report the same advantages regarding a megasession. Although more wounds are created in a megasession, the number of complications (bleeding, pain, infection) was not increased.[8] This is the same for our patients.

We are allowed to use the operating rooms with general anaesthesia once every 4-8 weeks. On these days we perform MMS under general anaesthesia, or megasessions as described before.

During a megasession patients are under general anaesthesia for approximately 8 hours. Although this is a relatively long period, no complications are seen. Patients do sometimes complain about pain in their back after lying on the operating table.

We chose to combine MMS, standard surgical excision and PDT in most of the megasessions. MMS was especially used to irradicate the aggressive parts of the BCC. To preserve skin we discontinued MMS when only superficial BCC was left in the Mohs sections. When nodular BCCs were not radically excised, a re-excision only took place when nodular parts were present, for superficial BCC PDT was used in the next megasession.

The use of PDT under general anaesthesia in a megasession requires adequate planning. The photosensitizer should be applied prior to MMS (Figure 1, 2, 3). While preparing and examining the frozen sections of the MMS procedure, the illumination of the lesions can take place (Figure 4).

Several case reports describe the use of PDT in NBCCS patients. [6,9,10] Oseroff et al for example noted a 90-98% clearance of BCCs in 2 children with NBCCS.[6] After 5-6 years follow-up, they did not see any new or recurrent BCCs. We find it difficult to say if our patients have recurrences and if they do, how many. These patients develop so many BCCs, that it is hardly impossible to define a BCC as a primary or a recurrent tumour. We do get the idea that our patients develop BCCs at a lower rate. During control visits, once or twice a year, the skin treated with PDT does show less BCCs than the untreated skin and this effect lasts for a couple of months.

Combining treatments for the management of BCCs has several advantages, in particular for NBCCS patients, but also for other patients with a history of extensive skin cancer. Extensive, multiple excisions will leave disfiguring scars and poor functional results. This risk can be diminished when skin is preserved as much as possible. Aggressive, high risk BCCs should be treated surgically, to prevent invasion in the deep underlying structures. Superficial BCCs and small nodular BCCs, however, can be treated with non-surgical therapies like; PDT, imiquimod 5% cream and 5-fluorouracil cream. [4,11,12,13,14] These non-surgical therapies can also be used as an adjuvant treatment for remaining superficial BCC after surgical excision or MMS. Thissen

et al described the use of imiquimod 5% cream for residual superficial BCC after removal of the invasive part by MMS. Kuijpers et al used PDT for remaining superficial BCC after MMS. [15,16]

Conclusion

No evidence based advice exists for the treatment of NBCCS patients. Many treatment options are available, surgical and non-surgical. Most of them can be combined, depending on the type of tumour. Besides the medical indications and treatment options, patient's wellbeing is very important. We and others have positive experience with treatment in a megasession. This is an excellent way to avoid the multiple excisions and visits to the hospital, which brings along a social burden for patients.

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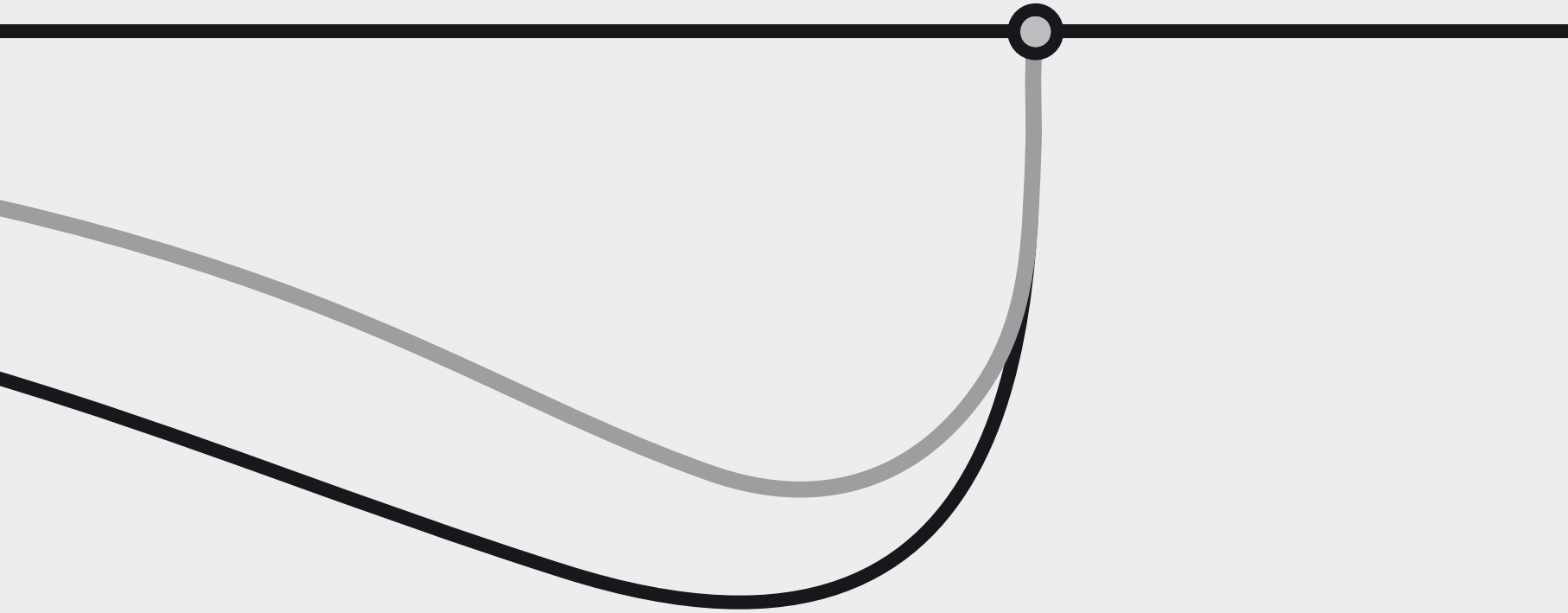
4

Disease management system for chronic skin cancer



4.1

Need for a new skin cancer management strategy

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Abstract

The worldwide incidence of skin cancer (especially non-melanoma skin cancer) has increased markedly during the last decades. Skin cancer should be considered a chronic disease. To manage the future costs and quality of care for patients with skin cancer, a revised health strategy is needed. These new strategies should be combined into a disease management system that organizes health care for one well-documented health care problem using a systematic approach. This article explores multiple opportunities for the development of a disease management system regarding skin cancer that will provide structured and multi-disciplinary care.

Introduction

The worldwide incidence of skin cancer (especially non-melanoma skin cancer) has risen dramatically over the last decades.[1,2] The ramifications for health care systems worldwide are enormous, as will be outlined in this paper. An evaluation of the diagnosis-treatment codes combined with the zip codes of the patients of a large outpatient dermatology clinic at the Catharina Hospital Eindhoven in the Netherlands shows that over 50% of dermatologists' time is spent on skin cancer and skin pre-malignancies. (Non-published data) When evaluating and extrapolating the figures of this database for the Netherlands, we found an incidence of about 80.000 skin malignancies in 2007 in our country (non-published data), indicating at least the double amount of skin cancers, compared to the expected incidence in 2015 of 37.000 skin cancers in The Netherlands.[2]

New groups at risk for developing multiple skin cancers have been identified. (Table 1) Since the population is aging and skin cancer incidence is on the rise in the younger population, young adults will be confronted with multiple new tumours for the rest of their lives.[6,7,8,9,10,11,12] Skin cancer can therefore be regarded as a chronic disease as defined by The World Health Organization (WHO); a disease of long duration and generally slow progression.[13] Progression should in our case be regarded as progression of the development of new tumours.

Non-melanoma skin cancer (NMSC) has been considered to be a relatively mild health problem for a long time because of the low mortality rate. However, morbidity and the burden for the health care system caused by NMSC are high, as are the costs related to skin cancer.[14] In the U.S.A. skin cancer has taken the fifth position with respect to cancer costs,

Table 1.Groups of patients at risk for multiple skin cancers during life.

	Elderly male (>65 years)	Youngeradults (15-34 years)	Organ transplant patients
Incidence BCC In 2000 in the Netherlands (de Vries)[3]	438/ 100.000 person years	322/ 100.000 person years	N.A
Expected Incidence BCC in 2015 in the Netherlands (de Vries)[3]	546/ 100.000 person years	676/ 100.000 person years	N.A
Incidence NMSC Ireland (Moloney)[4]	N.A	N.A	After 10 years 6.4% of patients has NMSC
Annual incidence NMSC in Australia (Carroll)[5]	N.A	N.A	28-45%
Australia (Carroll)[5]	N.A	N.A	50% of patients develop NMSC within 20 yrs after transplant

N.A = not available

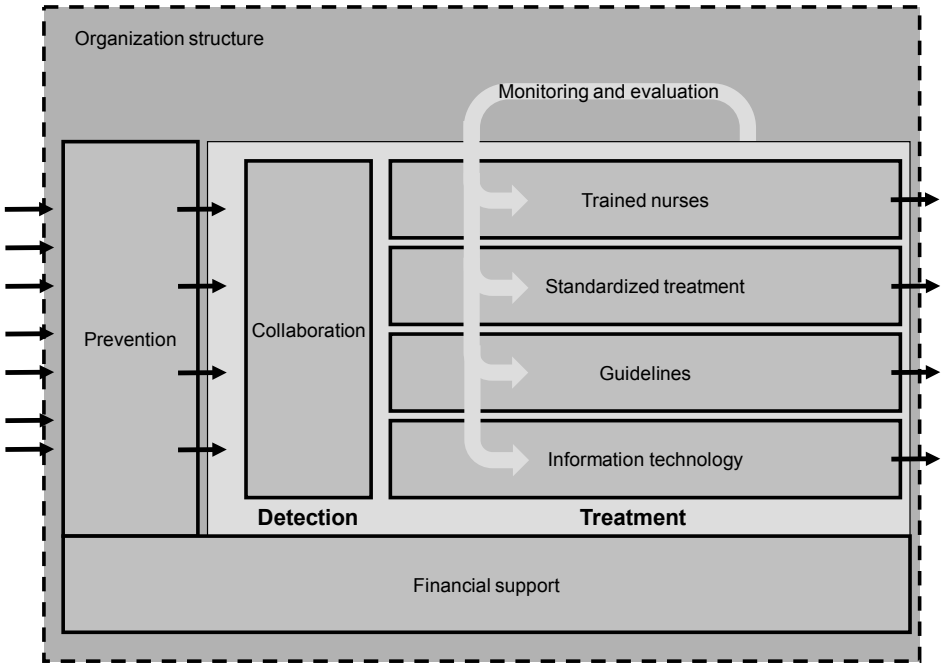

Figure 1. Healt care system for chronic skin cancer

behind prostate, lung and bronchus, colon and rectum, and breast carcinomas.[15] To manage the future costs and quality of care for skin cancer patients, a revised health strategy is needed. These strategies should be combined in a disease management system, a system that organizes health care for one well documented health care problem with a systematic approach, which includes prevention, education, multidisciplinary care, information technology and management (Figure 1).[16]

Several organizational models of management of chronic diseases have been proposed and implemented internationally.[17] WHO recently discussed how to operate these programmes across care settings and providers.[13] While there is increasing evidence that disease management systems provide more efficient, high quality, and cost-effective care,[18] not all studies of disease management programmes or nurse-led care show statistically significant improvements. For chronic diseases, like diabetes mellitus and heart failure, these systems are already in place and they demonstrate significant improvement of disease control and a reduction of complications.[19,20,21] The differences in the outcomes of various studies may be related to methodological weaknesses, confounding factors, and inherent differences in populations at risk for various diseases. [22,23,24]

There is a clear and immediate opportunity to evaluate the potential benefits as part of a renewed health strategy for effective chronic care in our aging society.[18] By applying the disease management systems approach, multiple opportunities for chronic skin cancer care

become apparent in prevention, education, multidisciplinary care, information technology and management.[16] (Figure 1)

The figure visualizes the disease management system as being embedded within a supportive overall *organization structure*. At its basis, firm *financial support* must be available for all aspects of the disease management system, including prevention. Proper *prevention* is mandatory to manage the inflow of future patient groups to the core detection and treatment parts of the system. The figure further shows how the disease management system emphasizes *collaboration* in the detection of skin cancer, while multiple aspects (*trained nurses*, *standardized treatment*, *guidelines*, and *information technology*) contribute to an effective treatment of patients. By a close *monitoring and evaluation* of treatments, various aspects of the system can be fine-tuned and improved. Further details will be provided in the following sections.

Prevention

Population-based primary prevention is an important part of chronic disease management.[18]

Targeted approaches are needed to reach young children, adolescents, young adults and skin cancer patients since these groups are at high risk. Messages need to create awareness of the problem since most people underestimate the problem and their susceptibility to skin cancer, they need to highlight the advantages of protection, and discuss how to cope with barriers of adopting protective behaviours to create feelings of self-efficacy.[25] Most of the previously implemented interventions have been based on the assumption that health behaviour change can be achieved by targeting and changing motivational determinants, such as attitudes and self-efficacy expectations. This would lead to an increased intention to perform health behaviour. However, intentions account only for 20-40% of behavioural change.[26] Intentions need to be translated into actual behaviour.[26] Specific action-plans, how and when to use sunscreen for example, are needed to promote the actual implementation of the sun protective measures.[26,27]

In chronic disease management, self-management support of patients is central to improving care and outcomes.[28] Online information, questionnaires and checklists, with photographs of skin cancer could help people to recognize skin malignancies. Early detection of skin cancer has multiple advantages: it leads to the diagnosis of smaller skin cancers, which are less difficult to treat. When primary skin cancers are diagnosed and treated correctly, this leads to fewer recurrences, which are more difficult to treat and involve a higher risk of recurring, and that at higher costs.[28,29,30]

Collaboration

As full members of the multidisciplinary treatment team, general practitioners should be able to more actively participate and collaborate with dermatologists in the prevention and care process. They should be fully informed about prevention, treatment, prognosis and follow-up plans with the help of an e-skin cancer file. This could be achieved with the use of a central electronic medical record that crosses institutional borders, or by using Web-access to medical records in hospitals.[31,32]

Store-and-forward teledermatology (a dermatologist evaluates photographs with the help of historical and demographic information) has been demonstrated to be an effective, accurate and valid approach for the routine management of patient referrals by general practitioners in skin cancer. It has helped to improve prioritization, efficiency of service and patient care.[33,34] May et al. demonstrate that 51% of visits to dermatologists are unnecessary and could be avoided with store-and-forward teledermatology.[34] Hsiao et al show that the overall mean time intervals for initial evaluation, biopsy and surgery were respectively 44 days, 19 days and 21 days shorter for teledermatology than for conventional consultation.[35]

For skin cancer patients, online questionnaires could be used to improve diagnostic visits at hospitals. These questionnaires could help provide information needed for the first hospital visit, that is, information about general health, medication, medical history and allergies. This would facilitate a complete diagnosis, improved and efficient documentation of skin cancer patient complaints, and skin cancer prevention practices of patients.

