PATIENT CENTRED SURGERY

IN DERMATOLOGY

Xiaomeng Liu

Patient Centred Surgery in Dermatology

Xiaomeng Liu

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Patient Centred Surgery in Dermatology

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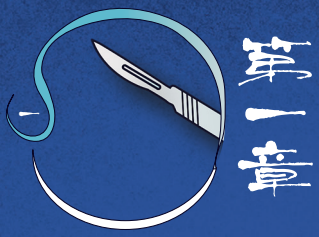

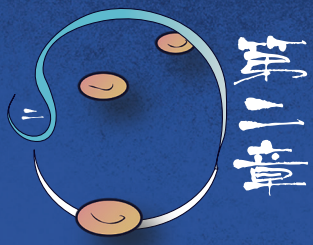

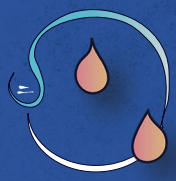

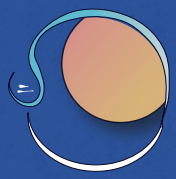

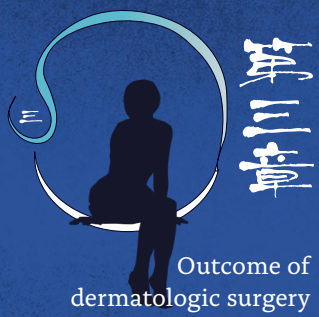

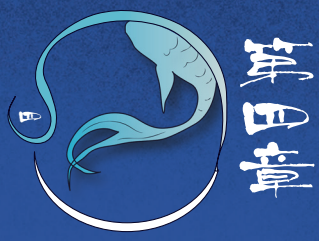

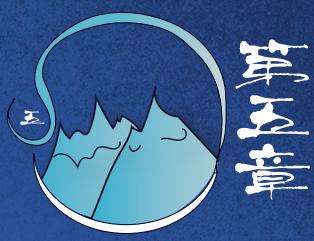

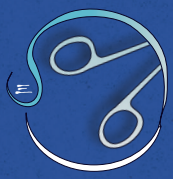

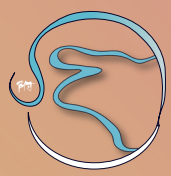

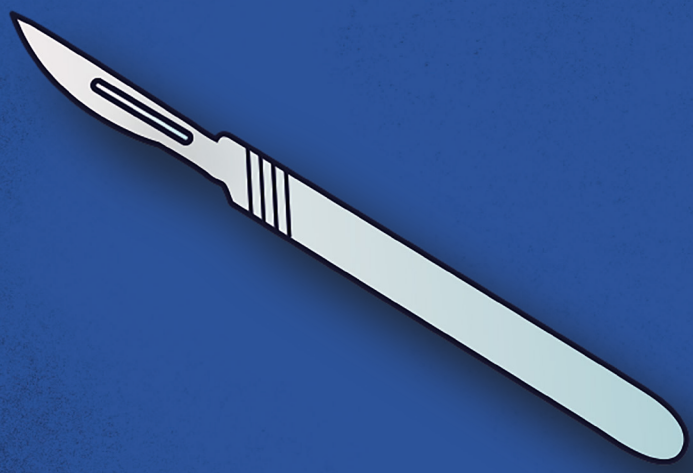

第一章

Introduction

Dermatologic surgery

Dermatologic surgery deals with operative treatments to repair and/or improve the function and cosmetic appearance of the skin. In the past decades, surgical treatments have become more and more important in the daily practice of the dermatologist.(1-3)

The most important indication for dermatologic surgery is the eradication of skin cancer as surgery is still the most effective treatment. Malignancies arising from the skin have a high incidence and prevalence, especially in the Caucasian population.(4-6)They include melanoma and non-melanoma skin cancer such as basal cell carcinoma and squamous cell carcinoma.

Not only malignant lesions are treated with dermatologic surgery. Diagnostic excisions are performed when there is uncertainty about the behaviour of the lesion (often moles). In addition, patients with benign lesions might also seek surgical treatment due to irritation, pain or cosmetic concerns.

Complications of surgery

Postoperative haemorrhage and surgical site infection (SSI) are the most common complications of surgery in dermatology.(7, 8) Wound dehiscence, necrosis and flap or graft failure can result from SSI and/or haemorrhage. These adverse events often cause anxiety for the patient and may ultimately result in suboptimal scar formation.

Other complications following surgery are transient and permanent hyper and hypo-aesthesia around the surgical site. Nerve injuries leading to numbness and/or functional loss may occur, especially at certain locations in the head and neck area.(9) Allergic reactions to anaesthetics, antiseptics, dressing or other operation related agents are incidentally observed.(10)

Haemorrhage

Bleeding during the procedure and the recovery period is one of the most common complications in dermatologic surgery.(7, 9) Due to the limited size of wounds of surgery in dermatology, life-threatening haemorrhage has never been reported. However, bleeding can initiate other complications such as haematoma formation, infection, wound dehiscence and necrosis of the skin. In literature, the risk of bleeding after cutaneous surgery is estimated below 2% in general.(11, 12) However, this rate is higher in patients on certain antithrombotic medication.(13-15) Conversely, although extremely rare, life-threatening

thrombotic events due to withdrawal of antithrombotic medication have been reported in literature.(16) With the increasing number of patients on antithrombotic medication presenting for surgical procedure, the preoperative management of haemostasis has been a matter of debate.(13, 17) Surveys illustrate great discrepancies in the advice given to patients, especially when larger procedures such as Mohs micrographic surgery are performed.(18-20) In addition to management of antithrombotic medication, meticulous haemostasis during the procedure and postoperative pressure dressings also contribute to minimize the chance of haemorrhage.

Surgical site infection

SSI is the other most common complication in dermatologic surgery.(7, 11) It is defined as an infection related to the procedure, occurring at or near the incision site within 30 days after the procedure.(21)The most common pathogen isolated in SSI is *Staphylococcus aureus*.(22) SSIs can significantly impair wound healing and cause discomfort and morbidity. Furthermore, serious adverse events due to bacteraemia may occur. (23, 24) Fortunately, the rate of such complications in dermatologic surgery is low in general (<5%), but higher rates are reported in literature for specific risk factors. Many studies have tried to identify those risk factors including patient, surgery and environment related factors, but a consensus has not been reached to date.(7, 12, 13, 25-29) In addition, the definition of SSI varies between the studies performed and many studies included patients who received antibiotics in the perioperative period. As it is difficult to identify patients at risk for SSI, surveys suggest that dermatologists tend to routinely overprescribe antibiotics pre- and postoperatively in order to prevent SSI.(30-32) The overuse of antibiotics is associated with potential adverse effects and antibiotic resistance, a growing problem in today's medical world. A recent guideline published by the World Health Organisation on the prevention of SSI advocate preoperative bathing, antiseptic surgical site and hand preparation and the use of triclosan-coated sutures to reduce the risk of SSI. This guideline does not formulate a recommendation when to prescribe antibiotic prophylaxis due to the lack of evidence.(33) The same conclusion is drawn in both the American and the newly developed Dutch guidelines for the prevention of SSI.(34, 35)

Outcome of dermatologic surgery

The evaluation of the outcome of dermatologic surgery through the eye of the patient is important to deliver patient centred care. A recent study has shown that the two aspects most valued by patients presenting with skin cancer are cosmetic outcome and the rate of tumour recurrence.(36) This is confirmed by an earlier study conducted in the

Netherlands in healthy individuals.(37)This thesis will focus on the aesthetic outcome after dermatologic surgery.

Aesthetic outcome

The majority of skin cancer arises on cosmetic important areas such as the face. Together with the increasing incidence of skin cancer among people younger than 40, achieving an optimal cosmetic result after facial surgery has become a major concern.(38)In addition to normal scarring, surgery is sometimes complicated by the development of keloids and hypertrophic scars. The pathogenesis of this abnormal scarring is not completely understood but it seems to involve alterations in the sequential process of wound healing and to be influenced by multiple local and genetic factors.(39, 40)Besides the uncontrollable factors such as genetic predisposition and location of surgery, there are potentially important factors that can be controlled, such as a moist wound healing environment and suturing technique.(41, 42)

To optimally assess scar formation after surgery, different evaluation tools have been developed in literature, including objective and subjective measurements of scarring. Most of these scales are initially developed for burns and larger surgical wounds; therefore, some of the items are not applicable for relative small surgical scars in dermatology. The assessment scales applied in surgical scars are shortly discussed here.

The Wound Evaluation Scale (WES) is the oldest assessment scale developed and meant to assess surgical scars at the time of suture removal.(43)This 6-item dichotomous scoring scale consists of 'step-off of borders', 'contour irregularities', 'margin separation', edge inversion', excessive distortion' and 'overall scale'.

The Manchester Scar Scale (MSS) was developed for assessment of a wider range of scars. (44) It is a multi-item categorical scale including aspects on 'colour', 'contour', 'distortion' and 'texture'. In addition, an overall global assessment is made using a visual analogue scale (VAS) represented by a 10cm line.

The Patient and Observer Scar Assessment Scale (POSAS) was first developed for burn scars but is now widely used for surgical scars.(45) It incorporates both assessments of the patient and observer on different aspects of the scar according to a numeric scale. The observer rates the scar on 'vascularisation', pigmentation', 'thickness', 'relief', 'pliability' and 'surface area' while the patient rates the scar on 'pain', 'itchiness', 'colour', 'stiffness', 'thickness' and 'relief'. In addition, both the patient and the observer give an overall opinion of the scar on a 1-10 scale.

The 4-point scale is a quick tool assessing the scar as excellent, good, fair or poor.(46) It was initially developed for the evaluation of scars following non-surgical treatment of skin cancer but has been applied in clinical practice for other scars due to its simplicity.

The Scar Cosmesis Assessment and Rating scale (SCAR) was recently developed incorporating assessments by the observer and patient but limiting the patients' assessment on two yes/no questions on itchiness and pain only. The observer rates 'scar spread', 'erythema', 'dyspigmentation', 'suture marks', 'hyper or atrophy' and 'overall impression' on a categorical scale.(47)

Outline of the thesis

The aim of this thesis is to contribute to the current evidence for complications (Chapter 2) and outcome (Chapter 3) of surgery in dermatology. The results will help improve the safety and quality of dermatologic surgery in order to provide better patient centred care.

Complications of dermatologic surgery

What is the frequency of postoperative haemorrhage and thrombotic events in patients continuing and those temporarily withholding their antithrombotic medication prior to Mohs micrographic surgery? (Section 2.1)

Many patients presenting for dermatologic surgery use antithrombotic medication. It remains controversial whether or not this medication should be withheld prior to surgery. We evaluated the frequency of postoperative haemorrhage and thrombotic events in patients continuing their antithrombotic medication and those temporarily withholding this medication prior to Mohs micrographic surgery. The results are important to offer recommendations with respect to the management of the antithrombotic medication in patients presenting for surgery in dermatology.

What is the independent effect of multiple risk factors for the development of SSI in dermatologic surgery? (Section 2.2)

Current literature on risk factors of SSI in dermatologic surgery is limited. We retrospectively evaluated patients presenting for dermatologic surgery who did not receiving any antibiotics in the perioperative period. Patient, procedure and tumour related risk factors were studied in order to correctly identify patients at risk of acquiring a SSI.

How can we accurately predict a patient's risk of acquiring a SSI after dermatologic surgery? (Section 2.3)

In Section 2.2, specific risk factors that increase the risk of acquiring a SSI have been identified. To adequately assess the risk of SSI in a clinical setting, the combination of different risk factors in each patient should be evaluated. Clinical prediction models could serve this purpose by risk estimation for individual patients based on combinations of multiple predictors. In Section 2.3, a model is developed to identify the patients at risk for SSI in order to reduce the rate of SSI while minimizing the overuse of antibiotics.

Outcome of dermatologic surgery

What is the reliability of the POSAS and the 4-point scale in the assessment of cosmetic outcome of facial linear scars? (Section 3.1)

In order to evaluate and improve aesthetic outcome for patients undergoing dermatological surgery, a reliable evaluation tool must be used. The POSAS and 4-point scale are both developed for this purpose. However, their reliability in the assessment of facial linear scars has never been studied before as the scales were initially developed for non-surgical scars. Therefore, our goal was to study their reliability and the influence of different scar characteristics on the general impression of the cosmetic outcome as reported by the patient and the physician.

What are the long term aesthetic results and the incidence of complications of facial wounds closed with simple interrupted sutures (SIS) compared with running subcuticular sutures (RSS)? (Section 3.2)

The suturing technique may influence the final cosmetic result. SIS and RSS are frequently used in dermatologic surgery. Currently, due to a lack of evidence, the choice of suturing technique is largely dependent on the surgeon's preference. Therefore, we have performed a randomized controlled trial to compare the cosmetic result 12 months post treatment and complications associated with SIS versus RSS in facial surgery.

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第二章

Complications of dermatologic surgery

Preoperative management of antithrombotic medication in Mohs micrographic surgery

X. Liu, L. Lammers, P.J. Nelemans, K. Mosterd and N.W.J. Kelleners-Smeets

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Introduction

Many patients presenting for dermatologic surgery use antithrombotic medication. It remains controversial whether or not this medication should be withheld prior to cutaneous surgery. Different studies, including one meta-analysis, have assessed the risk of bleeding when antithrombotic medication was continued and showed controversial results.(1-8) Furthermore, case reports illustrated the potential life-threatening risk of temporary discontinuation of antithrombotic medication: pulmonary embolus, acute venous thrombosis, thromboembolic strokes and clotted prosthetic aortic valve were reported.(9-11)

We evaluated the frequency of postoperative haemorrhage and thrombotic events in patients continuing their antithrombotic medication and those temporarily withholding this medication prior to Mohs micrographic surgery.

Methods

We retrospectively retrieved information from patients who underwent Mohs micrographic surgery from July 2010 to July 2012 at the Maastricht University Medical Centre. During the first year a regional guideline required platelet inhibitors (PI's) to be discontinued 7 to 10 days prior to surgery and Vitamin K antagonists (VKA's) to be tapered to reach an International Normalized Ratio of 2.0 or less 24 hours prior to surgery. As a result of a national discussion, the guideline was changed from July 2011. Patients did not need to discontinue their antithrombotic medication with the exception of surgery performed at the medial canthus of the eye. In addition to patient and operation characteristics, we extracted information on postoperative adverse events including bleeding, infection, necrosis and wound dehiscence as well as vascular events within seven days post surgery. Patients with known bleeding diathesis (such as hemophilia or von Willebrand disease) were excluded. Bleeding was defined as severe if it required coagulation and/or suturing, as moderate if it required a new pressure dressing, and as mild if it could be resolved by advices through the telephone. Frequency of bleeding was compared between three groups: patients continuing their anti-thrombotic medication, patients discontinuing their anti-thrombotic medication and patients not using anti-thrombotics (controls). This study protocol followed the principles of the 1975 Declaration of Helsinki and was approved by the institution's medical ethical committee.

The Chi-square test or Fisher's exact test was used to test for statistical significance of differences in proportions. For continuous variables the t-test for independent samples or

Mann-Whitney U test were used. Multivariate logistic regression analysis was performed to evaluate the relationship between haemorrhage and antithrombotic therapy and to adjust for potential confounders. P-values ≤0.05 were considered to indicate statistical significance. Analysis was performed using IBM SPSS Statistics version 20.0.0.1.

Results

A total of 598 Mohs procedures in 534 patients were performed in the study period. After excluding 175 procedures (151 patients) due to unclear documentation regarding the use and/or management of antithrombotic medication, 423 procedures (383 patients) were left for analysis. Baseline characteristics are shown in table I. Patients using antithrombotic medication were significantly older and were more often male than patients not using them. In the group that discontinued the antithrombotic medication, more operations were done in the eye region, reflecting adjustment to the protocol. There was no statistically significant difference in the diameter of the surgical defect or the closure type among all three groups.

A total of 18 haemorrhages in 18 patients were recorded (4.3% of procedures). The haemorrhage rates and their severity are shown in table II. No life-threatening bleeds occurred. After adjustment for age, which was a significant co-variant, the relative risk (RR) of haemorrhage in patients discontinuing their medication compared to controls was 3.52 (95% confidence interval, CI:0.93–13.38) and in patients continuing their medication compared to controls 3.84 (95%CI:1.13–12.98). No wound dehiscence, necrosis or infection occurred in patients who have experienced postoperative haemorrhage. In patients using PI (n=88) the RR of postoperative haemorrhage was 1.20 (95%CI:0.12-12.21) when comparing patients continuing versus discontinuing. In patients using VKA (n=54), the RR of postoperative haemorrhage in continuing compared to discontinuing was 1.32(95%CI:0.19 –9.24).

Two vascular events were identified. One patient withheld acenocoumarol 4 days preoperatively and developed a cerebellar infarction three days after surgery. Another patient discontinued carbasalatecalcium 7 days preoperatively and experienced a myocardial infarction during the operation.

Table I Characteristics of included procedures

Characteristic	Antithrombotics discontinued	Antithrombotics Continued	No Antithrombotics	p-Value
Procedures, n	59	84	280	
Age, mean in years (SD)	75.5 (±9.4)	76.3 (±8.8)	66.0 (±11.9)	<0.001
Sex, n(%)				0.041
Male	36 (61.0)	52 (61.9)	136 (48.6)	
Female	23 (39.0)	32 (38.1)	144 (51.4)	
Anticoagulant, n (%)				n.a.
PI	24 (40.7)	52 (61.9)	n.a.	
VKA	31 (52.5)	18 (21.4)	n.a.	
2 x PI	1 (1.7)	11 (13.1)	n.a.	
VKA + PI	3 (5.1)	2 (2.4)	n.a.	
Unknown agent	0 (0.0)	1 (1.2)	n.a.	
Localization, n (%)				<0.001
Eye	16 (27.1)	5 (6.0)	33 (11.8)	
Nose	23 (39.0)	25 (29.8)	129 (46.1)	
Cheek	6 (10.2)	9 (10.7)	46 (16.4)	
Ear	5 (8.5)	20 (23.8)	24 (8.6)	
Other	9 (15.3)	25 (29.8)	48 (17.1)	
Diameter defect, mean in mm (SD)	25.9(±14.4)	25.4(±14.3)	22.6(±13.2)	0.094
Reconstruction, n (%)				0.122
Secondary granulation	5 (8.5)	12 (14.3)	25 (8.9)	
Primary closure	17 (28.8)	33 (39.3)	73 (26.1)	
Plasty	29 (49.2)	28 (33.3)	119 (42.5)	
Graft	2 (3.4)	7 (8.3)	33 (11.8)	
Postponed closure	4 (6.8)	4 (4.8)	22 (7.9)	
Unknown	2 (3.4)	0 (0.0)	8 (2.9)	

SD: standard deviation, PI: platelet inhibitor, VKA: vitamin-K antagonist, n.a.: not applicable

Table II Number of procedures with postoperative haemorrhage, n (%)

Patient group	Mild	Moderate	Severe	Total
Antithrombotics discontinued (n=59)	0 (0.0)	2 (3.4)	1 (1.7)	4 (6.8) [a]
Antithrombotics continued (n=84)	2 (2.4)	2 (2.4)	2 (2.4)	6 (7.1)
No antithrombotics (n=280)	1 (0.4)	5 (1.8)	1 (0.4)	8 (2.9)[a]

[a] In one patient the type of intervention was not registered

Discussion

In this study, similar risks of postoperative haemorrhage were observed in patients continuing or temporarily withholding their antithrombotic medication prior to Mohs surgery. Both groups showed a significantly higher bleeding risk than patients who did not use antithrombotic medication.

Several earlier studies have compared the risk of haemorrhage in patients continuing antithrombotic medication prior to dermatologic surgery with healthy controls. The results are however controversial.(1-8) For daily practice, the RR of postoperative haemorrhage in patients continuing versus discontinuing their antithrombotic medication is of more relevance. Only one prior study focussed on this comparison and found similar risks in both groups which is in agreement with our findings.(12) In this earlier study, the decision to stop antithrombotic medication or not was left to the treating physician which could potentially have introduced a selection bias. In our study this selection bias was minimized due to a uniform protocol. However, patients using antithrombotics are probably more aware of bleedings and are more likely to contact a doctor. This could also have contributed to the higher rate of registered bleedings in patients using antithrombotics.

Some studies have concluded that the use of VKA did increase the risk of bleeding while that of aspirin did not.(4, 13) In our study, both patients on VKA and PI had an increased risk of bleeding compared with control patients (results not shown). Nonetheless, we have showed that the haemorrhage rate was similar in patients continuing and discontinuing their VKA. This is important for the decision prior to dermatologic surgery. Two other studies have suggested that combinations of different agents could increase the rate of bleeding complications.(7, 8) In this study, none of the patients who received a combination of antithrombotics had experienced a haemorrhage. This group was however small.

In our study, two patients who had discontinued their anticoagulation developed a vascular event within one week after surgery. Although these complications are rare, they should not be ignored due to the life-threatening potential. On the contrary, bleeding complications are mostly not life threatening but can be extremely stressful for the patient and a potential threat for wound healing. Nevertheless, in this study, no dehiscence or necrosis appeared in the group with postoperative haemorrhage indicating that this threat is minimal.