Guidelines

Clear guidelines in order to provide standardized evidence-based treatments that will result in the best care need to be available and need to be up to date. Currently, it takes several years to make and implement a guideline. It took over two years to develop and implement the Dutch guideline of cutaneous melanoma and even longer for the guideline of basal cell carcinoma.[36,37] During these years of making and implementing guidelines, new studies with new evidence have become available. These results, however, are not implemented in the guidelines, something which could fail in providing quality care.

A substantial acceleration of guideline adjustment can be achieved when clinics make the data on their patients, treatment types, and treatment effectiveness available as registered in their IT-systems. This data can then be included as supplementary evidence for good practices. Automated techniques can be used to detect differences between guideline-prescribed and actual execution of (medical) processes.[38] Such differences can be used as a starting point to discover the reasons for non-adherence in order to create the most optimal treatment plan.

Trained nurses

Nurse care management interventions have been shown to improve medical, psychosocial and lifestyle outcomes for patients with chronic diseases such as diabetes.[23] Taylor et al showed that nurse care managers can improve medical outcomes, without increasing physician visits.[23] A review of a nurse-led care in dermatology concluded that nurses are managing and treating a number of dermatological conditions, like eczema and leg ulcers, primarily by using treatment protocols. The nurses work in a variety of clinical contexts, including in-patient, out-patient and community settings. Patients report various benefits such as faster access to treatment, reduction in referral to the general practitioner or dermatologist and an increase in knowledge of their condition.[22] Nurses are also being trained to participate in dermato-oncology care for organ transplant patients.[39]

At the Catharina Hospital Eindhoven, on the job trained nurses in dermato-oncology participate in secondary prevention and counselling. They also perform skin biopsies, photodynamic therapy, cryotherapy and small excisions. Nurse-led care effectively results in the reduction of the high workload of dermatologists regarding skin cancer and has enhanced the capacity not only at our department, but also in others.[40] In the future a larger number of tasks could be performed by trained nurses. For instance, a diagnostic questionnaire assessing demographics, medical histories, medications, etc, which is filled in by the patient at home, could be checked by the nurse during the first visit and adjusted if necessary. The nurse could perform the first clinical examination and inform the dermatologist. The dermatologist would remain responsible for the final clinical diagnosis, the diagnostic process and treatment scheme (preferably the standardized schemes unless specific contra-indications).

Information Technology

Modern information technology plays an important role in shaping a disease management system.[16] First, this system supports the classical functions of consulting, as well as manipulating and retrieving patient-related data. Second, these systems are pro-active and allow diagnostic and treatment advice for clinically diagnosed lesions at any time. Over the past years, insights have been gained on how such clinical decision support could be effectively integrated into the care process.[41] Third, the system facilitates communication amongst the health care teams, for instance assisting nurses in ascertaining which actions need to be executed or have already been completed for patients. The features pertaining to this so-called 'workflow management technology' are customary for managing various chronic diseases.[42] Yet, the potential of this technology has not been fully exploited in the healt care domain in general, and certainly not for skin cancer management.[43] For example, workflow management systems could be used to enforce adherence to standardized treatment practices, while being sufficiently flexible to allow for incidental deviations. Also, these systems could monitor dead-

lines and signal missing medical information, contributing to improved treatment quality. At the department at the Catharina Hospital Eindhoven, workflow management has increased the number of patients treated with photodynamic therapy from 6 to 10 patients per day.

Monitoring and Evaluation

It is feasible to use the enormous amount of data on dermato-oncology, with the help of the above-mentioned information technology system, to evaluate the adherence to the guidelines and the effectiveness of treatments (complications, recurrences etc). On the other hand it can lead to adjustment of guidelines so that the effectiveness can be improved or their associated costs be reduced. So-called "process mining techniques" have recently been applied to achieve these goals in the treatment of strokes.[44] The study showed differences between two hospitals in treatment strategies and in the treatment itself. The differences could be analyzed to gain a better understanding of these treatment strategies and their outcomes.[44]

Financial support

It is obvious that the development of the disease management system proposed above requires sufficient financial resources, thus justifying the strong emphasis to put this item on the political agenda and the agenda of insurance companies. As shown in Figure 1, financial support is necessary for all items of the disease management system, including prevention. Health insurance companies now focus on reducing costs of treatment of skin cancer, while primary and secondary prevention of skin cancer is not reimbursed. Funds need to be allocated to restructuring, to financial incentives (including prevention), to training staff and to monitoring progress.[13]

Organization structure

A chronic disease demands a robust organization, as shown in Figure 1, with central coordination by the health care provider; for skin cancer this would be the dermatologist. Dermatologists need to demonstrate their value as providers and the collective capacity to organize and deliver efficient and high quality dermatologic care.[45] The organization should focus on benchmarking and optimizing skin cancer treatment processing. Business management strategies (Six Sigma for instance) are needed to identify and remove causes of defects (any factor that negatively impacts profitability) and errors in manufacturing and business processes. In the past years, health care organizations and providers have begun implementing these types of business strategies with significant success; financial savings mounted to 2.9 million over a 3-year period and annual savings of even $5 million.[46,47,48]

Conclusion

Skin cancer needs to be regarded as a chronic disease and should not be considered a solitary tumour anymore. The workload for all medical personnel involved in the treatment of skin cancer will significantly rise in the next few years. Population-based chronic disease management is a necessary approach to deal with the growing burden of chronic illness. Adjustments in health care need to be made regarding prevention, education, multidisciplinary care, information technology, and management. Combining these strategies in a disease management system will lead to efficient, evidence-based, high quality care, in order to deal with chronic diseases like skin cancer pro-actively.

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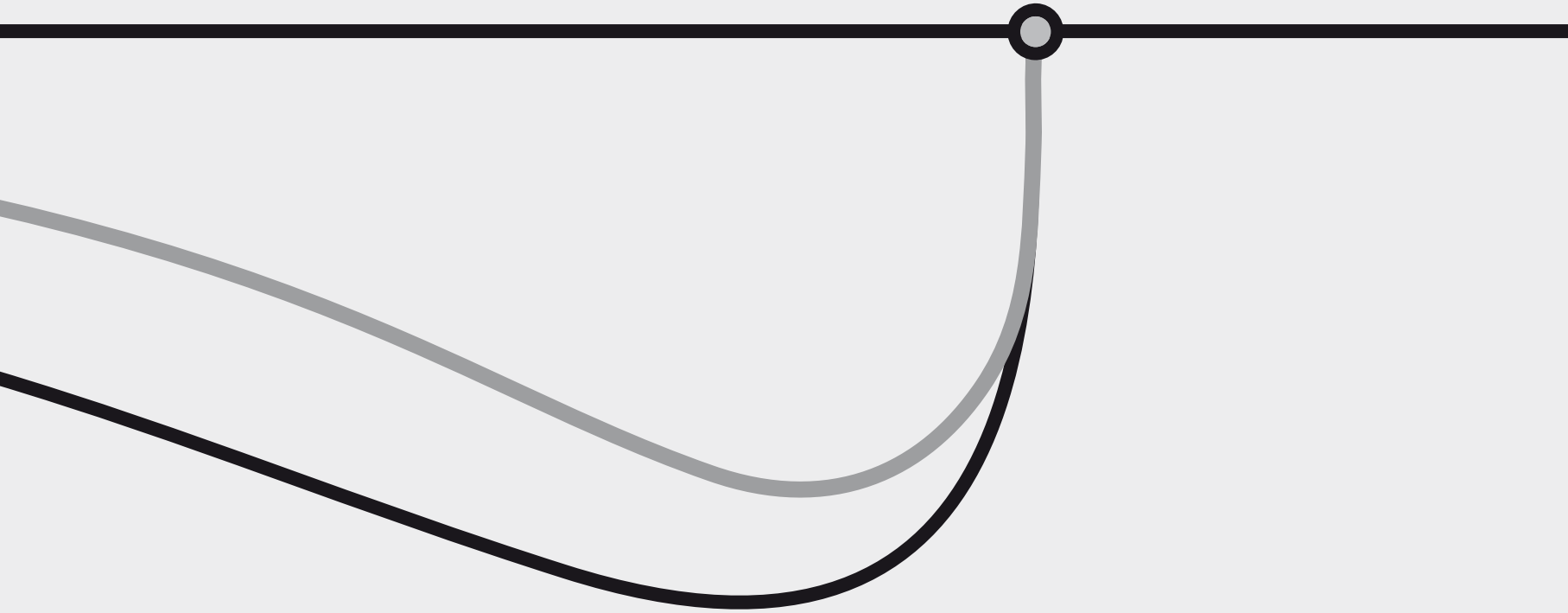
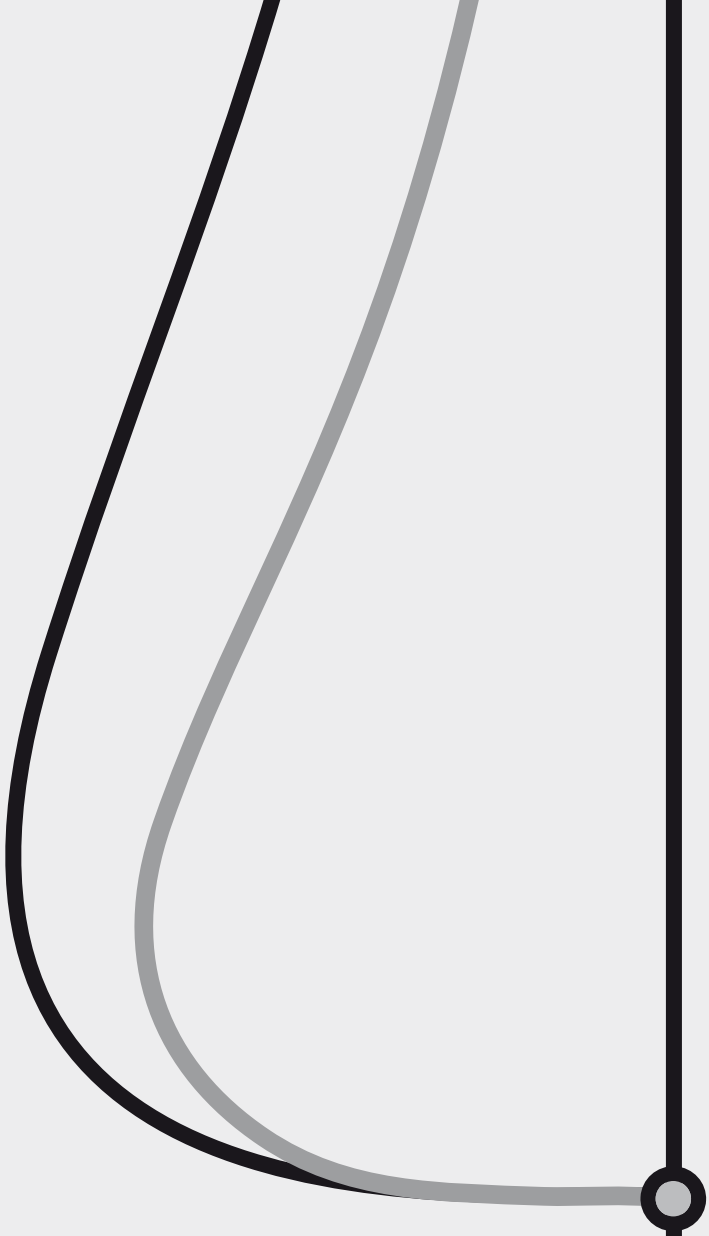
Innovations in the treatment process of chronic skin cancer





5.1

Imiquimod 5% cream as pre-treatment of Mohs Micrographic Surgery for nodular basal cell carcinoma in the face, a prospective randomized controlled study

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Abstract

Background: Imiquimod 5% cream can reduce or clear superficial and small nodular basal cell carcinoma (BCC). It could be used as a pre-treatment of Mohs' micrographic surgery (MMS) to decrease defect size.

Objective: To study if a pre-treatment with imiquimod 5% cream decreases defect size after Mohs' micrographic surgery. In addition the effect on the number of Mohs stages and reconstruction time was studied.

Methods and Materials: 70 patients >18 years with a primary nodular BCC in the face were included. The imiquimod group used imiquimod 5% cream during 4 weeks, followed by MMS. The control group was treated with MMS only.

Tumour and defect sizes were measured. We noted the number of Mohs-stages, reconstruction time and side-effects.

Results: The median percentage increase in area from tumour size at baseline to the post-MMS defect for the imiquimod group was significantly less compared to the control group, 50% vs147% (p=.0.00).

A tendency towards less Mohs stages in the imiquimod group was observed. Reconstruction time was significantly shorter in the imiquimod group (0.01)

Conclusion: Imiquimod 5% cream as pre-treatment before MMS significantly reduced tumour size in primary nodular BCC and reduced the surgical defect size.

Further research is necessary to investigate cost-effectiveness.

Introduction

Basal cell carcinoma (BCC) is the most common malignancy of the skin.While the mortality rate due to this tumour is insignificant, an increasing group of especially younger patients are concerned about the cosmetic outcome of the treatment of a facial tumour. Various therapeutic modalities exist.[1] In most cases surgical excision will take place. Mohs micrographic surgery (MMS) is an advanced technique, which is used mainly for BCC in the face and with high risk for recurrence, in the H-zone or > 2 cm.[2] The size of the defect after excision of the tumour can significantly be reduced by using MMS, compared to the standard surgical excision. The cosmetic outcome is therefore overall better.[3] MMS has the lowest recurrence rate in the treatment of BCC. It is however, a time consuming method and therefore costs are higher.[1,3]

Non-surgical treatments for BCC are available, such as imiquimod 5% cream (Aldara®), an immune response modifier. Studies show that imiquimod has a beneficial effect on small superficial and small nodular BCCs, total or partial clearance is obtained.[4,5,6,7,8,9]

Adverse events that have been reported are mainly mild local skin reactions; these include erythema, itching, pain, erosions, and excoriations. Systemic reactions are described as well.[4,5,7] Imiquimod has been used as an adjuvant treatment for MMS before.[10,11,12]

In this study we investigated the effect of a pre-treatment with imiquimod 5% cream before MMS for larger nodular (or nodular and partially superficial) BCC in the face. We hypothesized that this pre-treatment could reduce tumour size and could result in a smaller defect after MMS.