There are limitations to this study that should be noted. First of all, due to the retrospective design, data are missing and a limited sample prohibited potentially relevant sub-group analyses, such as the method of wound closure. The limited sample size is

also associated with a reduced power to detect statistically significant results. Secondly, the recorded severity of the bleeding is subjective, but the potential misclassification of bleeding severity does not affect the results concerning total number of haemorrhages. Other possible confounders, such as patients coping ability or surgeon's skill could not be addressed in this paper due to its retrospective design.

In conclusion, this study found a similar risk of postoperative haemorrhage after Mohs micrographic surgery in the groups continuing and discontinuing antithrombotic therapy. Two severe vascular events were reported, both in the group discontinuing their medication. Balancing both risks favours continuation of anticoagulants in dermatologic surgery. Future prospective studies are needed to confirm our results.

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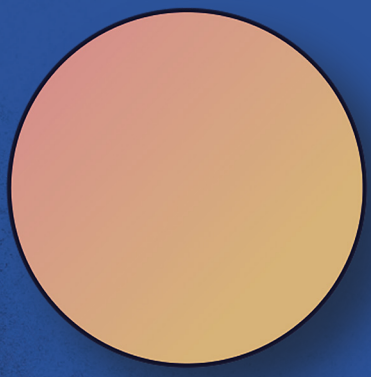
Risk factors for surgical site infections in dermatologic surgery



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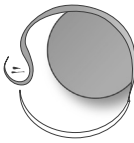
Introduction

It is well known that worldwide, dermatologists are confronted with increasing numbers of patients with skin malignancies who often receive surgical treatment.(1, 2) These procedures are generally associated with a low risk (<5%) of surgical site infection (SSI).(3-10) However, there is ongoing debate that under certain circumstances, the risk of SSI is significantly increased and could surpass the acceptable threshold.



Different factors could influence the risk of SSI after dermatologic surgery. The first group consists of 'patient related factors' which include diabetes and immunologic status. The impact of these factors on the risk of SSI in dermatologic surgery is a matter of debate.(5-7, 9) The second group of potential risk factors are 'procedure related factors' such as environmental circumstances, type of procedure and method of closure. Several studies compared the risk of SSI after Mohs micrographic surgery (MMS) and excision and found no significant difference.(6-8) Studies have not come to consensus whether the method of closure is a significant independent risk factor.(6, 7, 9, 10) The last and most studied group consists of 'lesion related factors' such as the anatomical site and size of the defect. Regarding anatomical site, the nose, ears, genital/groin, and location below the knees and on extremities have been identified as risk factors in various studies.(3, 6-8, 11) Several studies have also shown that larger defects were associated with an increased risk of SSI.(4, 8, 11)

Many published studies evaluating risk factors in dermatologic surgery included a group of patients who received antibiotic treatment during the perioperative period. To our knowledge, the only large study including patients who did not use antibiotics was published by Dixon in 2006 including 5091 procedures in 2424 patients.(6) Although the study presented an in depth evaluation of different risk factors of SSI, no multivariate analysis was performed to assess the independent effect of risk factors. Routine use of antibiotic prophylaxis should be avoided as this could lead to adverse reactions and increase bacterial resistance. In 2008, an advisory statement in the United States was published on this topic suggesting antibiotic prophylaxis for certain patients or operations on high risk locations.(12) The authors, however, emphasised that the evidence available was very limited and encouraged future researchers to further identify important risk factors.

The aim of this study was to perform a comprehensive evaluation of the independent effect of multiple risk factors on the risk of SSI using a multivariate approach in patients not receiving any antibiotics in the perioperative period.

Methods

We conducted an observational cohort study at the Department of Dermatology in the Maastricht University Medical Centre for one year. All patients who received surgery under local anaesthesia were eligible. A waiver to obtain written informed consent was authorized by the local Ethical Committee as the study protocol did not differ from standard care. Biopsies, curettages, shave-excisions or laser procedures were excluded. Patients who received antibiotics in the perioperative period (one month prior or after the procedure) were excluded as well.

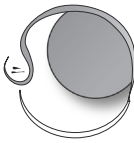
Data on patient (age, gender, diabetes and immunosuppression), surgical procedure (setting, number of separate procedures on one day, type of procedure and type of closure) and lesion (type, location and defect size) related characteristics were retrospectively collected from the electronic patient charts.

Surgical procedures were performed at two locations. At the operation theatre, both the patient and healthcare professionals were dressed in clean surgical gowns. The surgeons and assistants wore scrub hats, masks and sterile gloves. If the operation involved a large skin tumour, sterile gowns were also worn. At the outpatient clinic, patients wore their own clothing. The healthcare professionals did wear clean surgical gowns, scrub hats, masks and sterile gloves. At both locations, the surgical site was prepared sterilely. During conventional excision the surgical site was disinfected once, prior to incision, with chlorhexidinedigluconate 0.5% solution in ethanol 70%. Local anaesthesia was achieved with lidocaine hydrochloride 1% and epinephrine 1:100,000 injections. In case of MMS, the surgical site was disinfected prior to each stage. After every stage the wound was dressed with sterile gel with 0.5% chlorhexidine and sterile gauze. Instruments are changed after every third stage or before closure when more than one stage was performed with the same instruments.

Wounds were sutured in layers with dermal absorbable sutures and cutaneous sutures. The sutured wounds were supported by adhesive closure strips and a clean pressure dressing. Patients were advised to keep the wounds dry until suture removal (approximately one week on the face and two weeks on the trunk). Open wounds were dressed with paraffin impregnated gauze for 3-7 days. After these first days, patients were instructed to rinse the wound daily with clean tap water.

Most patients received follow-up at least until suture removal. Patients who had not returned for suture removal were contacted by phone and questioned about adverse events. In case of an adverse event, patients had follow-up until the wound had healed. At the start of the study, all doctors working at the department received instructions on

the definition of SSI and were asked to obtain wound cultures in case a SSI was suspected. Two definitions of SSI were used. According to the strictest definition, a SSI required local symptoms indicative of wound infection (purulent drainage, pain, swelling, erythema and/or heat) combined with a positive culture occurring within 30 days after the surgery. Wound culture was considered positive if it yielded appropriate pathogenic bacteria and was interpreted as such by the clinical microbiologist. As culture was not available in all cases, we also defined a second group wherein all patients with clinical symptoms were considered to have a SSI.



Statistical analysis

The distribution of baseline characteristics in groups with and without SSI was summarized by absolute numbers and percentages for categorical variables and by mean values with standard deviations or median with range for continuous variables. Univariate and multivariate logistic regression analyses were performed and odds ratios (OR) with 95% confidence intervals (CI) were used to quantify the association between potential risk factors and risk of SSI. The multivariate model included all potential risk factors as covariates in order to evaluate the independent effect of single risk factors. In some patients multiple procedures were performed. Observations in these patients are likely to be correlated. Robust standard errors were calculated, because ignoring this correlation can lead to misleadingly small estimates of the standard error and consequently too small 95% CI. Multiple imputation was used for dealing with missing values for risk factors. P-values ≤0.05 were considered to indicate statistical significance. Analyses were performed using IBM SPSS Statistics version 23.0.0.2 and Stata version 13.

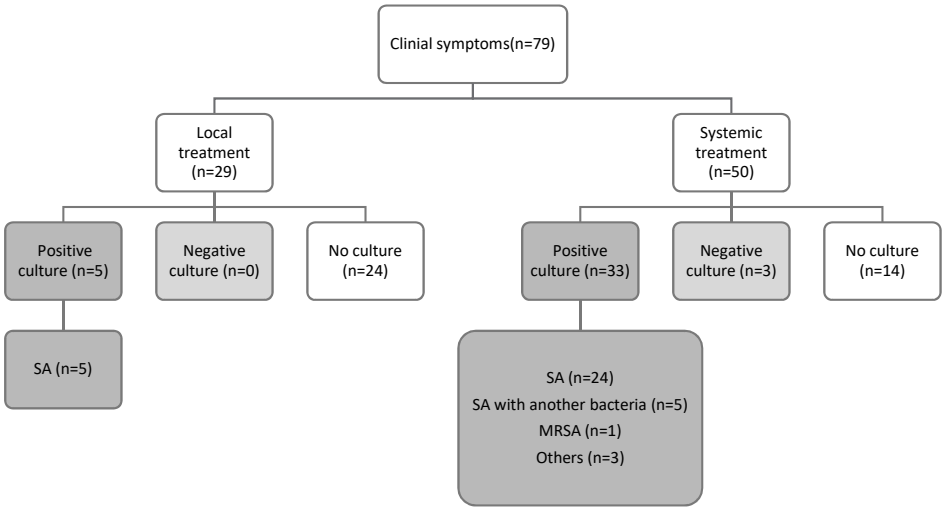
Results

From April 1st 2014 to April 1st 2015, 2058 surgical procedures were performed in 1459 patients. Twenty-seven procedures (20 patients) were excluded because antibiotic prophylaxis was required for prosthetic valves or joints as these patients received surgery at locations were mucosal membrane could potentially be breached. Twenty-one procedures (16 patients) were excluded because the patient received antibiotics in the peri-operative period unrelated to the procedure. Thirty-three procedures (16 patients) were excluded because the occurrence of a SSI could not be verified. These were patients who had not visited their dermatologist or general practitioner after the procedures and could not be contacted.

The final study population consisted of 1977 procedures in 1407 patients. Baseline characteristics are shown in Table I. Of the 81 procedure with delayed closure, 3 were closed

primarily, 40 received grafts and 38 received a flap. Seventy-nine cases (4.0%) presented with clinical symptoms suspicious for a SSI and were treated as such. Wound cultures were obtained in 41 of 79 cases with clinical suspicion and were found positive in 38 (2.0%). (Fig.1)

Fig 1. Clinical presentation of SSI with culture results



MRSA: methicillin-resistant Staphylococcus aureus, SA:*Staphylococcus aureus*, SSI: Surgical site infection

In 50 of 79 cases, oral antibiotics were prescribed. Of all patients treated with oral antibiotics, four experienced gastrointestinal side effects. No other side effects were recorded. No re-operation occurred due to impaired wound healing. Of the five patients who developed a SSI after delayed closure, two of them developed it before the closure and three after. Postoperative haemorrhage occurred in 58 procedures (2.9%). Wound dehiscence occurred in 45 procedures (2.3%). Both complications occurred more frequently in the group of patients with SSI.

In the primary analysis, the 38 patients with clinically suspected SSI and a positive culture were considered as having SSI. These patients were compared with 1898 cases without any clinical suspicion of SSI. However, not all patients with clinically suspected SSI had a wound culture and therefore we performed a secondary analysis, in which we considered all 79 patients with clinical suspicion as having SSI. Table II presents the numbers and percentage of procedures with the two definitions of SSI, according to the presence of potential risk factors.

Table I Base-line characteristics		
Patient characteristics		
Age (year, mean ± SD) [a]		66.2 ± 15.9
Gender	Female	848 (42.9%)
	Male	1129 (57.1%)
Diabetes	No	1516 (76.7%)
	Yes	151 (7.6%)
	Missing	310 (15.7%)
Immunosuppression	No	1554 (78.6%)
	Yes	107 (5.4%)
	Missing	316 (16.0%)
Operation characteristics		
Setting	Operation theatre	931 (47.1%)
	Outpatient clinic	1046 (52.9%)
Nr. of operations on one day	One	1346 (68.1%)
	Two or more	631 (31.9%)
Type of excision	Excision	1641 (83.0%)
	MMS	336 (17.0%)
Type of closure	Primary	1592 (80.5%)
	Flaps	123 (6.2%)
	Grafts	34 (1.7%)
	Secondary intention	147 (7.4%)
	Delayed	81 (4.1%)
Lesion characteristics		
Type of tumour	Benign/pre-malignant	368 (18.6%)
	Malignant	1609 (81.4%)
Location	Head and neck area except nose/lips/ears	730 (36.9%)
	Nose	216 (10.9%)
	Lips	21 (1.1%)
	Ears	102 (5.2%)
	Arms/hands	148 (7.5%)
	Lower legs/feet	114 (5.8%)
	Upper legs	70 (3.5%)
	Trunk	570 (28.8%)
	Axillary/groin/genital area	6 (0.3%)
Defect size (cm^2,median with range) [a]		2.26 (0.06-78.54)

MMS: Mohs micrographic surgery, SD: standard deviation

[a] Age is presented as mean with standard deviation as it follows a normal distribution while defect size is presented as median with its range as its distribution is not normal.

Table II Numbers and percentages with SSI according to presence or absence of potential risk factors.

		Culture confirmed SSI	Clinical symptoms of SSI	No clinical suspicion of SSI
Age (year)	≤65	8 (1.0%)	29 (3.6%)	774
	> 65	30 (2.6%)	50 (4.3%)	1124
Gender	Female	15 (1.8%)	33 (3.9%)	815
	Male	23 (2.0%)	46 (4.1%)	1083
Diabetes	No	29 (1.9%)	57 (3.8%)	1459
	Yes	3 (2.0%)	9 (6.0%)	142
Immunosuppression	No	28 (1.8%)	61 (3.9%)	1493
	Yes	4 (3.7%)	7 (6.5%)	100
Setting	Operation theatre	24 (2.6%)	46 (4.9%)	885
	Outpatient clinic	14 (1.3%)	33 (3.2%)	1013
Nr. Of operations	One	27 (2.0%)	57 (4.2%)	1289
	Two or more	11 (1.7%)	22 (3.5%)	609
Type of excision	Excision	31 (1.9%)	63 (3.8%)	1578
	MMS	7 (2.1%)	16 (4.8%)	320
Type of closure	Primary	21 (1.3%)	49 (3.1%)	1543
	Flaps	5 (4.1%)	7 (5.7%)	116
	Grafts	1 (2.9%)	2 (5.9%)	32
	Secondary	9 (6.1%)	16 (10.9%)	131
	Delayed	2 (2.5%)	5 (6.2%)	76
Type of tumour	Benign/pre-malignant	1 (0.3%)	5 (1.4%)	363
	Malignant	37 (2.3%)	74 (4.6%)	1535
Location	Head and neck[a]	12 (1.6%)	30 (4.1%)	700
	Nose	4 (1.9%)	7 (3.2%)	209
	Lips	0 (0.0%)	1 (4.8%)	20
	Ears	9 (8.8%)	15 (14.7%)	87
	Arms/hands	1 (0.7%)	3 (2.0%)	145
	Lower legs/feet	3 (2.6%)	6 (5.3%)	108
	Upper legs	1 (1.4%)	2 (2.9%)	68
	Trunk	8 (1.4%)	14 (2.5%)	556
	Axillary/groin/genital	0 (0.0%)	1 (16.7%)	5
Defect size (cm^2)	≤3	11 (0.9%)	32 (2.6%)	1214
	>3	27 (3.7%)	47 (6.4%)	684
Total		38 (1.9%)	79 (4.0%)	1898

Percentages of the two definitions of SSI are shown of the total population (n=1977)
MMS:Mohs micrographic surgery, SSI: surgical site infection.
[a] Except nose, lips and ears

Table III The odds ratios from multivariate logistic regression analyses.

		Culture confirmed SSI			Clinical symptoms of SSI		
		OR	95% CI	p	OR	95% CI	p
Patient characteristics							
Age (year)		1.03 [a]	0.99-1.07	0.14	0.99 [a]	0.97-1.01	0.40
Male (vs. female)		0.79	0.37-1.71	0.55	0.78	0.46-1.32	0.36
Diabetes (yes vs. no)		1.03	0.25-4.33	0.96	1.45	0.55-3.86	0.43
Immunosuppression (yes vs. no)		2.21	0.66-7.35	0.20	1.60	0.62-4.16	0.33
Operation characteristics							
Outpatient clinic (vs. operation theatre)		0.59	0.24-1.41	0.23	0.62	0.33-1.15	0.13
> 1 operation (vs. 1) on one day		0.87	0.41-1.86	0.73	0.93	0.55-1.58	0.79
Mohs micrographic surgery (vs. excision)		0.62	0.13-3.03	0.55	0.94	0.35-2.50	0.90
Type closure	Primary	1 (Reference)			1 (Reference)		
	Flaps	6.35	1.33-30.28	0.02	2.17	0.71-6.58	0.17
	Grafts	1.64	0.13-20.25	0.70	1.32	0.23-7.53	0.76
	Secondary intention	3.01	1.11-8.13	0.03	2.34	1.16-4.70	0.02
	Delayed	0.99	0.11-8.75	0.99	1.01	0.33-3.11	0.99
Lesion characteristic							
Malignant (vs. benign/pre-malignant)		3.53	0.56-22.19	0.18	2.52	0.75-8.54	0.14
Location	Head and neck [b]	1 (Reference)			1 (Reference)		
	Nose	1.06	0.29-3.95	0.93	0.78	0.27-2.23	0. 65
	Lips	Empty [c]			1.41	0.17-11.63	0.75
	Ears	6.03	2.12-17.15	0.001	4.01	1.90-8.63	<0.001
	Arms/hands	0.37	0.03-4.02	0.41	0.47	0.14-1.64	0.24
	Lower legs/feet	1.85	0.50-6.84	0.36	1.33	0.54-3.27	0.54
	Upper legs	1.77	0.36-8.72	0.48	0.98	0.26-3.70	0.97
	Trunk	1.30	0.46-3.69	0.62	0.62	0.30-1.31	0.21
	Axillary/groin/genital	Empty [c]			9.49	0.85-106.55	0.07
Defect size (cm^2)		1.08 [a]	1.03-1.14	0.003	1.08 [a]	1.02-1.13	0.01

The multivariate models included all potential risk factors as covariates in order to evaluate the independent effect of single risk factors.
CI: confidence interval, OR: Odds ratio, SSI: surgical site infection, vs.: versus
[a] Odds ratios per unit increase
[b] Except nose, lips and ears
[c] No infection occurred in this group, therefore odds ratios could not be calculated.

The results of multivariate logistic regression analyses are presented in Table III. When using the strictest definition of SSI (clinical symptoms with confirmation by culture) location on the ears (OR 6.03 95%CI 2.12-17.15), larger defects (OR 1.08 95%CI 1.03-1.14 per unit (cm^2) closure by flaps (OR 6.35 95%CI 1.33-30.28) and healing by secondary intention

(OR 3.01 95%CI 1.11-8.13) were identified as significant risk factors. In the secondary analyses, considering all 79 patients with clinical suspicion as having SSI regardless of culture results, the same risk factors were associated with significantly increased risk, but the associations were less strong. In this analysis, procedures performed in the axillary, groins and genital area were also associated with a higher risk of clinical SSI (OR 9.49, 95% CI 0.85-106.55). However, only six procedures were performed at these sites and the OR did not reach statistical significance.

Discussion

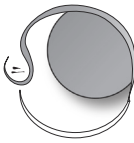
The current study comprehensively evaluated the independent effect of patient, surgery and lesion related factors on the risk of SSI. The results indicate that the risk of SSI is significantly increased in procedures performed on the ears, in larger defects and in surgical wounds closed by flaps or secondary intention.

The increased risk of SSI in procedures done on the ear was firstly suggested by Futoryan et al. in 1995.(8) Other studies examined the risk of wedge excision including those on the ear and on the lips, and showed conflicting results(6, 10) No multivariate analysis was performed in those two studies and therefore the independent effect of location could not be evaluated. In our study, accounting for other potential risk factors by multivariate regression analysis, location of the lesion on the ear was identified as a significant independent risk factor for SSI.

The method of closure as a risk factor for SSI has been studied previously.(3, 6, 7, 10) The former studies have not reached consensus and did not adjust for other risk factors which can be correlated with the method of closure, such as the location of the tumour and the defect size. In the present study, the independent effect of closure method was estimated using multivariate regression analysis and the risk of SSI is significantly increased in wounds closed with flaps. A seemingly contra-intuitive finding is that healing by secondary intention was associated with a significantly higher risk of SSI. This specific risk factor has not been previously identified in literature. It is imaginable that an open wound is more susceptible for an infection occurring after the procedure. This is however only a hypothesis, as the mean time to the onset of SSI in this subgroup did not differ from the other closure methods. Future research is needed to confirm and clarify this finding.

One limitation of the study is the low prevalence of some risk factors which limited the power to detect small but relevant increase in risk for SSI with statistical significance. Secondly, the conclusions of this study are based on a single centre experience. Extrapo-

lating the results to other centres should be done with care. Thirdly, the results of wound cultures were not available for some patients who had clinical suspicion of SSI. For this reason, separate analyses were performed using two different definitions of SSI. The strongest associations were observed when using the strictest definition of SSI: clinically diagnosed infection verified by a positive culture. The weaker associations found in the secondary analysis using a less strict definition of SSI could be the result of misclassification of SSI. Such misclassification of outcome is known to bias odds ratios towards finding no effect. Finally, the authors are aware that not all potential risk factors were studied. For example, we did not routinely report the skin condition such as ulceration prior to operation and whether or not a patient was a present smoker and therefore these risk factors could not be evaluated. The effect of these potential risk factors should be examined in a multivariate model, together with the risk factors found in the current study, in the future.



The clinical question remains: when is antibiotic prophylaxis justified in dermatologic surgery? It is generally accepted that antibiotic prophylaxis is not routinely indicated in clean wounds where the risk of infection is below 5%.(13, 14) Taking into account the average low incidence of SSI, it is debatable whether an increase of risk of SSI in patients with a single risk factor requires antibiotic prophylaxis, bearing in mind the potential side effects of prophylaxis. Therefore, it would be interesting to develop a model to predict probability of SSI based on combinations of several risk factors in patients receiving dermatologic surgery. Such predicted probabilities could then be used to guide clinical decision making.