Methods

We included patients with histologically proven nodular (or nodular and partially superficial) BCC in the face. Patients above 18 years with a BCC size of 1-5 cm in diameter were eligible to participate. All patients were included at the outpatient clinic Dermatology at the Catharina Hospital in Eindhoven. Inclusion took place in the period between October 2007 and September 2011. All patients were randomly assigned in a ratio of 1:1 to the imiquimod group or control group according to a confidential computer-generated list (via www.randomization.com). This list was kept by the secretary; she informed the investigator about the type of treatment.

We excluded pregnant women, women who breastfeed, patients with recurrent BCC, aggressive growth pattern (squamous, morpheaform, infiltrative), patients with BCC within 1 cm from the eyes, lips or mucosa of the nose, patients with another skin tumour within 5 cm of the target tumour and patients with an allergy for imiquimod 5% cream or substances

of the cream. The study was approved by the Medical Ethical Committee (METC), and all patients gave written informed consent.

Patients were followed according to the intention-to-treat principle. Control visits were planned 3, 6 and 12 months after MMS, from then, follow-up took place according to the Dutch guidelines for BCC.

Study procedures

Baseline characteristics including age, sex, Fitzpatrick skin type and tumour localisation were noted. Before treatment, the tumours were measured in two directions. The tumours were marked and then photographed. In addition a template of the tumour was created with local landmarks, using a permanent marker on translucent paper divided in squares, by mm. A software programme (Visitrak®) was used to calculate the exact area size in mm^2 obtained with the template for all tumour and defect sizes.

Patients in the imiquimod group used the imiquimod 5% cream once a day, 5 days a week, during 4 weeks. The cream was applied at night, so that it was left in place for at approximately 8 hours. It had to be applied on the BCC and 1 cm around the tumour.

Patients were asked to fill out a diary about the application of the cream and side-effects.

A control visit was planned after two weeks. Adverse events and local skin reactions were noted by the investigator. If no serious adverse events occurred, the patient was motivated to continue the cream. After treatment with imiquimod 5% cream for four weeks, adverse events were noted again during a control visit. MMS was performed four to six weeks after the last day of treatment by one of the Mohs residents and one of the three qualified Mohs surgeons of the department of dermatology. The control group only underwent MMS, at 12 weeks from baseline.

The tumours were measured, marked and photographed just before MMS was performed.

After the MMS procedure, the defect was measured and photographed in both groups, and time needed for reconstruction was measured.

Endpoints

The main outcome was difference in defect size after MMS between both groups. Increase in area from baseline lesion to post-MMS defect was calculated and compared between both groups. The secondary outcomes were differences in tumour size within the imiquimod group and between both groups. We also studied the number of Mohs' stages and reconstruction time after MMS.

Statistical analysis

To calculate sample size, we used results from a previous study.[12] The mean observed percent increase in area from baseline lesion to post-Mohs defect for the control group was 173% and the standard deviation was 134%. The mean percent increase for the imiquimod group was 75% and the standard deviation was 104% (Note: These numbers were obtained by pooling the data for the 4 week and 6 week dosing regimens). With a type 1 error rate set at 0.05 and a power of 90% to detect a difference of 98%, we needed 32 patients in each group. We assumed a dropout rate of 10%. This led to a number of 35 patients in each group.
The software program SPPS version 19was used to analyze the data.
The Mann-Whitney U test was used for continuous variables without a normal distribution.
For variables with a normal distribution, the independent t-test was used.
The Chi-squared test was used for categorical variables.

Results

Patients

70 Patients, 46 men and 24women were enrolled in the study. 35 Patients were included in the imiquimod group, 35 patients in the control group. The mean age was 68 years in the control group and 69 years in the imiquimod group. Median tumour size area at baseline was

Table 1.Baseline characteristics.

Characteristics	Imiquimod group (N=35)	Control group (N=35)	p-value
Men	22 (63%)	24 (69%)	0.62
Women	13 (37%)	11 (31%)	0.62
Mean age in years	69 (65-73)	68 (64-72)	0.68
Median diameter tumour (in mm)	13 (25% 11; 75% 18)	14 (25% 12; 75% 18)	0.24
Median tumour area (in mm^2)	95 (25% 60; 75% 173)	110 (25% 80; 75% 160)	0.27
H-zone			
Yes	20 (57%)	23 (66%)	0.46
No	15 (43%)	10 (34%)	0.46
Localisation			
Nose	8 (23%)	9 (26%)	0.77
Ear	4 (11%)	6 (17%)	0.77
Scalp+frontal	8 (23%)	5 (14%)	0.77
Face, other regions (cheek,temporal, chin)	15 (43%)	15 (43%)	0.77
Skin type			
1	10 (31%)	9 (26%)	0.87
2	23 (66%)	23 (71%)	0.87

95 mm^2 in the imiquimod group and 110 mm^2 in the control group. Baseline characteristics did not significantly differ between both groups. Most tumours in both groups were located in the H-zone (Table 1).

None of the patients were lost to follow up or had to leave the study because of severe adverse events or other reasons.

Median follow-up after treatment was 20 months for the control group and 19 months for the imiquimod group.

Efficacy

The median increase in area from tumour size at baseline to the post-MMS defect for the imiquimod group was 50%.The increase for the control group was 147%. This resulted in a statistical significant difference (p = 0.00)(Table 2). In two patients of the imiquimod group total tumour clearance was clinically observed and MMS was not performed.

Within the imiquimod group patients had a median decrease of tumour size (size of tumour at baseline, compared to tumour size before MMS) of 20 mm2. In the control group, median change in tumour size was 0. This was a significant effect between both groups (p= 0.02).

The median number of Mohs stages was 1 in both groups. In the imiquimod group the 75 percentile remained 1. In the control group the 75 percentile was 2. Therefore a tendency of a favourable effect for the imiquimod group was seen (p=0.04)

Table 2. Results

	Imiquimod group (N=35)	Control group (N=35)	p-value
Median tumour size before MMS (in mm^2)	60 (25% 35; 75% 100) 2 missing	110 (25% 80 75% 203) 1 missing	0.00
Median Defect size (in mm^2)	160 (25% 100; 75% 240) 2 missing	310 (25% 208; 75% 488)	0.00
Median increase defect size in relation to tumour size at baseline (in %)	50 (25% 17; 75% 150)	147 (25% 82; 75% 230)	0.00
Median number of Mohs stages	1 (25% 1; 75% 1) 2 missing	1 (25% 1; 75% 2)	0.04
Median reconstruction time (in min)	20 (25% 15; 75% 30) 5 missing	30 (25% 20; 75% 40) 5 missing	0.01
Type of closure defect			
Secondary granulation	4 (11%)	2 (6%)	0.15
Primary closure	21 (60%)	18 (51%)	
Graft	1 (3%)	6 (17%)	
Flap	7 (20%)	9 (26%)	
Closure defect			
Plastic Surgeon	6 (18%)	12 (34%)	0.13
Dermatologist	27 (82%)	23 (66%)	0.13

The median reconstruction time in the control group was 30 minutes compared with 20 minutes in the imiquimod. (p= 0.01) There were no significant differences between groups concerning type of closure (Table 2).

Safety

Most important adverse events reported were local erythema, itching, crusting and irritation, with erythema occurring most often(Table 3). One patient reported irritation of the eye during the use of imiquimod cream. The tumour of this patient was located on the proximal

Table 3. Side-effects

Side effects reported by patient	After using imiquimod for 2 weeks (N= 35)	After using imiquimod for 4 weeks (N= 35)
	Number of patients (percentage)	Number of patients (percentage)
Erythema	23 (66%)	26 (74%)
Edema	8 (23%)	18 (51%)
Scaling	8 (23%)	13 (37%)
Erosions	7 (20%)	14 (40%)
Bleeding	11 (31%)	10 (29%)
Crusts	24 (69%)	23 (66%)
Pain	1 (3%)	8 (23%)
Irritation	17 (49%)	20 (57%)
Itching	17 (49%)	21 (60%)

side-wall of the nose, these complaints resolved completely after treatment.

None of the subjects needed to use pain medication or had to visit the general practitioner because of the side effects.One patient reported severe diarrhoea during the use of imiquimod cream. In each group one patient had a secondary bleeding after MSS.

Discussion

This randomized controlled study showed a significant effect of imiquimod 5% cream as a pre-treatment of MMS. We used imiquimod 5% cream with a shorter application period (4 weeks) than is prescribed for the treatment of superficial BCC (6 weeks). With a shorter treatment period, less side-effects are reported.[4,5,6,7] In addition, it was not our goal to achieve complete clearance; our aim was to decrease the size of tumours and defects. Although clearance rates of imiquimod 5% cream are highest for superficial BCC, it has shown to be able to (partially) clear nodular BCC as well.[13,14,15] We focused our study on nodular BCC (or partially superficial). Diagnosis was made by means of a biopsy that only represents a part of the tumour. It is known from literature that BCC tumours often consist of mixed subtypes and can have superficial areas.[11,16] Although the tumours in our study were histological diagnosed

as nodular BCC, the decrease in size could have been partially or mainly due to clearance of superficial parts. No aggressive tumour nests were found in the histology slides during the MMS procedures. Tumour size within the control group did not change during the 12 week period, from baseline to the MMS procedure. This supports the fact that BCC grow very slowly, which is an important finding since we do have waiting lists for MMS procedures that reach 3 months.[17]

In the imiquimod group a significant decrease in tumour size was noticed, which resulted in a significant smaller defect afterMMS (p= 0.00).Torres et al. performed a study on imiquimod as a pre-treatment before MMS for BCC as well.[12] They compared a pre-treatment period of 2, 4 and 6 weeks. Control patients were treated with a vehicle. They reported a significant reduction in the size of the target tumour and a smaller surgical defect after MMS in patients treated with imiquimod 5% cream compared to patients treated with a vehicle.[12] In another study of Butler et al. a decrease in defect-size was found as well, this was however not significant.[10]

A treatment free period of 6 weeks is advised after treatment with imiquimod, before excision or MMS is performed, to prevent the presence of excessive inflammation.[12] In our study, time between the last day of imiquimod and MMS was not exactly the same in all patients, time varied between 4 and 6 weeks. This period could be important for our results. Interpreting fresh frozen sections of a MMS procedure is more difficult when there is still inflammation caused by treatment with imiquimod. This could lead to unnecessary extra Mohs stages in case of doubt about clearance of the tumour, and actual defect size could therefore have been smaller.[12]

One could argue to use imiquimod 5% cream as an adjuvant therapy after MMS, to clear remaining superficial areas.[11] Then it would not interfere with the interpretation of the fresh frozen sections. It will have to be investigated if defects then still are significantly smaller, since parts of the superficial area will already be cut out before ending the MMS procedure. Some state that a destructive therapy like imiquimod has a certain risk of incomplete cure, leaving behind independent tumour nests, which could lead to false-negative results in the MMS procedure.[18] Studies that excised the complete area after treatment with imiquimod, did in some cases show remaining tumour, these rests were found in the dermis.[5,19,20] We do acknowledge this fact, but we believe risk is minimal since MMS is performed around the tumour, taking subcutis with the first stage, and MMS does show nearly 100% of margins. In addition, no treatment provides full 100% guarantee, even after MMS recurrences are seen. Basal cell carcinomas with an aggressive growth pattern were left out of the study and patients are followed after treatment to screen for recurrence or new tumours.

Less Mohs stages were needed in the imiquimod group compared to the control group (p= 0.04). The number of Mohs stages could be influenced by the operating Mohs surgeon. The size of the margin that was taken around the tumour was not standardized in this study and could differ among the various surgeons.In the study of Butler et al. 31 patients with

nodular nasal BCC were randomized to imiquimod or vehicle pre-treatment before MMS. The cream was applied during 6 weeks and after a treatment-free interval of 4 weeks, MMS was performed. They did not find a significant effect of the pre-treatment on the number of Mohs stages and they did not found a significant difference in costs either.[10] Less Mohs stages could reduce costs concerning MMS. It will need further research to investigate whether the tendency towards a decrease in Mohs stages will be cost-effective.

Reconstruction time in the imiquimod group was statistically shorter than in the control group. This could be related to the defect size, but other important issues are the location of the defect and type of closure. We compared both groups on localisation and type of closure, and did not find significant differences for these variables (Table 2).

A pre-treatment with imiquimod for 4 weeks costs 150 euro. That resulted in a significant smaller defect, a tendency towards less Mohs stages and a significant shorter reconstruction time. Taking these facts together, a higher level of efficiency and probably cost-effectiveness would be achieved, with more patients being treated on the same day. As a result waiting lists will decrease as well.

Local inflammatory reactions were reported by the majority of patients, but none of them had to leave the study due to side-effects. Most adverse events consisted primarily of local reactions, with erythema and crusting occurring most often. In literature comparable figures are reported.[4,5,7] Sapijaszko et al. report that 87% of patients report one or more side-effects.[21] In addition to local inflammatory reactions, 1 patient mentioned a systemic adverse event, diarrhoea. This has been described before.[4,5,7]

In two patients of the imiquimod group, total tumour clearance was concluded clinically, MMS was not performed on these patients. They were seen at a control visits and showed no signs of residual BCC. They werefollowed for 41 respectively 31 months now and still do not have signs of recurrence. Follow-up will be continued.We cannot conclude about recurrence rates at this time. 5 Year follow-up results will become available in the future. Median follow-up is 20 months for the control group and 19 months for the imiquimod and no recurrences have been seen so far.

Conclusion

The application of imiquimod 5% cream as a pre-treatment before Mohs' micrographic surgery significantly reduced tumour size and surgical defect size in primary nodular basal cell carcinomas in the face. Less Mohs stages and a significantly shorter reconstruction time are observed after the use of imiquimod 5% cream.

Long-term follow-up is necessary to be able to report on recurrence rates. Additional analyses on cost-effectiveness will give more insight in the clinical implication of this treatment process.

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5.2

ONE-STOP-SHOP treatment for basal cell carcinoma, part of a new disease management strategy

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Abstract

Background: The number of skin cancer patients, especially patients with basal cell carcinoma (BCC), is rapidly increasing. Resources available at dermato-oncology units have not increased proportionally, which affects the throughput time of patients.

Objective: To assess the feasibility and safety of implementation of the one-stop-shop concept for the treatment of patients with basal cell carcinoma at a dermato-oncology unit.