In conclusion, the results of a thorough multivariate analysis of 1977 invasive procedures suggest that patients with procedures done on the ears, larger defects and wounds healed by flaps or secondary intention are at increased risk for SSI.

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A clinical prediction model for surgical site infections in dermatologic surgery

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Introduction

Surgical site infection (SSI) is one of the major concerns in dermatological surgery. It impairs wound healing and could worsen the cosmetic outcome. Although rare, systemic infection might also result from a SSI and is associated with substantial morbidity. Fortunately, the incidence rate of SSI is generally below 5%.(1-8) Despite the low rate of SSI however, many dermatological surgeons prescribe antibiotic prophylaxis on a regular base.(9-11) The overuse of antibiotics could lead to a range of adverse events including allergic reactions. According to a recent study from the US, adverse events due to systemic antibiotics accounted for 14.1% of the visits to thethe emergency department.(12) In addition, over-prescribing of antibiotics will result in increased antimicrobial resistance.(13) Therefore, antibiotic prophylaxis should only be considered when there is a substantial risk of SSI.

In our previous study on SSI after dermatological surgery, specific risk factors that increase the risk of acquiring a SSI have been identified including the location of the tumour, size of the defect and the method of closure.(14) Other patient, environment and procedure related factors have been studied in literature with conflicting results. (1-8) To adequately assess the risk of SSI in a clinical setting, the combination of different risk factors in each patient should be evaluated. Clinical prediction models could serve this purpose by risk estimation for individual patients based on combinations of multiple predictors. Currently, such a prediction model is not available for dermatological surgery.

Correctly identifying the patients at risk for SSI could minimize the overuse of antibiotic prophylaxis and reduce the rate of SSI. The aim of this study was to develop a clinical prediction model to facilitate the decision whether to give antibiotic prophylaxis based on individual risk of SSI in patients undergoing dermatological surgery.

Methods

Patients

We conducted a retrospective cohort study at the Department of Dermatology in the Maastricht University Medical Centre.(14) All patients who received surgery under local anaesthesia from April 2014 to April 2015 were included. A waiver to obtain written informed consent was authorized by the local Medical Ethical Committee because the study protocol did not involve deviations from standard care. Patients with biopsies, curettages, shave-excisions or laser procedures were excluded. Patients who received antibiotics in the perioperative period (one month prior or after the procedure) were also

excluded. Data on patient, operation and lesion related characteristics were retrospectively collected from the electronic patient charts. More details on these characteristics were described in the earlier publication.(14) For patients receiving multiple procedures in the study period, only the first procedure was included because observations in the same patients are likely to be correlated.

To verify whether patients experienced SSI or not, patients received follow-up at least until suture removal. Patients, who had not returned for suture removal, were contacted by phone 2-3 weeks post surgery and were questioned about adverse events including SSI. Patients were additionally instructed to contact the department if any adverse events occurred after the phone call. In case of a SSI, patients were followed until the wound had healed.(14) SSI was defined as the presence of local symptoms indicative of wound infection (purulent drainage, pain, swelling, erythema and/or heat) occurring within 30 days after the surgery verified by a positive culture.

Selection of variables

In the previous study we have identified type of closure, tumour location and defect size as significant risk factors.(14)These factors were selected for incorporation in the prediction model.

The location of the tumour on the ears was associated with a significantly higher risk of SSI when compared with the head and neck area as a reference group. Although not statistically significant, localization on the upper extremities and trunk was associated with lower risk of SSI compared with head and neck area while slightly higher risk of SSI was found for lesions on the lower extremities. Therefore, tumour location was categorized into four categories: 1) head and neck area except ears, 2) ears, 3) trunk/upper extremities and 4) lower extremities. The defect size was categorized into three groups: <2 cm^2, 2-4 cm^2 and 4cm^2. Flaps and closure by secondary intention were associated with significantly higher risk when compared to primary closure as a reference category. Grafts and delayed closure were not associated with increased risk. For this reason, type of closure was categorized into primary closure, flaps, grafts/delayed closure and closure by secondary intention.

Development of the model

Multivariable logistic regression analysis was used for development of the prediction model. The dependent variable was SSI (yes versus no) and type of closure, tumour location and defect size were entered as independent variables. Reference categories were "primary closure" for type of closure, "head and neck except ears" for tumour location and "size< 2 cm^2 "for defect size. Regression coefficients and odds ratios (OR) with 95%

confidence interval (CI) were calculated. A nomogram was constructed to facilitate clinical calculation of the risk score for each patient based on the individual combination of risk factors.

Performance and validation of the model

The area under the receiver operating characteristic curve (AUC) and the Brier score were used to evaluate the performance of the prediction model. The AUC indicates how well the model can discriminate between patients with and without SSI and ranges from 0.5 (no discriminative ability) to 1.0 (perfect discriminative ability). To evaluate goodness of fit of the model, a scaled Brier score, corrected for the prevalence of SSI in the studied population, was calculated. The Brier score quantifies the distance between predicted and actual outcomes and has a range between 0 (the best score achievable) and 1 (the worst score achievable).(15) To evaluate calibration, the predicted probabilities of SSI are plotted against observed probabilities in a calibration plot.

As an internal validation step, bootstrapping was performed. A total of 1000 bootstrap samples were drawn from the original sample to mimic drawing samples from the underlying population. The aim of bootstrapping is to estimate how well the prediction model will perform on a hypothetical set of new patients. The prediction model was fitted in each bootstrap sample and tested on the original sample. To adjust for overfitting, the original regression coefficients have to be multiplied by a shrinkage factor obtained by bootstrapping. Furthermore, bootstrapping allows correction for optimism in the performance measures (AUC and Brier score).(16)

Implementation of the prediction model

A net benefit analysis is presented to evaluate whether the application of the prediction model does more good than harm. Correct identification of patients at risk for SSI (true positive rate) is beneficial, but unnecessary antibiotic prophylaxis in patients who would not develop a SSI (false positive rate) is harmful. Net benefit is a weighted sum of true positive minus false positive classifications.(17) Net benefit of a prediction model should be higher when compared with alternative strategies: prescribing all patients antibiotic prophylaxis (treat all) or prescribing no prophylaxis at all (treat none).

The key concept in this analysis is the threshold probability, which depends on the relative weight that is given to false positive and true positive classifications. True positives are usually valued higher than false positives; missing a patient with SSI, who should have received antibiotics, is in general considered as a more serious error than unnecessary treatment with antibiotics. In net benefit analysis the relative weights of harms and benefits are set by the threshold probability. For example, a threshold probability of

0.05 corresponds to the willingness to treat 20 patients in order to prevent one infection. In other words, the false positive classifications are valued at 1/19th of true positive classifications. When the prediction model is applied, patients with a predicted probability exceeding the chosen threshold probability will receive antibiotics while the remaining patients will not.

In practice, it is often difficult to define an optimal threshold probability, because relative weight of harms and benefits may differ for different doctors and patients. Decision curves are used to plot the net benefit of treating patients according to the prediction model relative to net benefits of the alternative strategies (treat all or treat none) over a range of plausible threshold probabilities.

Analyses were performed using STATA version 13 (StataCorp LP, Texas, USA) and R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

In total, 1407 patients received surgery without antibiotics in the studied period. Thirty-six patients were excluded because they received antibiotics in the peri-operative period. There were no significant differences between this group and the study group in baseline characteristics. Wound culture was not available in 32 patients and therefore the outcome of SSI could not be verified. To enable valid comparison of patients with verified SSI and patients without SSI these 32 patients were excluded leaving 1375 patients (624 females and 751 males) for analysis. The mean age in the studied population was 65 years (range 6-97). Thirty-one patients had clinically suspected SSI that was confirmed by wound culture (2.3%). In most of these cases, wound culture confirmed presence of S. aureus. Baseline characteristics are shown in Table I.

Performance of the model

Table II shows the results from the multivariable logistic regression analysis incorporating the pre-specified risk factors. Closure by flaps or secondary intention, location on the ears and larger defect size were associated with higher risk of SSI. Internal validation by bootstrapping (n=1000) resulted in a shrinkage factor of 0.83. The original regression coefficients were multiplied by this factor to calculate the final regression coefficients. (Table II)

Table I. Base-line characteristics

		No SSI	SSI	All
Age	≤65	575 (99.0%)	6 (1.0%)	581
	>65	769 (96.9%)	25 (3.1%)	794
Gender	Male	732 (97.5%)	19 (2.5%)	751
	Female	612 (98.1%)	12 (1.9%)	624
Type of excision	Conventional excision	1086(97.7%)	26 (2.3%)	1112
	Mohs micrographic surgery	258(98.1%)	5 (1.9%)	263
Type of tumour	Benign/ pre-malignant	292 (99.7%)	1 (0.3%)	293
	Malignant	1052 (97.2%)	30 (2.8%)	1082
Location	Head and neck except ears	713 (98.5%)	11 (1.5%)	724
	Ears	65 (89.0%)	8 (11.0%)	73
	Upper extremities and trunk	438 (98.2%)	8 (1.8%)	446
	Lower extremities	128 (97.0%)	4 (3.2%)	132
Defect size	<2cm²	657 (99.5%)	3 (0.5%)	660
	2-4 cm²	371 (98.1%)	7 (1.9%)	378
	>4cm²	316 (93.8%)	21 (6.2%)	337
Type of closure	Primary	1088 (98.4%)	18 (1.6%)	1106
	Flaps	92 (95.8%)	4 (4.2%)	96
	Grafts or delayed	66 (95.7%)	3 (4.3%)	69
	Secondary	98 (94.2%)	6 (5.8%)	104
Total		1344 (97.7%)	31 (2.3%)	1375

SSI: surgical site infection

Table II. Regression coefficients and Odds ratios before and after bootstrapping

		Before bootstrapping		After bootstrapping
		Regression coefficient	Odds ratios (95%CI)	Regression coefficient
Intercept		-6.05		-5.47
Location	Head and neck except ears		1.0	
	Ears	1.76	5.84 (2.05-16.58)	1.41
	Upper extremities and trunk	0.29	1.33 (0.47-3.81)	0.23
	Lower extremities	0.70	2.02 (0.58-7.02)	0.56
Defect size	<2cm²		1.0	
	2-4 cm²	1.34	3.80 (0.96-15.05)	1.07
	>4cm²	2.65	14.11 (4.09-48.72)	2.12
Type of closure	Primary		1.0	
	Flaps	1.37	3.94 (1.10-14.13)	1.10
	Grafts or delayed	0.48	1.62 (0.42-6.28)	0.39
	Secondary	1.01	2.91 (0.96-8.84)	0.86

CI: confidence interval

The mathematical prediction model is calculated as follows:

Ln(p/(1-p))= -5.47+ 1.41*ears+0.23*trunk/upper extremity+ 0.56*lower extremity+1.07* (size 2 - 4cm^2)+2.12*(size >4cm^2)+1.10*flaps+0.39*grafts/delayed+0.86*secondary closure.