Methods : A pilot study on a one-stop-shop concept for basal cell carcinoma was performed to investigate procedure safety and patient satisfaction. Fresh frozen sections were used to diagnose the tumours and subsequently treatment with photodynamic therapy or excision was performed on the same day. Time spent in the hospital was measured and questionnaires were used to evaluate patient satisfaction.Results: Sixteen patients, who together had 19 tumours, were included. Diagnoses were made within a mean time of 100 min (range 27-160 min). The mean throughput time was 4 hours and 7 minutes (range 60-420 min). No complications were observed and patient satisfaction was high. Conclusion: The one-stop-shop concept for the treatment of skin cancer patients is feasible and efficient for both patients and dermato-oncology units. Further research is necessary to investigate cost-effectiveness when larger patient groups are involved.

Introduction

The worldwide incidence of skin cancer has risen dramatically over the last decades.[1,2] Resources available at hospitals have not increased proportionally, resulting in long total throughput times, the time between patients' arrival at the clinic and the end of their treatments.[3,4] At the Catharina Hospital in Eindhoven, adjustments are being made on several levels of the dermato-oncology unit in collaboration with Eindhoven University of Technology.[3,4] We would like to present the results of a pilot study on the use of a one-stop-shop concept for basal cell carcinoma treatment. One-stop-shop implies that the initial consult meeting at the outpatient clinic, diagnosis, and treatment all take place in one day.

Methods

Our capacity analysis showed that it seems feasible to perform a one-stop-shop treatment on days that Mohs micrographic surgery (MMS) was performed.[5] On these days, 2 appointment slots for surgical excision and 3 for PDT needed to be reserved. We included 16 patients with (according to the dermatologist) clinically suspect, well-defined, superficial or nodular BCC. The one-stop-shop concept was offered to patients when they arrived at the hospital. Patients had to be older than 18 years, without any serious co-morbidity. Patients were excluded in case of pregnancy, breastfeeding, holiday or sports on the short term. Patients were also excluded in case of an MMS indication, like an aggressive BCC growth pattern or high risk location in the face.

Patients seen at the outpatient clinic before 11.00 AM were eligible to participate (with a maximum of 5 patients per day), which would leave enough time to diagnose and treat the lesion on the same day. A resident took a 4 mm punch biopsy and immediately afterwards, a technician made fresh frozen sections (carried out vertically). Part of the biopsy was used for examination on paraffin. Both the Mohs surgeon (a dermatologist) and a pathologist examined the fresh frozen sections. The time between the biopsy and the histopathological diagnosis was recorded. At a later moment, the pathologist examined the paraffin slides.

The resident discussed the diagnosis and appropriate treatment with the patient, and also provided additional information about sun protection and follow-up. The suggested treatment could be topical imiqimod 5% cream, photodynamic therapy, or standard excision, which were performed on the same day.

Questionnaires (answered at the intake and after treatment) were used to evaluate patient satisfaction about the one-stop-shop principle. The questionnaires included questions like; would you prefer to have the diagnosis and treatment on the same day? What do you think about the waiting time? Did you receive enough information about skin cancer and the treatment?

Results

Patients arrived at the clinic between 9.00 AM and 11.15 AM. Nineteen tumours, localized on the back, limbs and face, were included. Three patients had 2 lesions (Table 1). Mean time between arrival and diagnosis was 100 minutes (Table 2). Clinical diagnosis corresponded with the histopathological diagnosis for 13 of the 19 tumours. In all but one biopsy the pathologist confirmed the diagnosis of the Mohs surgeon. There was one inconsistent outcome (Table 2), concerning the diagnosis of an epidermal cyst in combination with a malignancy.

Three superficial BCCs in three patients were treated with PDT, 14 tumours in 13 patients were excised, all on the day of the diagnosis. One lesion, a squamous cell carcinoma, was treated with a slow MMS procedure. This procedure equals MMS regarding the mapping of the tumour. In a slow MMS procedure, however, paraffin slides are used instead of fresh frozen sections.[6] In our hospital, results of these paraffin slides become available after 4 to 5 days. The mean throughput time was 4 hours and 7 minutes (Table 2).

All patients were very satisfied with the one-stop-shop concept. Positive reactions were: good to know the diagnosis immediately and that the tumour is treated at once, less appointments, accompanying persons need to schedule only 1 day and less working days are lost.

Table 1. Baseline characteristics.

Patient	Age years (mean 67)	Clinical diagnosis	Localisation	Size (cm)
1	85	sBCC	Back	1,5 x 0,5
2	65	nBCC	Back	1 x 0,5
3	71	sBCC	Scapula	1 x 1
		nBCC	Back	2 x 2,5
4	85	nBCC	Back	0,7 x 0,8
5	61	nBCC	Chest	0,7 x 0,5
6	44	sBCC	Shoulder	1 x 1
		sBCC	Back	0,8 x 0,8
7	73	sBCC	Temporal	0,5 x 0,5
8	81	nBCC	Arm	N.A.
		nBCC	Cheek	N.A.
9	47	sBCC	Temporal	1 x 1
10	68	nBCC	Temporal	1 x 0,5
11	86	nBCC	Cheek	0,9 x 0,9
12	39	nBCC	Back	1 x 1
13	63	nBCC	Jaw	0,4 x 0,4
14	79	sBCC	Leg	0,6 x 0,5
15	62	nBCC	Nose	0,6 x 0,5
16	60	nBCC	Chest	N.A.

sBCC: superficial BCC
nBCC: nodular BCC
N.A.: not available

Table 2. Tumour characteristics

Patient	Time biopsy- diagnosis on FS by Mohs surgeon (min) Mean 68 min	Time arrival-definitive diagnosis on FS (min) Mean 100 min	Time arrival- end treatment (min) Mean 247 min	FS Mohs surgeon	FS Pathologist	ParaffinPathologist	Treatment
1	N.A.	160	N.A.	sBCC	sBCC	sBCC	PDT
2	N.A.	N.A.	N.A.	nBCC	nBCC	nBCC	SE
3	N.A.	84	N.A.	sBCC	sBCC	sBCC	SE
	N.A.	84	N.A.	Infiltr BCC	Infiltr BCC	Infiltr BCC	SE
4	N.A.	27	60	nBCC	nBCC	nBCC/ infiltr	SE
5	N.A.	120	147	nBCC	nBCC	nBCC	SE
6	N.A.	135	420	sBCC	sBCC	sBCC	PDT
	N.A.	105	165	nBCC/ infiltr	nBCC/ infiltr	nBCC/ infiltr	SE
7	36	119	375	nBCC	nBCC	nBCC	SE
8	110	115	345	sBCC/ infiltr	sBCC/ infiltr	No residual BCC	SE
	115	120	350	Epidermalcyst+BCC	Epidermalcyst	Epidermalcyst+SCC	SE
9	N.A.	N.A.	N.A.	sBCC	sBCC	sBCC	PDT
10	27	75	165	nBCC	nBCC	nBCC	SE
11	75	131	225	nBCC/ micronodular	nBCC/ micronodular	nBCC/ micronodular	SE
12	50	125	327	nBCC	nBCC/ sBCC	nBCC	SE
13	90	95	Next day	nBCC	nBCC	nBCC	SE
14	N.A.	45	N.A.	M Bowen	M Bowen	M Bowen	SE
15	N.A.	65	Next day	SCC	SCC	No residual SCC	Slow MMS
16	40	90	140	nBCC	nBCC	nBCC	SE

FS= frozen section
sBCC: superficial BCC
nBCC: nodular BCC
Infiltr: infiltrative
SE: standard excision
PDT: photodynamic therapy
MMS: mohs micrographic surgery
N.A.: not available

Patients reported the wish to have known about the possibility of the one-stop-shop concept beforehand, to be prepared practically and mentally. Afterwards, all patients reported that they would prefer the one-stop-shop treatment again. They mentioned that it would also be acceptable to be treated within the following week.

Discussion

One-stop-shop is a trendy subject nowadays. Many companies and several medical specialities are creating one-stop-shop concepts.[7,8,9] As early as 1999 Tagge et al. described a one-stop surgery approach for minor surgical paediatric procedures. They concluded that a variety of outpatient surgical procedures can be handled using a one-stop surgery method. [10] In dermatology, almost all surgical procedures are performed under local anaesthesia, which makes them suitable for a one-stop-shop approach. No additional screening by an anaesthesiologist is necessary and there are no post-operative complications due to general anaesthesia. By reducing the throughput time, the administrative workload, and therefore costs, will be decreased. Moreover, when fewer steps in the process must be taken, there is less risk of errors. Reducing throughput time is generally considered an important aspect of patient satisfaction, as this is a period of uncertainty for a patient. [9,11,12]

Our mean throughput time was 4 hours and 7 minutes. Photodynamic therapy caused the highest throughput time, 420 minutes. The actual treatment time of a surgical excision is significantly shorter, with an average of 30 to 45 minutes. The treatments of patients 13 and 15 were performed the next day due to a shortage of operation rooms and personnel. Because of the protocol and extra safety checks, the Mohs surgeon and a pathologist examined the fresh frozen sections. Time to diagnosis can be reduced when the fresh frozen biopsy is examined only by the Mohs surgeon and treatment follows immediately thereafter. The pathologist can check the slides at a later moment.

Mohs micrographic surgery is performed by specially trained dermatologists. From literature it is apparent that interpretations of fresh frozen BCC sections by Mohs surgeons are of an excellent quality. In 98.9% there is total agreement in interpretation among Mohs surgeons and pathologists.[13] In our study there was one inconsistent outcome, involving an epidermoid cyst in combination with a malignancy. After a careful re-examination with the pathologist we concluded that the fresh frozen sections did not show signs of a basal cell or squamous cell carcinoma. The paraffin slide showed an epidermoid cyst with some irregularity at the border, suspect for a squamous cell carcinoma. This case shows that fresh frozen sections are more difficult to interpret for lesions other than BCCs. In case of doubt, an extra paraffin slide can be examined. Diagnosis on paraffin slides could take less than 4-5 days, since technically this procedure could be performed within 24 hours. One could consider performing

immediate treatment based on the clinical diagnosis. This will reduce throughput time even more and therefore will be more cost-effective. A fresh frozen biopsy could be reserved for doubtful cases, larger tumours, and tumours in the head/ neck area. A biopsy provides the BCC subtype, which influences the treatment modality and excision margin. In our study, 2 clinically superficial BCC lesions turned out to be nodular BCC; the choice of treatment based on histopathology was surgical excision. For another 2 lesions, which turned out to be of an aggressive subtype, the surgical excision margin was increased from 3 to 5 mm. In patient number 15, histopathology showed a squamous cell carcinoma. Therefore a slow-Mohs procedure was performed.

There could be some legal aspects related to the one-stop-shop principle. In The Netherlands, the law prescribes that a physician is obliged to give a patient time to think about the proposed treatment. It is not specified, however, how much time this should be.[14] Lesions suspect for melanoma or squamous cell carcinoma are in many cases, for medical reasons, excised at the first visit. One could consider using the one-stop-shop principle especially for patients who are already familiar with skin cancer and the available types of treatment.

Special attention needs to be given to the reimbursement of this concept. In various countries, insurance companies do not reward treatment when it is performed on the same day as the diagnosis. Further research will be necessary to investigate the cost-effectiveness regarding the one-stop-shop process.

Conclusion

In our experience, diagnosing and treating patients on the same day is safe. We did not see any treatment-related complications. With the use of fresh frozen sections, diagnosis can be made on the same day. The interpretation of the histology slides can be made only by the Mohs surgeon, or together with a pathologist. Patients are satisfied with the fast diagnosis and treatment. Further research will be necessary to extend the principle and to examine cost-effectiveness.

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5.3

The development of a non-melanoma skin cancer detection model.

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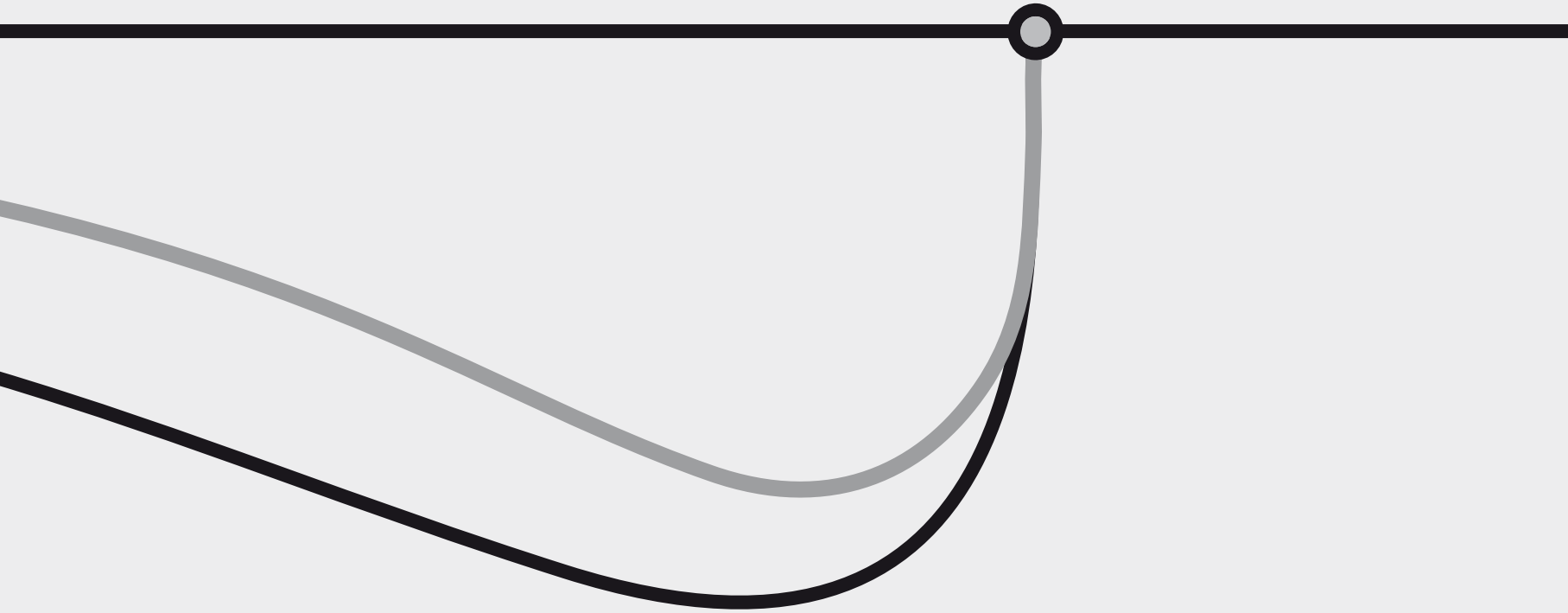
Submitted

6 General discussion



General discussion

Non-melanoma skin cancer (NMSC) is recognized worldwide as an expanding healt care problem.[1,2,3,4,5,6,7] Skin cancer research and healt care programmes have been focused on melanoma for a long time, since NMSC has a low mortality rate. However, the burden of NMSC regarding the number of patients, number of tumours, and costs is enormous. Exact figures for this most common type of cancer are, however, lacking. NMSC does deserve more attention from researchers, physicians (mainly dermatologists), and politicians.