The predicted probability (p) of SSI can be calculated by solving the equation above.

For example, for a patient with a defect on the ear with size of 3cm^2 that is closed by secondary intention, the predicted probability of SSI can be calculated as:
Ln(p/(1-p))
= -5.47+ 1.41*ears(=1)+0.23*trunk/upper extremity(=0)+ 0.56*lower extremity(=0)+1.07* size 2-4cm^2(=1)+ 2.12*size >4cm^2 (=0) +1.10*flaps (=0) +0.39*grafts/delayed (=0) +0.86*secondary closure (=1)
=-5.47+1.41+1.07+0.86
=-2.13

Therefore,

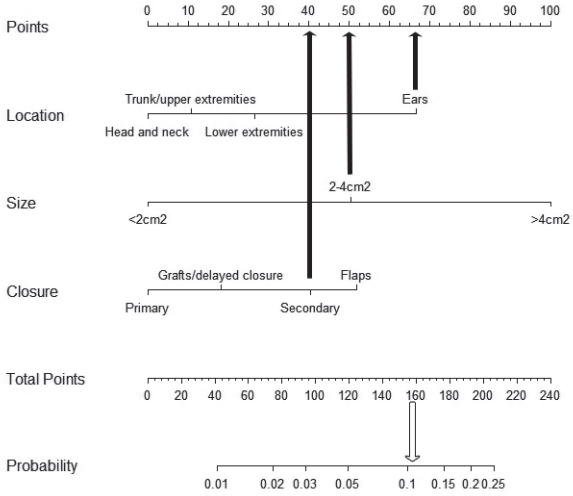
p/(1-p)=e^(-2.13)=0.12
p=0.12/(1+0.12)=0.11

The model calculates the predicted probability (p) of SSI for each patient in de dataset. To facilitate the computation of p clinically, a nomogram was constructed. (Figure 1) Each studied characteristic was given a 0-100 score according to the nomogram. The sum of the individual scores corresponds with a specific probability of SSI.

For example, for a patient with a defect on the ear with size of 3cm^2 that is closed by secondary intention, p can be inferred from the nomogram. Location on the ears receives 67 points. Size 2-4 cm^2 receives 50 points. Closure by secondary intention receives 40 points. A total of 157 is calculated by summing-up these individual scores which corresponds to a predicted probability of 0.11.

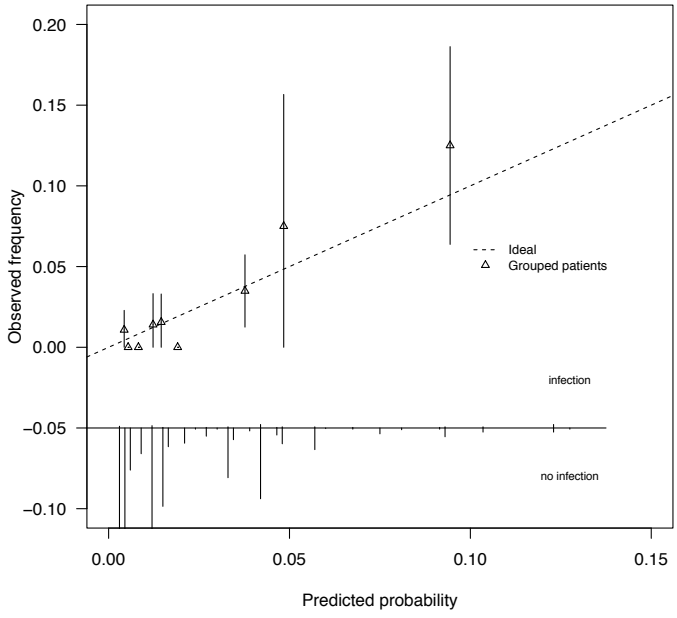
The calibration plot shows agreement between predicted probability and actually observed probability.(Figure 2) The Brier score is 0.023, with a scaled Brier score of 0.039. The ability of the model to discriminate between patients with and without SSI is visualized by the ROC curve, which shows the trade-off between sensitivity and specificity at various cut-off values of the predicted probability of SSI. The AUC is 84.1% (77.0%-91.2%).

Figure 1. Nomogram for the calculation of probability of surgical site infection with an example for a patient with a 3cm² defect on the ear closed by secondary intention.



Step 1: Read the number of points corresponding to each individual risk factor: 67 for ears, 50 for 2-4 cm², 40 for secondary closure (black arrows).
Step 2: Add the numbers up: 67+50+40=157.
Step 3: Draw a vertical line between "total points" and probability to read the probability of infection for this patient: 157 points corresponds to a predicted probability of 0.11 (white arrow).

Figure 2. Calibration plot showing agreement of the predicted probability with the observed rate of SSI.



The values for predicted probability ranged from 0.4% to 30.2% for the study population with an incidence of 2.3%. Table III shows the combinations of sensitivity and specificity at various cut-off values of the predicted probability of SSI. At a cut-off value of >0.01, sensitivity=97% and specificity=42%. At higher cut-off values, the sensitivity decreases and specificity increases. At a cut-off value>0.05, sensitivity is 45% and specificity is 93%. Predictive values (PPV and NPV) depend on the prevalence of SSI.

Clinical implementation of the prediction model: net benefit analysis

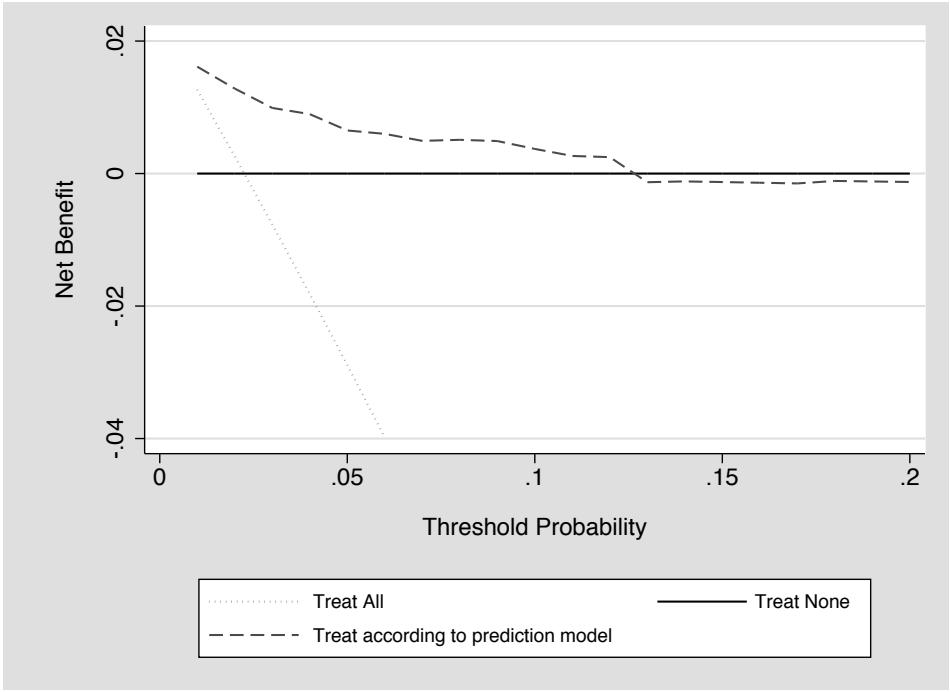
The prediction of a model with an AUC of 84.1% is good, but not perfect. Therefore, a net benefit analysis was performed to evaluate under which conditions use of the model provides higher benefit than alternative strategies. A decision curve shows the relative net benefit over a range of threshold probabilities from 0.01 to 0.20 (Figure 3) for three strategies: 1) always prescribe antibiotic prophylaxis for patients undergoing dermatological surgery (treat all) 2) never prescribe antibiotic prophylaxis (treat none) and 3) prescribe only antibiotic prophylaxis for patients with a predicted risk of SSI exceeding the threshold. It can be observed that the net benefit of treating according to the model is higher than the net benefit of the alternative strategies for thresholds between 0.01 and 0.125, but not for thresholds exceeding 0.125. This means that the model may be useful for patients and doctors who attach much higher value to preventing an infection than to unnecessary prophylactic treatment with antibiotics and are willing to treat at least eight patients (1/0.125=8) to prevent one SSI. For those who advocate more restrictive use of antibiotic prophylaxis and are not willing to treat more than 8 patients to prevent one SSI, the default strategy of treating no patients at all is the better choice in a population with low incidence of SSI. The net benefit of the strategy of "treat all" has the lowest benefit over the entire range of plausible threshold probabilities in this study population with an incidence of SSI of 2.3%.

How can net benefit of the model be interpreted? As an example we have chosen a threshold probability of 0.05, corresponding with the willingness to treat 20 patients in order to prevent one SSI. At this point, use of the prediction model results in higher benefit than the "treat none" strategy. The net benefit of use of the prediction model is 0.0065 and implies that for every 1000 patients where we apply the prediction rule, 6.5 extra true positives are identified without increasing the false positive rate. Although the number seems low, it must be interpreted in the context of the prevalence. The maximum possible value of net benefit which can be achieved in this study equals the incidence of 0.023; we can never do better than intervening in all patients with SSI and in none of the patients without SSI. Therefore, a net benefit of 0.0065 means that 28% (0.0065/0.023*100%) of the maximal benefit is achieved at this threshold probability.

Table III. Sensitivity, specificity, positive and negative predictive values (PPV and NPV) cut-off values of the predicted probability

Predicted probability	Sensitivity	Specificity	PPV	NPV
>0.01	0.97	0.42	0.04	1.00
>0.02	0.84	0.69	0.06	0.99
>0.03	0.81	0.73	0.06	0.99
>0.04	0.74	0.81	0.08	0.99
>0.05	0.45	0.93	0.13	0.99
>0.10	0.26	0.98	0.24	0.98
>0.15	0.00	0.99	0.00	0.98

Figure 3. Decision curves showing the highest net benefit of the strategy "treat according to the prediction model" when the threshold probability is below 0.125 .



Discussion

We have developed a prediction model to estimate the probability of developing SSI after dermatological surgery in order to select patients who might benefit from antibiotic prophylaxis. The overall performance of the model is good with an AUC of 84.1 %. Net benefit analyses show that at threshold probabilities below 0.125, when one is willing to treat eight patients or more with antibiotics to prevent one SSI, the application of the prediction model is of added value compared with treating nobody with antibiotic prophylaxis. The strategy of prescribing antibiotic prophylaxis to all patients is inferior to treatment according to the prediction model over a range of plausible threshold probabilities.