From the moment a patient is diagnosed with NMSC, the physician and patient need to be aware that this could be the start of a chronic disease, in other words: a disease of long duration and generally slow progression, as defined by the World Health Organization (WHO).[8]

The fact that NMSC can be regarded as a chronic disease is supported by our findings concerning the burden of NMSC in a dermatology practice that have been described in Chapter 2. Our figures show that 40% of NMSC patients developed multiple tumours. A mean of 2 skin cancers per patient was found in a follow-up period of almost 5.5 years. In this study, the burden that is caused by actinic keratosis (AK), which was present in 44% of patients, was even left out of the calculations.

Our figures might be difficult to compare with previously published incidence figures and estimates about prevalence.[9,7] Although the Eindhoven Cancer Registry does adequately register the first primary NMSCs, this does not contribute to the estimation of the actual problem in dermatology practices. For physicians in daily practice, the figures published by others are difficult to understand and do not give any insight into the real burden dermatologists have to deal with. Figures are provided as incidence rates per 100,000 person-years. For a physician, these rates are difficult to translate into figures that indicate the burden in their own practice. In addition, in dermatology practices, incident skin cancers are just part of the burden. A considerable amount of patients develop multiple tumours or present with recurrent tumours, and they are often known with pre-malignancies (both not mentioned by any registry). To be able to arrange high quality care according to guidelines, without increasing waiting lists, it is essential to know the actual burden of skin cancer. The official first primary figures of skin cancer registries cannot be used for health care planning in the Netherlands, they are misleading since they represent an underestimation of the actual burden.

To get more insight into the process of chronic NMSC, the Nevoid Basal Cell Carcinoma Syndrome (NBCCS) patients can serve as a model. For many years, dermatologists have been familiar with this rare genetic disease. The treatment of BCCs in patients with this syndrome and the difficulties of treatment have been described in Chapter 3. We have reported about treatment in a megasession, which is highly appreciated by NBCCS patients. We have shown that with adequate planning, by performing multiple treatments on the same day and by using treatments that the patient canperform outside the hospital, the number of visits to

the hospital can be diminished. This will lead to a decreased burden for the dermatology clinic and less disturbance of social life for patients.

For the large number of chronic skin cancer patients, we will need to implement a disease management system (DMS) to be able to control the increasing burden. A DMS starts in general with prevention. Primary prevention is not included in this thesis since prevention campaigns will need to be carried out on a large scale. We do recognize its importance, since primary prevention will diminish the number of patients entering the DMS (Figure 1). Primary prevention needs to start on a large scale as soon as possible to reduce future skin cancer costs. For the nearby future, the effect of primary prevention will, however, be limited.[10,11]

Secondary prevention does also play an important role. The goal is to treat and assist patients with the least amount of effort at the lowest costs. For the future, prevention of major (surgical and/ or radiotherapeutic) interventions for NMSC is important. Early detection of NMSC leads to the treatment of smaller tumours, which are less difficult and less expensive to treat.[12,13] De Leeuw et al. developed a method to detect (pre-) malignancies at a very early stage, with detection techniques based on fluorescence of tumour cells by means of the photosensitizer 5-aminolevulinic acid (5-ALA). The exact contribution of this technique in diminishing the workload for NMSC treatment needs further investigation.[14]

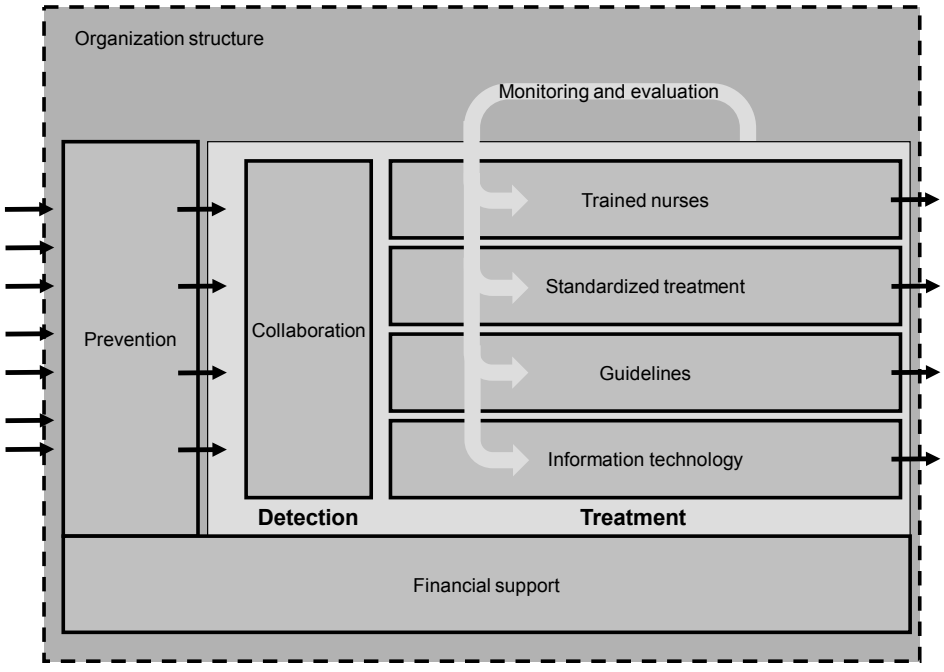


Figure 1. Healt care system for chronic skin cancer

Treatment of pre-malignancies can be considered as secondary prevention. Photodynamic therapy, oral retinoids, topical imiquimod and 5-fluorouracil, ablative laser therapy and chemical peels have been studied. Various studies have reported a decrease in the number of new tumours developing and the time intervals between the development of new tumours were prolonged.[15,16,17,18,19,20,21] Studies on cost-effectiveness need to be performed. It would be interesting to find out if one preventive treatment could reduce the number of therapeutic interventions in the life course of an NMSC patient. If the time interval between subsequent tumours can be significantly prolonged, this would indicate that follow-up schemes could be adjusted and visits to the hospital could be diminished, resulting in additional cost savings.

In literature, discussions are ongoing concerning the frequency of follow-up of NMSC patients.[9,22] We do support standard follow-up in this chronic disease, but another point of discussion is where the follow-up will take place and whom will carry it out. Studies have shown that recognition of skin malignancies by general practitioners (GPs) is disappointing and learning programmes about skin cancer have limited effect.[23,24] From our study, as described in Chapter 5, it becomes clear that general practitioners (GPs) adequately refer patients with actinic keratosis (AK) in only 15% of the cases. Unfortunately 30% of the cases were false-negative. Since we only meet the patients who are referred by a GP, we do not know the exact size of the NMSC problem when taking all the false-negative patients into account that do not enter the hospital at all.

We aim to get the true-positive skin cancer patients in to the DMS and to decrease the number of false-positive patients, since the false-positives unnecessarily increase the burden on the healt care system. In an attempt to improve logistic processes and to lower future costs, we have studied the development of a non-melanoma detection model for nurses. In our study we have shown that nurses ruled out or diagnosed AK and BCC correctly in a high percentage of cases. By means of a questionnaire that they filled out, a prediction model was made. The model correctly predicted AK and BCC in a comparable high percentage of cases. When we combined the model and the diagnoses made by nurses, the results further improved. This second model provided a limited amount of characteristics on which nurses would need to be trained to improve their outcomes. As described previously in other DMSs, we recommend to train nurses so they can do the follow-up of chronic NMSC skin cancer patients. The follow-up appointments or screening of patients could be performed at a GP's office, which makes it more convenient for the patient, increases the service of the GP, and diminishes the number of hospital visits as well.

We have studied the employment of nurses at the dermatology department; which means that there was a pre-selection by a GP. We recommend further investigation on the concept of follow-up in a GP's office. In addition, we have to address the fact that the use of nurses will not necessarily reduce the costs concerning NMSC. The salary of nurses is lower compared to physicians; on average they do, however, take more time per patient. So, in total the costs

might not be reduced, but this concept could solve part of the problem concerning the shortage of dermatologists. The use of nurses or nurse practitioners can be cost-effective as shown by Schuttelaar et al. regarding the treatment and support of children with eczema.[25] In diabetes, nurse-care management systems seem to be cost-effective when taking reduced future costs into account.[26]

It is essential that the DMSs are supported by intelligent information technology systems. Once patients have entered the disease management system, it is of great importance to have an optimal process within the system. Standardized treatment schemes are promoted for more structured and efficient care. Workflow management technology is necessary to create a system that supports the classical functions of consulting, as well as to manipulate and to retrieve patient-related data. Second, the system needs to be pro-active. Third, the system needs to facilitate communication amongst the healt care teams, for instance, assisting nurses in ascertaining which actions need to be taken or have already been completed for patients.[27,28]

The standardized schemes need to be based on the guidelines available and/ or evidence-based knowledge. For the larger skin cancer subgroups guidelines exist.[29,30,31] It is important to discuss how these guidelines are established. Most skin cancer guidelines take several years to be completed. New evidence becomes available regularly and this is not directly included in the guidelines. To improve guidelines, randomized controlled trials (RCTs) are considered the golden standard. RCTs, regarded as the highest level of evidence, take years to set up, execute, and evaluate. In addition, they are accompanied by high costs. A second-best option would consist of the comparison of large data sets. This would lead to faster and more efficient access to information on delivered treatments, care, and costs. With process mining techniques, information about the actual number of skin cancer, best treatments, recurrence rates, and complications becomes available continuously. This could efficiently adjust guidelines so that their effectiveness can be improved or their associated costs could be reduced.[32]

Existing treatments of skin cancer need to be optimized as well. In Chapter 5 we have described that improvements can be achieved by combining already available treatments. The use of treatments that can be performed by patients outside the hospital diminishes the workload at the outpatient clinic and in operating rooms. With topical imiquimod as a pre-treatment, we reduced the size of defects after Mohs micrographic surgery (MMS) significantly. In addition, there was a tendency towards less Mohs stages, and reconstruction time was significantly reduced. Combination of these positive effects could lead to a more cost-effective treatment: more patients could be treated on the same day, without increasing the available health resources. As described in earlier reports, topical imiquimod can also be used after MMS, to clear remaining superficial BCC.[33] The MMS procedure can be shortened and more tissue is spared, which is essential for patients with chronic skin cancer, especially

where the face is concerned. When multiple excisions have been done during a patient's life, it becomes more and more difficult to achieve a good functional and cosmetic outcome after surgery for NMSC.

We have studied the one-stop-shop concept for BCC to improve our skin cancer management strategy. With the same resources available at the dermato-oncology unit and only a change in logistic processes, throughput time of patients has been decreased. For the future we plan to extend this concept, since it has provided positive outcomes both for patients and the dermatology department. When a larger number of patients is included, we will need to adjust the capacity of operating rooms and operating physicians, since surgical excision is still the most frequently indicated treatment. A short-stop concept can be considered, with treatment of patients within a week. This can be an alternative for departments that do not have the possibility to perform fresh-frozen sections. It can also be a solution for the treatment of patients who need adjustments in their medication (endocarditis prophylaxis, anticoagulants).

An important issue concerns reimbursement. In many countries a one-stop-shop concept, with treatment on the day of diagnosis, is not rewarded by health insurance companies. This certainly needs adjustment; departments should be encouraged to create more efficient treatment processes. This illogical policy of health insurance companies demotivates the professionals in the development of cost-effective and patient-friendly NMSC care programmes.

Conclusion

The number of first primary histologically confirmed NMSCs, as usually reported by official registries, differs substantiallywith the actual burden in (dermatological) practice. The major part of the under-registration is due to a lack of adequate figures about multiple tumours in one and the same patient. Nevertheless, the existing incidence and prevalence figures are still rising; therefore NMSC needs to be considered as a chronic disease. In order to manage the increasing burden and to regulate costs, a revised disease management strategy for skin cancer is necessary. The on-going development and application of this new disease management system across the country will require efforts to be made by dermatologists with backup of the Dutch Society of Dermatology and Venereology (NVDV). Residents in dermatology, for example, need to be educated and trained in performing dermatologic surgery, which is still the main treatment of skin cancer. In addition, politicians, health insurance companies and policy makers need to become aware of the rising problem concerning chronic skin cancer and they need to be willing to cooperate in the development of this new disease management system. The proposed DMS is based on patient satisfaction, cost-effectiveness in diagnosis and treatment of NMSC, the use of nurses, adequate registration, attention for secondary prevention, and new treatment strategies.