A prediction model gives a predicted probability directly, but such probabilities must be compared against a threshold probability to aid clinical decision making. This threshold is chosen prior to application of the prediction model. In terms of antibiotic prophylaxis, there is always a trade-off between harm due to not adequately preventing a SSI in patients who would develop SSI and harm due to unnecessary treatment with antibiotics in patients who would not develop SSI. According to available literature, it is generally accepted that prophylaxis is not indicated when the risk of SSI is below 5%.(18-20) It is also widely accepted that contaminated wounds with a risk of SSI above the 20% should receive therapeutic antibiotics.(18)This suggests that there is consensus that the range of plausible threshold probabilities lies between 5% and 20% corresponding with willingness to treat at least five and at most twenty patient to prevent one SSI. However, patients and doctors may differ as how they rate the possible side effects of antibiotic treatment. While one doctor is willing to treat, for instance, seven patients in order to prevent one SSI, the other might be willing to treat fifteen. This is also dependent on the clinical scenario. It is imaginable that one is willing to treat a lower number of patients, who had experienced lots of side effects previously with antibiotic treatment, and a higher number of patients, who had a large reconstruction in the face where disturbance of wound healing would significantly impair the cosmetic outcome. The decision curves provide clinicians with an overview of the magnitude of the net benefit of acting according to the prediction model compared with other strategies at different threshold probabilities. The chosen threshold probability serves as cut-off value of predicted probability at which one decides to use antibiotic prophylaxis or not. When a threshold probability of 0.05 is chosen, patients with a predicted probability of 5 % (120 points according to the nomogram) or higher will be prescribed prophylaxis, whereas no prophylaxis will be given at predicted probabilities below 5%.

Net benefit analysis is a relatively simple decision analysis and is a method to assess the value of information provided by a prediction model expressing net benefit in units of true positive decisions. But an accurately predicted SSI does not mean that the SSI will indeed be prevented by means of prophylaxis if the intervention is not 100% effective. Effectiveness of the intervention is not accounted for by net benefit analysis.There are three trials in literature assessing the most effective method and optimal timing of antibiotic prophylaxis in dermatological surgery.(21-23) The first study performed by Bencini et al. randomized patients receiving skin surgery into four groups with group A not receiving prophylaxis, group B receiving antibiotics for three days after surgery, group C receiving antibiotic powder during surgery and group D receiving prophylaxis two days before and two days after surgery. The lowest percentage of SSI was seen in group D leading to the conclusion that prophylaxis should be given prior to surgery. (21) Two later studies confirmed this finding and have found that one single dose prior to incision (intramuscular cephazolin 1g 120min before surgery and oral cephalexin 2g 30-60min before surgery respectively) is the most effective method of reducing the incidence of SSI.(22, 23) This is in concordance with the recommendation in the most recent guideline on SSI prevention by the Centers for Disease Control and Prevention (CDC). (24) One recent Cochrane review studied the application of topical antibiotic after the wound has been closed once or several times until suture removal and concluded that it could possibly reduce the risk of SSI although no recommendation could be made due to small sample sizes.(25)

Potential limitations of the study need to be mentioned. We used a very strict definition of SSI, because antibiotic prophylaxis will only be beneficial in patients with a true SSI, and not prevent the development of postoperative redness and edema which is sometimes mistaken for a SSI. Unfortunately, cultures were not available for all patients who had a clinical suspicion of a SSI. Therefore, the incidence of culture confirmed SSI of 2.3% might be theoretically an underestimation of the reality. However, it is probably not much higher as the range of incidence reported in other studies that have examined the occurrence of SSI in dermatological surgery without antibiotics prophylaxis lies between 0.7% and 2.3%.(1, 4, 5, 8, 26, 27)

In addition, two of the predictors applied in the current model (defect size and type of closure) are not always predictable prior to surgery. Finally, the relative low number of patients with SSI and the single-centre setting are another limitation. External validation in other patient populations is necessary to validate the model.

In conclusion, the model for predicting the risk of SSI after dermatological surgery, that was developed and internally validated in this study, adequately identifies patients at risk for SSI prior to surgery. A decision curve analysis showed that the model is potentially useful when one is willing to treat more than eight patients with prophylaxis to avoid one infection. For those who prefer more restrictive use of antibiotic prophylaxis a default strategy of treating no patients at all is the best choice. External validation of the model is required before it can be widely applied in the clinical setting.

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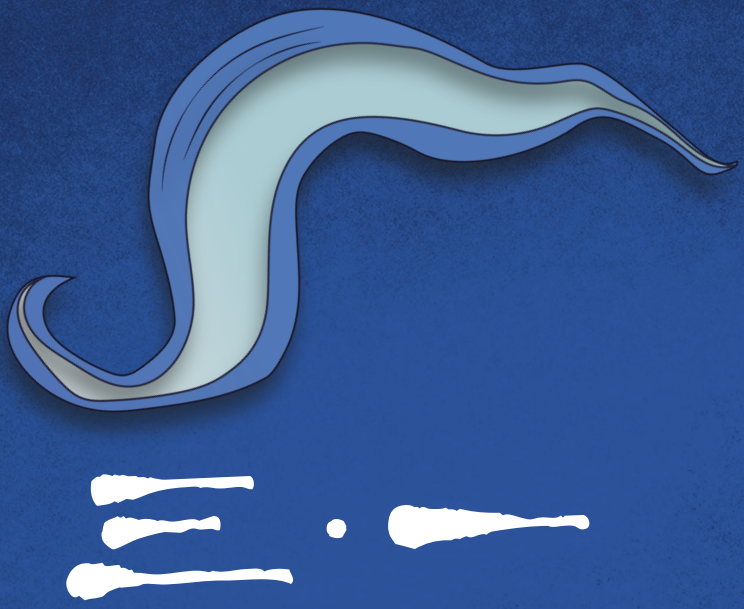
第三章

Outcome of dermatologic surgery



Reliability of the Patient and Observer Scar Assessment Scale (POSAS) and a 4-point scale in evaluating linear facial surgical scars

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Introduction

The incidence of skin cancer is on the rise over the past decades.(1-3) As surgery is the most frequently used treatment and skin cancer most often arises in the face, patients end up with permanent scars that may lead to functional and psychological distress.(4) Therefore, ensuring optimal cosmetic outcome after treatment has become a major concern.

In order to evaluate and improve aesthetic outcome for patients undergoing surgery, a reliable evaluation tool must be used. In daily practice the 4-point scale is frequently applied: assessing the appearance of scars as excellent, good, fair or poor.(5) This is a quick and easy tool that has proved to be excellently reproducible in non-surgical scars in the past.(6) However, its reliability in surgical scars following dermatologic surgery has never been studied. In addition, the4-point scale does not provide information on the factors distinctive for the cosmetic appearance of the scar. This information might be valuable to improve the aesthetic outcome for patients. In a research setting, the Patient and Observer Scar Assessment Scale (POSAS) is considered the most comprehensive and widely used scale for cosmetic evaluation.(7, 8)This scale allows both patients and physicians to give sub scores on characteristics that are assumed to be important in the assessment of scars. Another major advantage of this assessment tool, above the others available, is that it incorporates both the patient and the physician's perspective of the scar. When the POSAS was firstly developed, it was meant to evaluate burn scars.(9) Later on, it was validated for linear scars after breast surgery.(10) In 2005, one item was added to the original scale and more sub-classifications were added contributing to the current POSAS 2.0.(11)This version of the POSAS was tested in 100 different linear scars all over the body, but only ten were located on the face.

As the aesthetic results ofsurgery for skin cancer is especially relevant in the face. We compared the reliability of both scales for facial linear scars in the current study.(6) Secondly, we studied the influence of different scar characteristics on the general impression of the cosmetic outcome as reported by the patient and the physician.

Methods

Patients visiting the Outpatient Dermatology Clinics of the Maastricht University Medical Centre in the Netherlands were included if they had received surgical dermatological treatment in the face at least one month prior to the visit. Only linear scars were included. Patients with insufficient understanding of the Dutch language were excluded. Approval

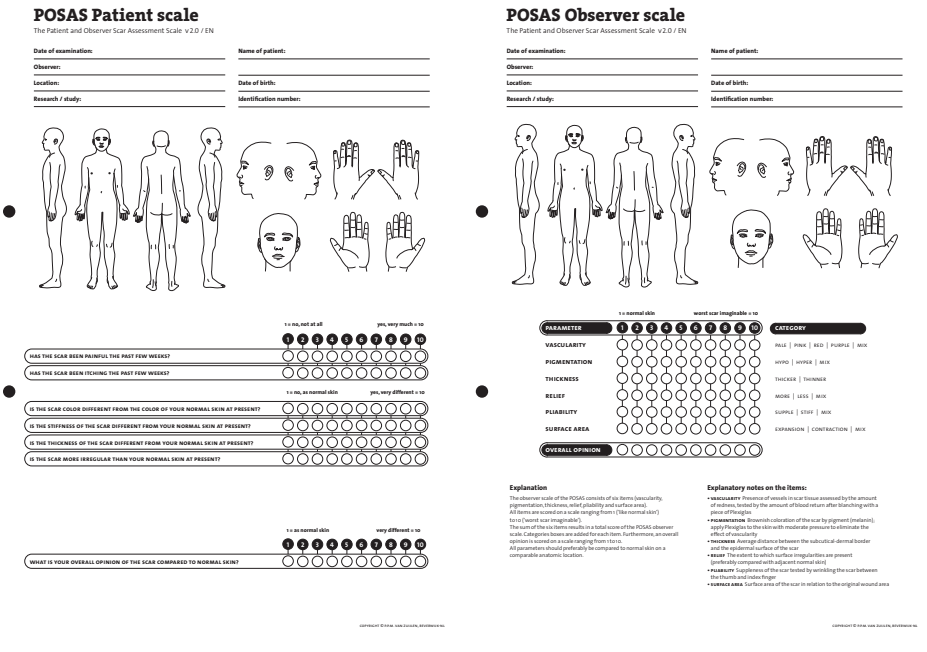
of the Ethics committee was obtained prior to the start of the study and all patients had given informed consent before participation.

Both the 4-point and POSAS scale were used for assessment of cosmetic appearance of scars and repeated assessments were collected. At first, the patient rated his or her scar according to the Dutch Patient Scar Assessment Scale (PSAS) version 2.0 (Fig.1) using a 1 to 10 scale on six aspects: colour, pliability, thickness, relief, itching and pain. This resulted in a total score of 6-60 with a higher score indicating a worse scar. In addition, the patient gave an overall opinion of the scar on a scale of 1 to 10 with 10 indicating the worst scar imaginable. Patients were asked to assess their own scar during the visit and again two weeks later. The second assessment was returned by mail. The interval of two weeks is chosen as it was long enough for individuals not to recall their scores and short enough for changes in the scar couldn't have occurred.(12)

Secondly, scars were assessed by three independent observers consisting of a dermatologist (DE), a dermatology resident(RE) and an intern(IN). The different observers assessed the scar on the same day and were blinded to each other's observations. The 4-point scale was rated before completion of the Dutch Observer Scar Assessment Scale (OSAS) as the examination of the individual scar characteristics might influence the overall opinion.