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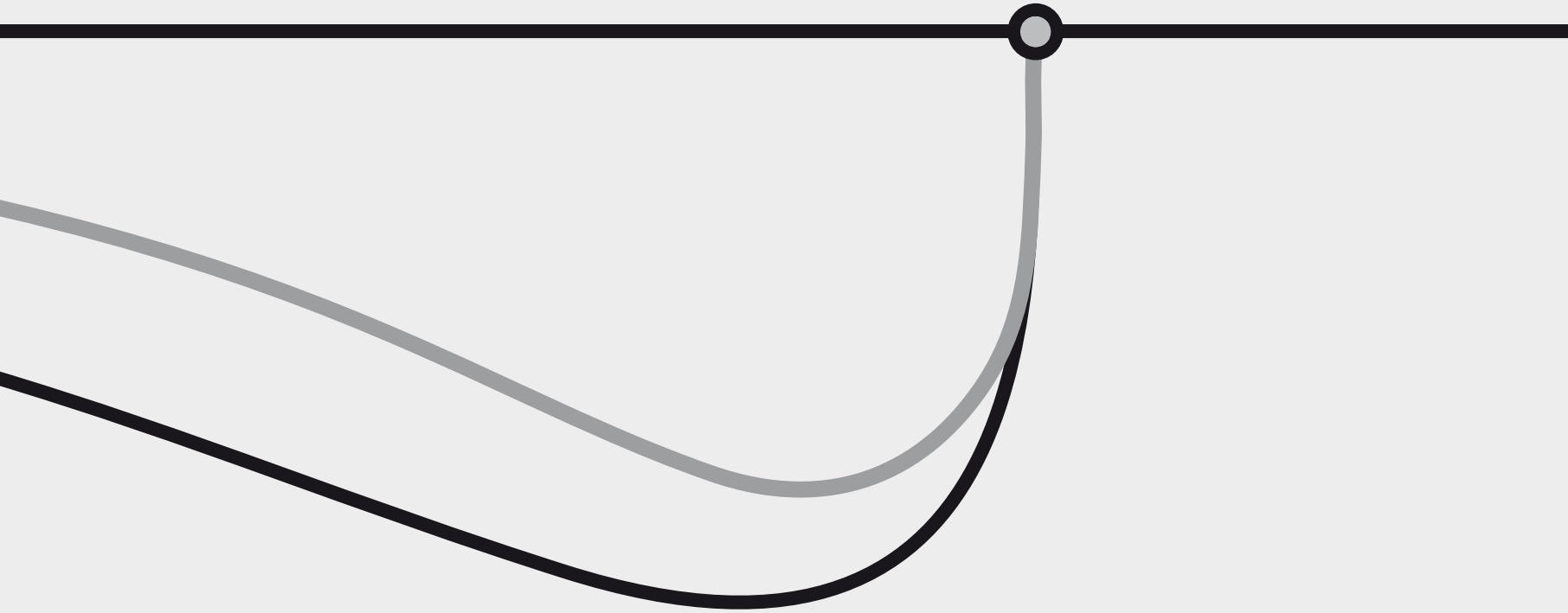
7

Summary



Chapter 1

In Chapter 1, the introduction, we highlight the context of this thesis. The enormous rise in non-melanoma skin cancer (NMSC) is recognized worldwide. This leads to expanding problems concerning adequate disease management of NMSC patients and has great impact on healt care economics. Exact figures for this most common type of skin cancer are however lacking, or are inadequate to use for calculations concerning healt care economics and management. The available NMSC figures show an increasing incidence and prevalence. NMSC should be regarded as a chronic diseasethat requests a new disease management strategy.

Chapter 2

In Chapter 2 we support the consideration that NMSC needs to be regarded as a chronic disease. The study on medical records revealed that 46% of patients developed multiple tumours. Patients developed a mean of 2.4 tumours in a period of 6 years and 2 months. The second tumour developed within a mean period of 10 months. These figures indicate that the actual burden in a dermatology practice is a lot higher than the figures of first primary NMSC indicate. Healt care economics regarding skin cancer should be based on the actual burden.

Chapter 3

In Chapter 3 we describe that Nevoid Basal Cell Carcinoma Syndrome (NBCCS) patients could serve as a model for chronic skin cancer patients. Combination of treatments and adjustments in treatment processes, like treatment in a megasession, are needed to provide adequate and efficient treatment of BCCs in chronic skin cancer patients. These innovations diminish the burden for patients, regarding the disturbance of their social lives. In addition, the decrease in hospital visits also diminishes the burden on the dermatology practice.

Chapter 4

As we describe in Chapter 4, skin cancer is suggested to be managed as a chronic disease, with help of a disease management system (DMS). The system includes prevention, education, multidisciplinary care, information technology, and management strategies. We describe how new strategies should address the care of people with chronic skin cancer. Standardized treatment schemes are promoted, for more structured and efficient care. Information

technology systems support these processes, by using workflow management technology. Process mining tecnhiques are needed to evaluate and optimize treatments and treatment processes. These techniques could also be used for the development and adjustment of guidelines. The DMS needs to be developed with a support of the Dutch Society of Dermatology and Venereology, health care policy makers and insurance companies.

Chapter 5

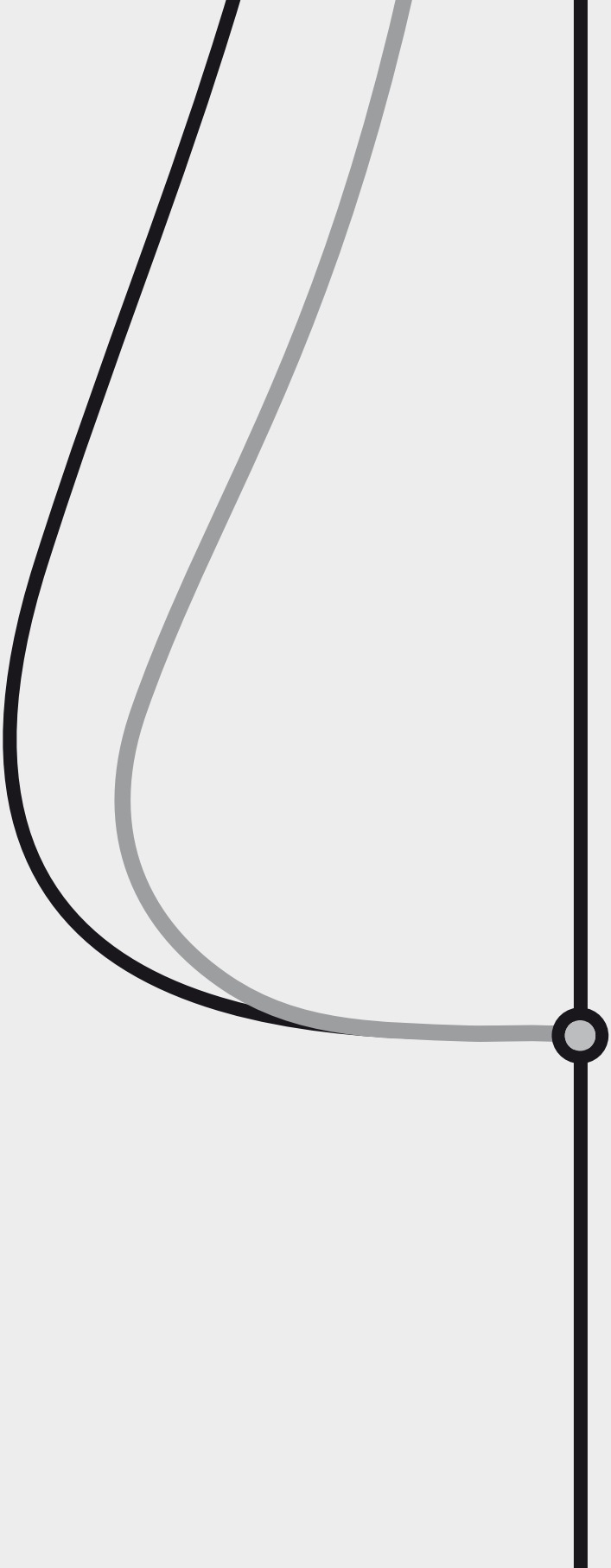
In Chapter 5 we describe three studies performed on innovations in the treatment process of chronic skin cancer. The first study showed that improvements can be achieved by combining available treatments. The use of treatments that can be performed by patients outside the hospital diminishes the workload at the outpatient clinic and in operating rooms. With imiquimod as a pre-treatment we reduced the size of defects after Mohs' micrographic surgery (MMS) significantly. In addition, less Mohs stages were needed and reconstruction time was significantly reduced. These improvements could lead to an increased capacity per day and possibly also to a more cost-effective treatment.

The second study showed that innovations in logistics in daily practice have a great impact for both patients and the Department of Dermatology. The one-stop-shop treatment of basal cell carcinoma demonstrated that with the same resources available at the dermato-oncology unit and only changes in logistic processes; throughput time of patients is decreased. Treatment of skin cancer in a one-stop-shop procedure provided a high patient satisfaction as well.

The third innovation we describe, concerns the development of a prediction model for AK and BCC. Special trained dermatology nurses will be necessary to reduce the high workload of dermatologists concerning chronic skin cancer. A detection model could support nurses in diagnosing skin cancer. We developed a detection model, based on 35 characteristics, which were scored by nurses by means of a questionnaire. The model predicted AK and BCC correctly in a high percentage of cases. Nurses predicted AK and BCC correctly in a comparable high percentage of cases. On the basis of these models, nurses might improve their percentage of correct diagnoses if they would be trained to attenuate the weight they attach to these predictors.

7.1

Samenvatting



Hoofdstuk 1

In Hoofdstuk 1, de introductie, wordt de achtergrond van dit proefschrift beschreven. De enorme toename van non-melanoma huidkanker (NMSC) wordt wereldwijd erkend. Daarbij ontstaan problemen rondom adequaat management van de ziekte en de kosten van de gezondheidszorg aangaande huidkanker stijgen. Exacte epidemiologische cijfers van NMSC ontbreken echter, of ze zijn onvolledig en ongeschikt voor berekeningen rondom de planning en kosten van de gezondheidszorg. De beschikbare cijfers laten een stijging van incidentie en prevalentie zien. NMSC zou beschouwd moeten worden als een chronische ziekte en dat vraagt om een nieuwe management strategie.

Hoofdstuk 2

In Hoofdstuk 2 wordt de aanname dat NMSC een chronische ziekte is ondersteund. Wij toonden op grond van dermatologische medische statussen aan, dat 46% van de patiënten multipele huidtumoren ontwikkelden. Patiënten ontwikkelden gemiddeld 2.4 tumoren in een periode van 6 jaar en 2 maanden. De tweede tumor ontwikkelde zich binnen een periode van gemiddeld 10 maanden. Dit betekent dat de echte burden van NMSC in de praktijk veel groter is dan de officiële cijfers van eerste primaire tumoren doen vermoeden. Berekeningen en planning van de gezondheidszorg rondom huidkanker zouden gebaseerd moeten zijn op de echte burden in de praktijk.

Hoofdstuk 3

In Hoofdstuk 3 wordt beschreven dat Basaalcel Naevus Syndroom (NBCCS) patiënten als model kunnen dienen voor de chronische huidkanker patiënt. Combinaties van behandelingen en aanpassingen in de logistiek, zoals behandeling in een megasessie, zijn belangrijk voor een adequate en efficiënte behandeling van BCCs bij chronische huidkanker patiënten. Daarbij wordt de belasting voor de patiënt verminderd, doordat er minder verstoring van zijn sociale leven is. Door de afname van het aantal poli-afspraken per patiënt wordt de belasting voor de dermatologie praktijk ook verminderd.

Hoofdstuk 4

In Hoofdstuk 4 beschrijven we dat er een disease management systeem (DMS) nodig is voor de behandeling van chronische huidkanker en hoe dit vorm zou moeten krijgen. Een

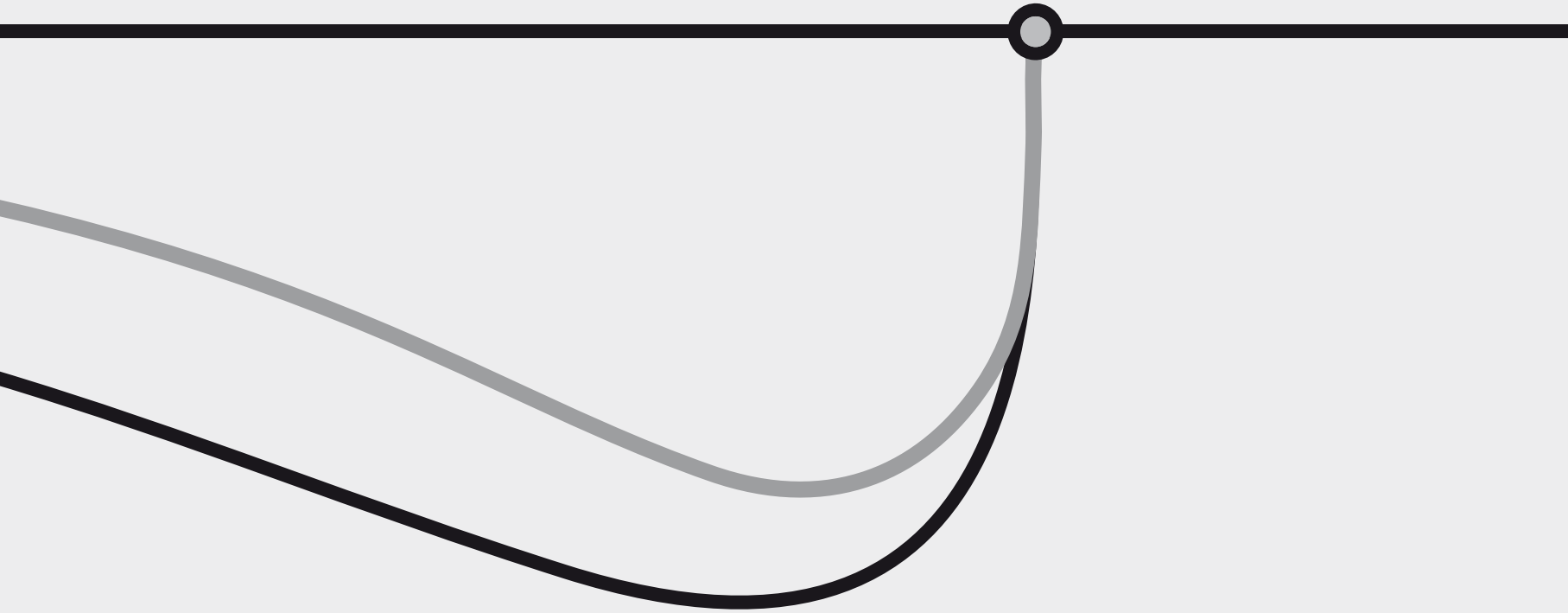
DMS bevat preventie, educatie, multidisciplinaire samenwerking, informatie technologie en management strategie. Wij geven een beeld van een DMS voor huidkanker. Hierbij wordt gebruik gemaakt van gestandaardiseerde behandelingen, ondersteund door informatie technologie en ondersteund door workflow management systemen. Daarnaast zijn processmining technieken van belang voor het evalueren en optimaliseren van de zorg- en behandelprocessen. Ook kunnen deze technieken gebruikt worden voor het ontwikkelen en aanpassen van richtlijnen. Het DMS zal moeten worden ontwikkeld met ondersteuning van de Nederlandse Vereniging Dermatologie en Venereologie, beleidsmakers binnen de gezondheidszorg en ziektekostenverzekeringen.

Hoofdstuk 5

In Hoofdstuk 5 worden drie studies beschreven op het gebied van innovaties rondom de zorg van huidkanker patiënten. In de eerste studie werd duidelijk gemaakt dat verbeteringen in uitkomsten kunnen worden bereikt door een combinatie van bestaande behandelingen. Met behulp van imiquimod 5% crème als voorbehandeling werden de defecten na Mohs' micrografische chirurgie significant verkleind. Er waren minder Mohs rondes nodig en de reconstructietijd was significant korter. Dit zou kunnen leiden tot een verhoogde capaciteit en mogelijk een meer kosteneffectieve behandeling.

De tweede studie richtte zich op een aanpassing in de logistiek op de werkvloer. De one-stop-shop procedure toonde aan dat met dezelfde capaciteit binnen de dermatologie afdeling, de doorlooptijd van patiënten verkort kon worden. De one-stop-shop procedure leverde tevens een hoge patiënt tevredenheid.

De derde studie onderzocht de ontwikkeling van een detectie model voor actinische keratose (AK) en BCC. Verpleegkundigen zullen nodig zijn om de werkdruk van dermatologen rondom huidkanker te verminderen. Een detectiemodel zou hen kunnen helpen in het diagnosticeren van huidkanker. Wij ontwikkelden een detectiemodel met behulp van 35 kenmerken die werden gescoord door verpleegkundigen aan de hand van een vragenlijst. Het detectiemodel dat werd ontwikkeld, scoorde een hoog percentage goede diagnoses. De verpleegkundigen stelden de juiste diagnose bij een vergelijkbaar hoog percentage van de patiënten. Verpleegkundigen zouden moeten worden getraind op enkele kenmerken om het aantal goede diagnoses te verbeteren.



Dankwoord

Ik ben veel mensen dankbaar voor hun steun, medewerking en inzet rondom mijn proefschrift en promotie. Ik zal mijn dank, voor een aantal mensen in het bijzonder, in woorden proberen uit te drukken.

Beste professor, promotor, of nu dan toch eindelijk; beste Martino. De maatschap dermatologie van het Catharina Ziekenhuis Eindhoven schoof mij in 2010 naar voren om te starten met de opleiding en gelukkig kreeg ik van u de kans. Als een van de eerste AIOS volgde ik de opleiding deels in Eindhoven en deels in Rotterdam. Ik voel me bevoorrecht dat ik zo veel van u heb mogen leren. Dit promotie-traject was al gestart tijdens mijn periode in Eindhoven, en wederom gaf u mij de kans en het vertrouwen om hiermee door te gaan. U wilde zelfs meegaan met mijn vernieuwende voorstel om het proefschrift grotendeels digitaal te laten publiceren. Ontzettend bedankt voor… alles!

Gertruud, dankzij jou als co-promotor, is deze promotie tot stand gekomen. Ik ken niemand die zo ver vooruit kan kijken, die zo veel goede ideeën heeft en ook de kracht en het enthousiasme om ze tot uitvoering te laten brengen. Jij overziet altijd het grote geheel. Disease management was voor jou al een heel gewoon begrip, terwijl iedereen om je heen nog goed moest bedenken wat dat eigenlijk inhield. Ook zag jij een promotie in het geheel van mijn onderzoeken en artikelen. Dankzij jou ben ik er enthousiast voor geworden en heb ik doorgezet. Jij stond altijd klaar voor mijn vragen en had altijd een antwoord of een oplossing, zodat ik weer verder kon. Jij bent voor mij een groot voorbeeld en een hele waardevolle collega. Ik hoop dan ook dat we nog lang samenwerken en meer projecten gaan opstarten rondom disease management.

Graag wil ik ook mijn maatschapsleden bedanken. Beste Judith, Marc en Gertruud. Ik zou nergens beter terecht kunnen zijn gekomen dan bij jullie. Al sinds mijn co-schappen en assistenten-tijd zijn jullie mijn grote voorbeeld. Dankzij jullie heb ik mij kunnen ontwikkelen tot dermatoloog en Mohs chirurg. Daarnaast zijn jullie altijd enthousiast geweest over het opzetten en uitvoeren van onderzoeken en het schrijven van artikelen.

Mijn eerste kennismaking met een promotie-traject was via jouw promotie, Judith. Je had alle vertrouwen in mij om je promotie te helpen afronden, door de laatste artikelen mee te schrijven. Dat was een goede oefening en daar ben ik je nog steeds heel erg dankbaar voor.

Gertruud, zoals ik al heb genoemd in het voorgaande: zowel als persoon, dermatoloog, opleider en als co-promotor ben je iemand die met volle overtuiging en gepassioneerd de zaken aanpakt. En dat werkt aanstekelijk! Bedankt voor alle inspiratie.

Marc, ik ging net van het CZE naar het Erasmus toen jij de maatschap in Eindhoven kwam versterken. Vooral de afgelopen twee jaar hebben we elkaar beter leren kennen. Je bent voor

mij een zeer waardevolle collega. En ik denk dat ik dat ook voor jou ben….. of zijn er nog meer publicaties nodig?

Prof.dr.Prens, beste Errol, bedankt voor het plaatsnemen in de kleine commissie en het beoordelen van mijn proefschrift. Daarnaast natuurlijk ook voor de prettige samenwerking tijdens mijn opleiding in Rotterdam.

Dr. Hoekzema (inmiddels Prof.dr.Hoekzema als het goed is!) ik wil u ook hartelijk danken voor het plaatsnemen in de kleine commissie en het beoordelen van mijn proefschrift.

Dr.ir. Reijers, beste Hajo, hartelijk dank voor het plaatsnemen in de kleine commissie, het beoordelen van mijn proefschrift en alle inzet om mijn artikelen en proefschrift tot een hoger niveau te tillen.

Dr. Berretty, beste Paul, bedankt dat je wilt plaatsnemen in de grote commissie. Als mijn opleider had je al veel meegekregen van de onderzoeken die ik deed. Je was altijd enthousiast, ook als ik weer een artikel had gepubliceerd. Ik ben je erg dankbaar, voor mijn opleiding, de fijne samenwerking en de gezellige kookavonden. Mede dankzij het toeval dat u met pensioen ging toen ik afgestudeerd was, kreeg ik de eer u op te volgen in de maatschap. Bedankt voor alles.

Prof.dr.Rutten, ik wil u bedanken dat u, als hoogleraar Economische Evaluatie van Zorginnovaties voor chronisch zieken, wilt plaatsnemen in de grote commissie.

Prof.dr. Koes, hartelijk dank dat u, als hoogleraar Huisartsgeneeskunde, wilt plaatsnemen in de grote commissie.

De mede-onderzoekers van de Technische Universiteit Eindhoven wil ik ontzettend bedanken voor hun inspirerende inzet en samenwerking: Hajo Reijers, Harry van Tuijl, Ad Kleingeld, Nico Dellaert, Monique Jansen-Vullers en Kees Kokke.

Via Gertruud en Harry werden de contacten tussen de Dermatologie van het CZE en de TUE gelegd. Harry bracht diverse mensen bij elkaar om te brainstormen over een zorgstraat dermato-oncologie. Dankzij een hele fijne en effectieve samenwerking op diverse vlakken heeft dat veel goede ideeën, onderzoeken, afstudeerprojecten en artikelen opgeleverd. Zonder jullie stond ik hier niet vandaag, bedankt!

Lieve Eric, broer en paranimf. Wie had gedacht dat onze vakgebieden toch nog zoveel raakvlakken zouden hebben? Jij op de TUE en ik als dermatoloog in het ziekenhuis. Na al deze onderzoeken wordt het tijd dat we samen een nieuw project starten. Bedankt voor al je steun

op diverse vlakken. Je las regelmatig Engelse teksten door, hielp me bij vreselijke statistische vraagstukken, brainstormde mee over stellingen en deelde je creativiteit bij het ontwerp van dit proefschrift. Super bedankt voor alles!

Lieve Anke, ik ben heel erg blij met je als collega, vriendin en paranimf. Jouw promotie volgt nog, en dan hoop ik dat ik jou net zo goed kan bijstaan als jij mij nu.

Ik wil alle studenten van de TUE die mee hebben meegewerkt aan de onderzoeken van harte bedanken voor hun inzet. Zoveel kennis en kunde, dat is zeer waardevol voor toekomstige projecten!

Mijn collega A(N)IOS uit Eindhoven en Rotterdam, en de semi-artsen wil ik bedanken voor hun steun. Degenen die de onderzoeken mee hebben uitgevoerd en geanalyseerd wil ik in het bijzonder bedanken voor hun bijdrage. Vooral de imi-mohs studie heeft heel veel tijd en energie gekost en dankzij jullie is het tot een mooie afronding gekomen.

De stafleden van de afdeling Dermatologie Erasmus MC, wil ik hartelijk danken voor hun steun tijdens mijn opleidingsjaren in Rotterdam.

Alle mede-auteurs die ik nog niet heb vernoemd, hartelijk bedankt voor jullie bijdrage!

Ik wil alle medewerkers van de afdeling dermatologie bedanken voor de samenwerking op de poli en de ondersteuning bij alle onderzoeken. Het secretariaat zag me regelmatig allerlei artikelen uit de printer vissen en de verpleging werd geconfronteerd met extra metingen, vragenlijsten en omschakelingen in de logistiek. Bedankt voor jullie medewerking en steun.

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De afdeling Pathologie van het CZE, met name Thomas Demeijere en de analisten, wil ik bedanken voor hun medewerking bij de one-stop-shop studie. Er werd zeker een extra aanslag gedaan op de rekbaarheid van de capaciteit, met de extra vriescoupe biopten en de extra onmiddellijke check door de patholoog. Doordat jullie openstaan voor vernieuwingen konden we dit project starten en ik ben heel trots dat er nu een vervolgstudie gaande is.

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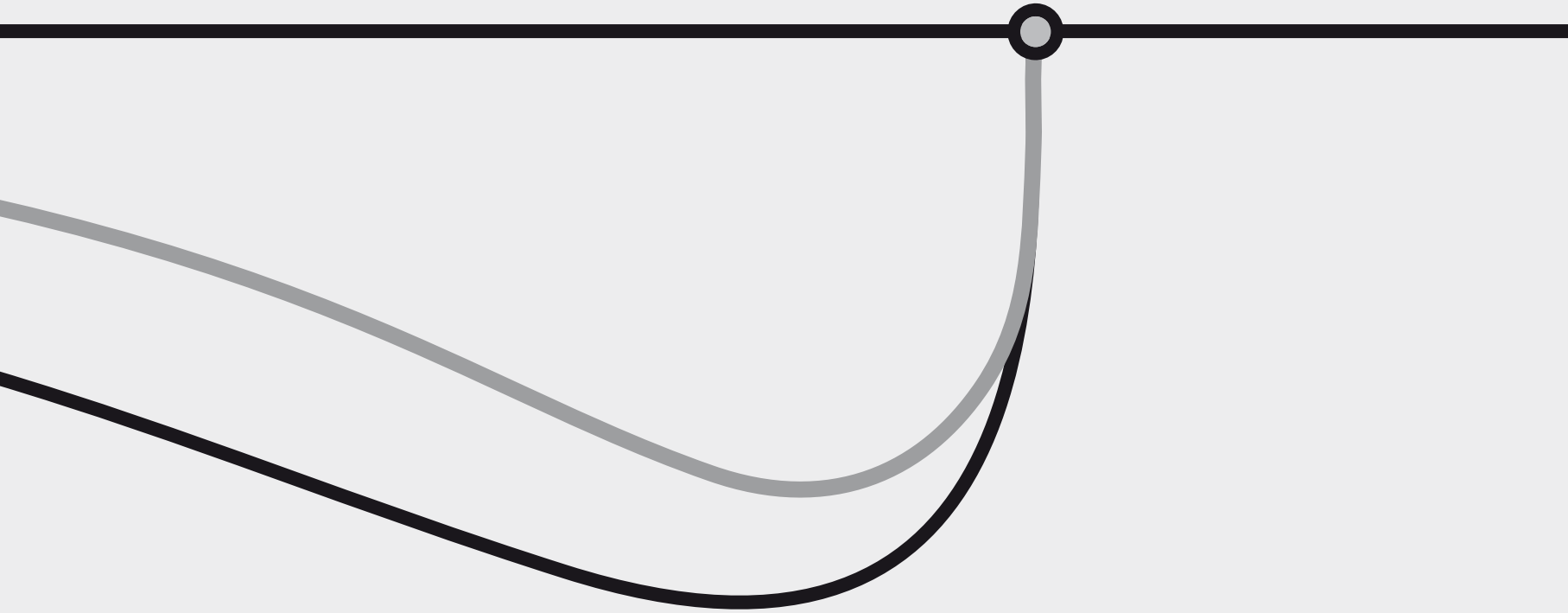
Juul, mijn lief, klein, eigenwijs, ruwharig dwergteckeltje. De laatste maanden waren extra druk, met jou als pup in huis, maar wat heb jij mij veel energie gegeven! De wandelingen door weer en wind waren fantastisch om mijn hoofd leeg te maken, gedachten te ordenen en er met frisse moed weer tegenaan te gaan.

8.1 List of co-authors



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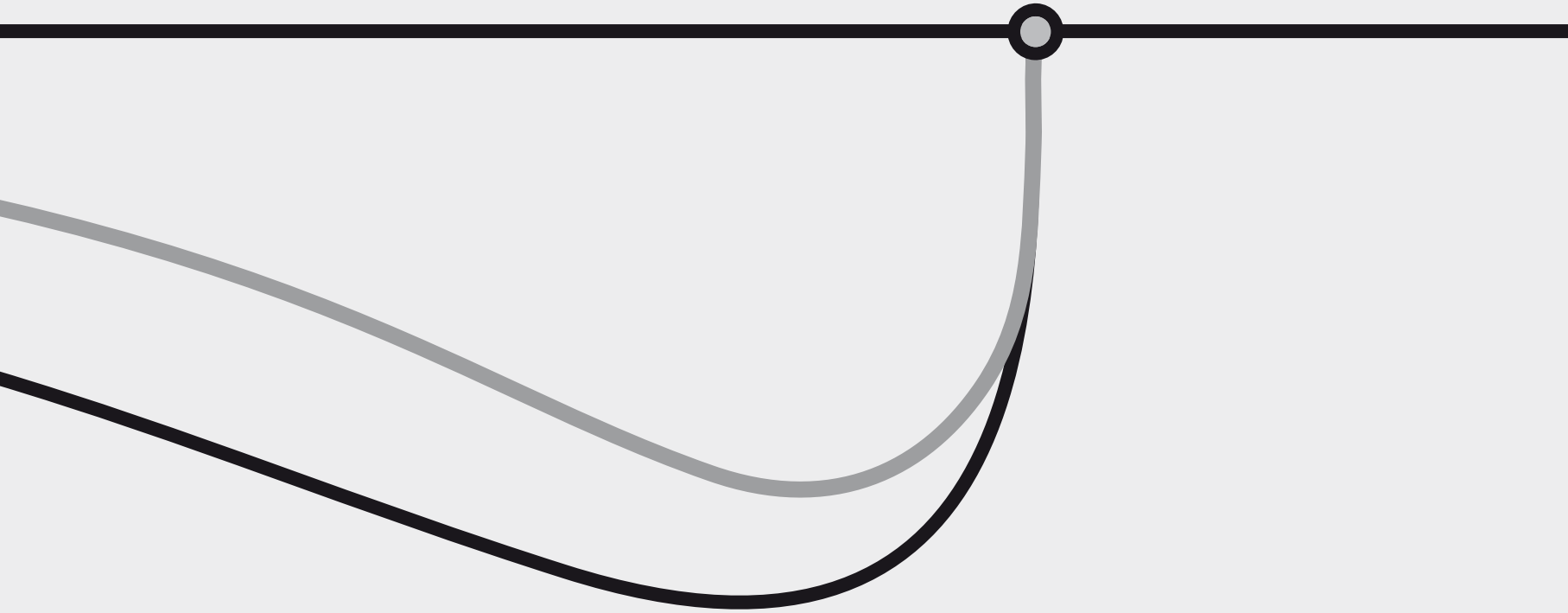
Department of Health Education and Health Promotion, University of Maastricht, Maastricht, the Netherlands

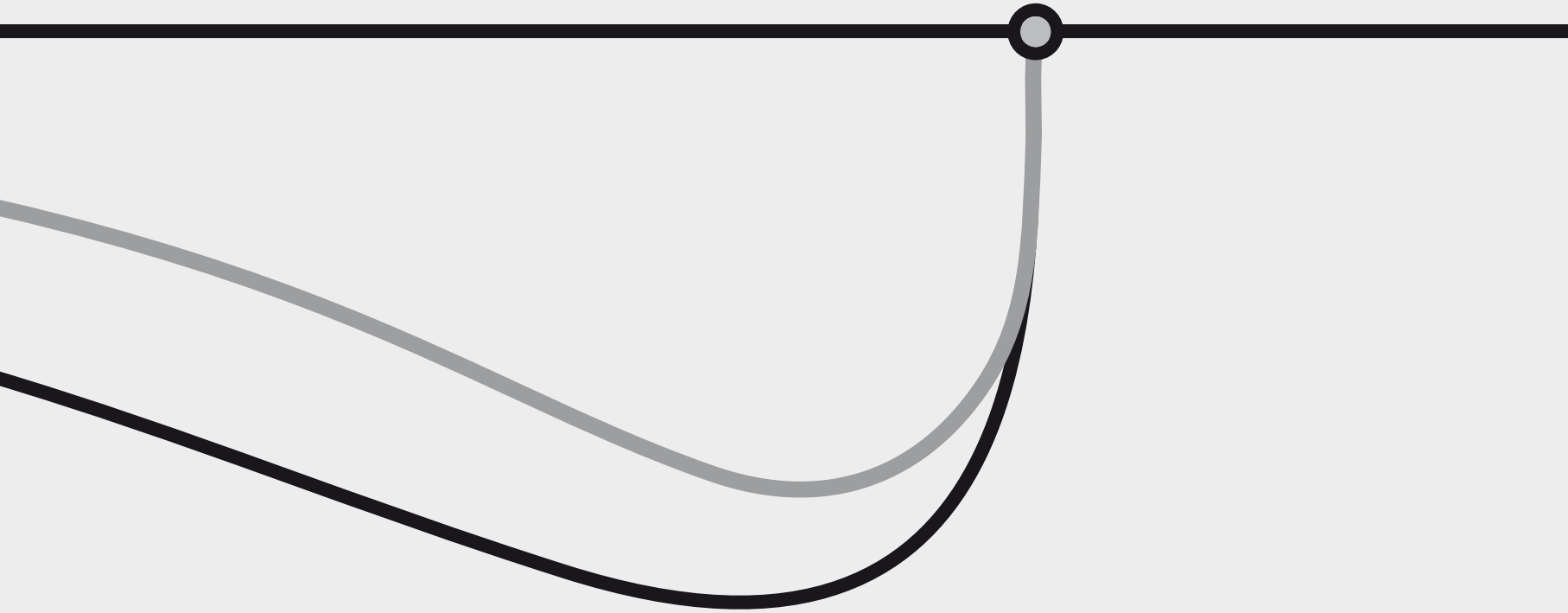
8.2 Curriculum Vitae



Curriculum Vitae

Simone van der Geer-Rutten werd geboren op 16 december 1978 te Aalst-Waalre. Als kind verhuisde zij met haar ouders naar Leende en later naar Achel in België. Zij behaalde haar VWO diploma aan het Sint Joriscollege te Eindhoven. Na het behalen van haar Propedeuse gezondheidswetenschappen aan de Universiteit Maastricht, kon zij in 1998 starten met de opleiding geneeskunde, eveneens in Maastricht. In 2004 studeerde zij Cum Laude af, waarna zij als AGNIO kon starten bij de afdeling Dermatologie in het Catharina Ziekenhuis Eindhoven. Op 1 juli 2005 begon zij als AIOS Dermatologie. De eerste 2 jaar van de opleiding werden genoten in het Catharina Ziekenhuis onder leiding van dr. P.J.M. Berretty. Voor de laatste 3 jaar ging zij naar de afdeling Dermatologie in het Erasmus MC, onder leiding van professor H.A.M. Neumann. Onder supervisie van dr. G.A.M. Krekels werd het wetenschappelijk onderzoek naar chronische huidkanker opgezet. Sinds enkele jaren bestaat er een intensieve samenwerking met de Technische Universiteit Eindhoven, in het bijzonder op het gebied van disease management voor chronische huidkanker. De opleiding tot dermatoloog heeft zij 1 juli 2010 afgerond, waarna zij als waarnemer terug ging naar het Catharina Ziekenhuis. Met veel genoegen is zij sinds 2 april 2011 lid van de maatschap dermatologie in het Catharina Ziekenhuis Eindhoven.

8.3 List of publications



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Van der Geer S, Siemerink M, Reijers HA, Verhaegh MEJM, Ostertag JU, Neumann HAM, Krekels GAM. The burden of skin cancer in dermatology. Submitted.

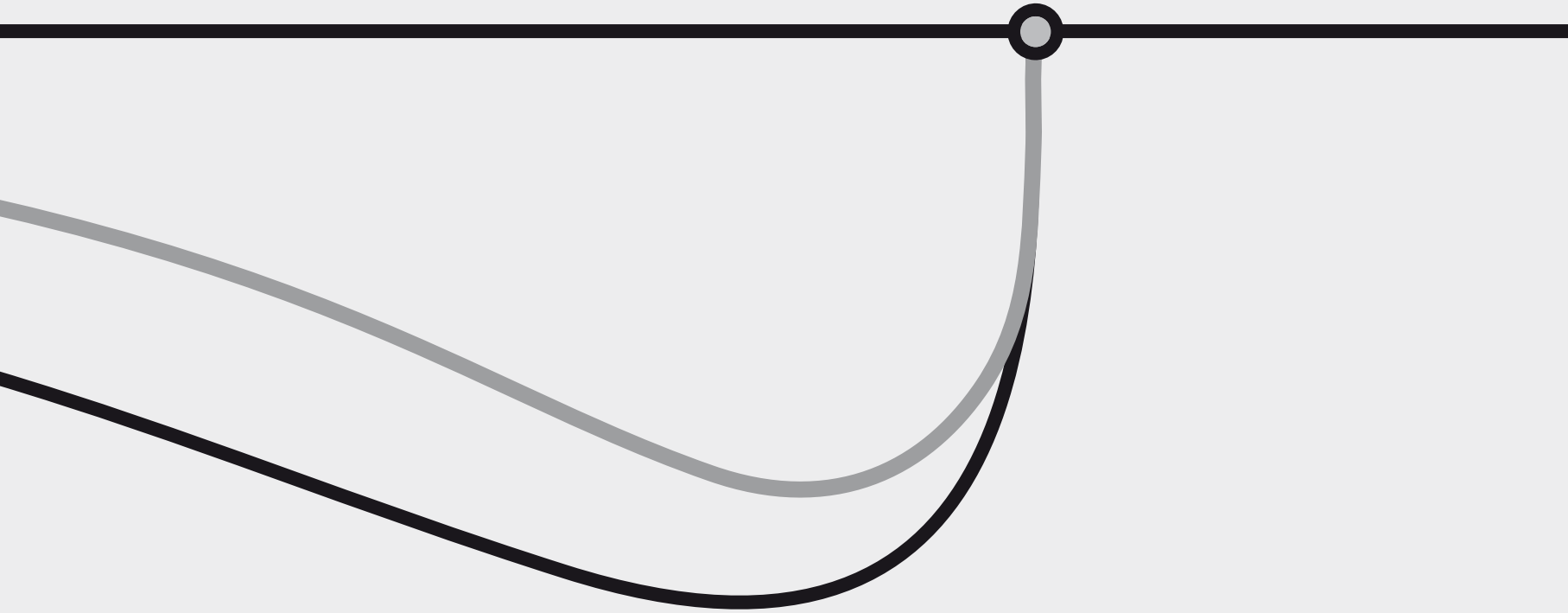
Van der Geer S, Kleingeld A, Snijders CCP, Rinkens F, Jansen G, Neumann HAM, Krekels GAM. The development of a non-melanoma skin cancer detection model.Submitted.

Bijdrage aan boeken:

GAM Krekels, **S van der Geer**. Non-melanoma huidkanker. 2010 Academic Pharmaceutical Productions bv. Utrecht. ISBN 978 90 5761 097 4.

8.4

PhD Portfolio



PhD Portfolio

Summary of PhD training and teaching activities

Name PhD student: S van der Geer-Rutten
Erasmus MC Department: Dermatology

PhD period: Juli 2005 – January 2012
Promotor(s): Prof. Neumann
Supervisor: Dr. Krekels

1. PhD training

	Year	Workload (Hours/ECTS)
Research skills		
- Statistische begrippen in de medische literatuur, CZE	2006	16 uur
In-depth courses		
- Basis cursusimmunologie	2005	3 uur
- Dermato-chirurgie cursus. Catharina Ziekenhuis Eindhoven	2005 2005	1 ECTS 2 ECTS
- Greenway's Annual superficial anatomy and cutaneous surgery, San Diego, USA	2006	1,5 ECTS
- Basic Surgical Skills	2006	8 uur
- Intern en extern management voor de arts. Brabant Medical School, Tilburg	2009	1 ECTS
- Ziekenhuismanagement Desiderius Rotterdam		

	Year	Workload (Hours/ECTS)
Presentations		
- Nieuwe behandelingen non-melanoma huidkanker, Stichting Melanoom De Reehorst Ede 2005	2005	1 ECTS
- Improving cosmetic outcome of Mohs surgery with PDT, Cosmoderm Rotterdam 2006	2005	1 ECTS
- Treatment of the NBCCS patient, World Skin Cancer congress, Amsterdam 2007	2006	1 ECTS
- Disease management skin cancer, EADV Parijs 2008	2008	1 ECTS
- A social, financial and medical approach of PDT, World skin cancer congress, Tel Aviv 2009	2008	1 ECTS
- Interim analysis of a randomised controlled trial imiquimod as a pre-treatment for Mohs micrographic surgery. EADV Berlijn 2009	2009	1 ECTS
- One-stop-shop treatment of basal cell carcinoma. Dermato-oncology Spa	2010	1 ECTS
- One-stop-shop treatment of basal cell carcinoma. EADV Lissabon	2011	1 ECTS
International conferences		
- ISDS, Dublin.	2005	1 ECTS
- Cosmoderm. Rotterdam	2006	1 ECTS
- EADV Rhodos	2006	1 ECTS
- Mikroskopischkontrolliertechirurgie, Tubingen	2007	1 ECTS
- EADV Parijs	2008	1 ECTS
- EADV Berlijn	2009	1 ECTS
- EADV Lissabon	2011	1 ECTS
Other		
- Nascholingeczeem en plaveiselcelcarcinoom, Amsterdam	2006	1 ECTS
- SNNDV Therapeutischeinnovaties	2008	1 ECTS

2. Teaching activities

	Year	Workload (Hours/ECTS)
Lecturing		
- Huidtumoren en Mohs, Discipline overstijgende onderwijs CZE 2006, aan AIOS, AGNIOS, specialisten, co-ass.	2006	0,5 ECTS
- Herkennen van huidtumoren voor verpleegkundigen IKR	2009	0,5 ECTS
- Non-melanoma huidkanker en premaligniteiten voor huisartsen	2010	1 ECTS
- Huidtumoren voor fysiotherapeuten	2010	0,5 ECTS
– Huidmaligniteiten voor huisartsen	2011	1 ECTS

	Year	Workload (Hours/ECTS)
Supervising practicals and excursions		
- Hechtcursus tijdens Dermato-chirurgie cursus CZE 2005	2005	4 uur
- Workshop Mohs micrografische chirurgie. Dermato-oncologie congres Spa 2010	2010	2 uur
- Begeleiden 1e jaars TUE studenten, DVA-groep technische bedrijfskunde in de gezondheidszorg. Analyse huidmaligniteiten in CZE	2009	1 ECTS
- Begeleiden 1e jaars TUE studenten, DVA groep Technische Bedrijfskunde in de Gezondheidszorg. Analyse pre-maligne huidafwijkingen in CZE	2009	1 ECTS
- Begeleiden afstudeerstudent TUE,Technische Bedrijfskunde. One-stop-shop voorbasaalcelcarcinomen.	2009	2 ECTS
- Mede-begeleiden afstudeerder TUE, Technische Bedrijfskunde. The development of a non-melanoma skin cancer detection model.	2010	1 ECTS
- Begeleiden 2e jaars TUE studenten, Technische Bedrijfskunde in de Gezondheidszorg. Zorgpad ulcus cruris	2010	1 ECTS
- Begeleiden 2e jaars TUE studenten, Technische Bedrijfskunde in de Gezondheidszorg. Zorgpad ulcus cruris	2011	1 ECTS
- Workshop 'eenvoudige sluitingen voor defecten in het gelaat', onderdeel van cursorisch onderwijs dermatologie. AIOS jaar 1-3.	2011	1 ECTS
- Begeleiden afstudeerstudent TUE, Technische Bedrijfskunde. Development of a skin cancer detection model.	2011	1 ECTS
- Begeleiden 2ejaars TUE studenten, Technische Bedrijfskunde in de gezondheidszorg. DVA opdracht. Capaciteits analyse ' benenpoli' .	2011	1 ECTS

	Year	Workload (Hours/ECTS)
Other		
- Live operatie tijdens Dermato-chirurgie cursus CZE 2005	1	4 uur

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