The 4-point scale classifies scars as "excellent" (no obvious scarring, atrophy or induration and slight or no redness or change in pigmentation compared with adjacent skin), "good" (no obvisou scarring, atrophy or induration and/or moderate redness or increase in pigmentation compared with adjacent skin, "fair" (slight to moderate occurrence of scarring, atrophy, induration and/or significant redness or increase in pigmentation compared with adjacent skin) or "poor" (extensive occurrence of scarring, atrophy, induration and/or redness or increase in pigmentation compared with adjacent skin). Assessments with the OSAS were based on vascularity, pigmentation, pliability, thickness, relief and surface area. A Plexiglas was pressed against the scar and adjacent skinto distinguish between redness and pigmentation.(13)Each variable was scored 1-10 with 1 resembling normal skin and 10 the worst scar imaginable. Sub-classification was possible for each item, for example to distinguish hyper- from hypopigmentation. The total OSAS score was the sum of all six items. In addition, an overall opinion was given on a scale of 1 to 10. Finally, the observer could add remarks on aspects of the scar which he or she felt not adequately addressed by the OSAS.

Figure 1. The Patient and Observer Scar Assessment Scale.



Statistical analysis

Reliability was quantified using the intra-class correlation coefficient (ICC) with corresponding 95% confidence intervals for both the 4-point scale and the OSAS. This reliability parameter relates the variability from repeated assessments (measurement error) to the variability between patients and expresses how well patients can be distinguished from each other despite measurement error. If the variability between patients is high compared to variability between assessments the ICC approaches 1. If the variability between assessments is much higher than the variability between patients the ICC approaches 0.The two-way random effect model with absolute agreement was used to calculate the ICC and assessed the reliability of single scores by one observer (single measurement) and of average scores from three observers (average measurement). The sample size calculation was aimed at obtaining a 95% confidence interval with acceptable width (± 0.1) around the estimated ICC. Based on the literature an ICC of at least 0.8 was expected. With two measurements per patient (test-retest) the required sample size was 50 and with three measurements (three observers) the required sample size was 35.(14) Linear multivariate regression analyses were performed to evaluate the impact of each aspect on the overall opinion. The dependent variable was the overall opinion as rated by the observer or patient and the independent variables were the scores of the individ-

ual scar characteristics. The regression coefficient with the corresponding 95% CI were calculated. A p-value ≤0.05 was considered to be statistically significant. All data were analysed using SPSS, version 20.0.

Results

Fifty scars were assessed in 50 patients (26 males and 24 females). The mean age of the patient was 66 years (range 34-91 years). The average age of the scar was 55 months (range 1-216 months). After two weeks 48 patients returned their second PSAS, however, some questions remained unanswered.

Overall, patients gave their scar a mean score of 3.8 (±2.5) on the first assessment and 3.6 (±2.2) two weeks later. The mean total PSAS was 13.0 (±8.2) on the first assessment and 15.5 (±9.8) on the second assessment. The mean overall opinion of the scar as rated by the observers in the OSAS was 3.7 (±2.0, DE), 4.2 (±1.9, RE) and 3.4 (±1.6, IN). The mean total OSAS score was 11.6 (±4.7, DE), 14.9 (±5.1, RE) and 15.7 (±5.2, IN) for the three observers. The ratings on the 4-point scale by the observers are shown in Table 1. The most common remark added was the presence of "railroad track" suture marks which clearly influenced the appearance of the scar.

Table 1. Ratings on the 4-point scale for all observers.

	DE	RE	IN
Excellent	12 (24%)	8 (16%)	8 (16%)
Good	19 (38%)	14 (28%)	24 (48%)
Average	18 (36%)	26 (52%)	16 (32%)
Bad	1 (2%)	2 (4%)	1 (2%)

DE: dermatologist, RE: resident, IN: intern.

The ICCs of the PSAS and its individual items for single and two measurements (test and re-test after two weeks) are shown in Table 2. For the patient, the itchiness and stiffness had a higher ICC than other items of the scale.

Table 3 summarises all ICCs for single and multiple observers. The 4-point scale and the overall opinion scores of the OSAS showed a higher ICC than the scores on individual items or the sum of those (total OSAS score).

Table 2. ICCs of single and multiple assessments regarding to the PSAS.

	N	Single assessment (95%CI)	Multiple assessments (95%CI)
Pain	47	0.411 (0.140-0.624)	0.583 (0.246-0.769)
Itch	48	0.868 (0.777-0.924)	0.930 (0.875-0.960)
Colour	47	0.412 (0.153-0.621)	0.584 (0.266-0.766)
Stiffness	48	0.786 (0.646-0.875)	0.880 (0.785-0.933)
Thickness	47	0.500 (0.242-0.690)	0.667 (0.390-0.817)
Surface	48	0.555 (0.323-0.724)	0.714 (0.488-0.840)
Total PSAS	45	0.736 (0.524-0.854)	0.848 (0.688-0.921)
Overall opinion	37	0.796 (0.640-0.889)	0.886 (0.780-0.941)

ICC: Intra-class correlation coefficient, PSAS: Patient Scar Assessment Scale, CI: Confidence Interval.

Table 3. ICCs of single and multiple observers regarding to the 4-point scale and the OSAS.

	N	Single observer (95%CI)	Multiple observers (95%CI)
Vascularity	50	0.377 (0.205-0.549)	0.645 (0.437-0.785)
Pigmentation	50	0.380 (0.204-0.554)	0.648 (0.434-0.789)
Thickness	49	0.410 (0.220-0.588)	0.676 (0.459-0.810)
Relief	50	0.144 (0.002-0.315)	0.335 (0.006-0.580)
Pliability	50	0.396 (0.215-0.571)	0.663 (0.451-0.800)
Surface area	50	0.301 (0.118-0.487)	0.563 (0.287-0.740)
Total OSAS	49	0.546 (0.287-0.726)	0.783 (0.547-0.888)
Overall opinion	50	0.652 (0.502-0.773)	0.849 (0.752-0.911)
4-point scale	49	0.602 (0.447-0.734)	0.819 (0.708-0.892)

ICC: Intra-class correlation coefficient, OSAS: Observer Scar Assessment Scale, CI: Confidence Interval.

The results of the linear multivariate regression analyses are shown in Table 4. For the patients, colour had the biggest impact on the total PSAS score. Relief was also important but did not reach a statistically significant level. For observers, the importance of the different aspects varied: pigmentation and colour were both of great importance to the overall opinion. One exception was the assessment made by the intern, which was not influenced significantly by pigmentation of the scar. For one of the three observers pliability had great impact on the overall opinion and for another observer the thickness of the scar was of great importance.

Table 4.The regression coefficients with the corresponding 95% CI and p-values for the scores in individual characteristics of the OSAS and the PSAS

	Dermatologist			
	B	Lower 95%CI	upper 95% CI	p
Vascularity	0.545	0.164	0.925	0.01
Pigmentation	0.629	0.333	0.926	<0.01
Thickness	0.015	-0.595	0.626	0.96
Relief	0.162	-0.362	0.686	0.54
Pliability	0.738	-0.061	1.538	0.07
Surface	-0.591	-1.248	0.066	0.08
	Patient			
	B	Lower 95%CI	upper 95% CI	p
Pain	0.192	-0.703	1.087	0.67
Itching	0.131	-0.528	0.790	0.69
Colour	0.485	0.106	0.865	0.01
Pliability	0.102	-0.657	0.861	0.79
Thickness	-0.230	-1.146	0.687	0.62
Relief	0.509	-0.176	1.195	0.14

CI: Confidence Interval, OSAS: Observer Scar Assessment Scale, PSAS: Patient Scar Assessment Scale.

Discussion

The overall opinion of the POSAS and the 4-point scale were associated with higher reliability compared to the total POSAS score or sub-items of the POSAS score. Furthermore, we have shown that observers do not seem to weight individual scar characteristics equally to arrive to an overall opinion, which challenges the assumption that calculating a total POSAS score by summing of the scores on the individual items is a valid approach.

ICCs on the 4-point scale and the overall opinion of the POSAS score were consistently higher than the ICC for the total OSAS score. The reliability for both scales increases when average results of multiple measurements are used for cosmetic assessment. Averaging the results of two measurements by patients and three measurements by observers gives more stable results and assessment becomes less dependent on the method used for evaluating cosmetic outcome. This is in line with earlier findings for non-surgical facial scars.(6)

Resident				Intern			
B	Lower 95%CI	upper 95% CI	p	B	Lower 95%CI	upper 95% CI	P
0.702	0.408	0.997	<0.01	0.299	0.014	0.584	0.04
0.373	0.097	0.649	0.01	0.145	-0.167	0.456	0.35
0.399	0.085	0.713	0.01	0.251	-0.046	0.547	0.10
0.090	-0.218	0.398	0.56	0.178	-0.114	0.471	0.23
-0.063	-0.342	0.215	0.65	0.261	-0.043	0.565	0.09
0.264	-0.09	0.618	0.14	0.224	-0.027	0.476	0.08

Both investigated scales have their own cons and pros. The 4-point scale is easy to use and has proved to be reliable. However, it lacks specific information on individual scar characteristics. The POSAS, on the other hand, do obligate observers to explicitly assess individual scar characteristics that determine the cosmetic outcome. This approach is intuitively appealing, because measurements are performed in a more standardized way, but the scores on individual POSAS sub items showed great variability among observers. Furthermore, the underlying assumption that scores on individual items can be summed to get a total POSAS score is challenged by the findings from the multivariate regression analyses. These findings suggest that observers attach different weights to items to arrive to an overall opinion. This overall opinion is also part of the POSAS questionnaire and when this overall opinion is formed in a different way than the total POSAS score, discrepancies may arise making interpretation difficult. An Additional disadvantage of the current scoring system is that the presence of "railroad track" suture marks and "dog ear" formation on the edges of the scar are not examined, although they tended to increase the score on overall opinion In a comprehensive evaluation of scars, those items need to be incorporated in the grading system.

There are some limitations of the study. First of all, the three observers who assessed the scars varied in their levels of experience which could have contributed to lower inter-observer correlation rates on different items. However, this reflects the clinical setting in which scars are evaluated and does not affect the comparison between different scales. Of note, all observers have read and discussed the instructions of the two scales prior to assessment and reached consensus on the way of evaluation. Secondly, at the second assessment not all items were completed by all the patients who returned their questionnaire, limiting the sample size for overall opinion of the PSAS. Apparently, for some patients, the PSAS is too difficult to complete.

Our findings raise the question whether the use of the POSAS score for assessment of cosmetic outcome for linear scars in the face has additional value when compared to the 4-point scale and the POSAS overall opinion score. The latter tools are easy and quick to use and are not inferior in their ability to discriminate between patients with good and poor cosmetic outcome. However, Both scales have their limitations and the findings point to the need for improved and more optimal scales for cosmetic evaluation of linear scars.

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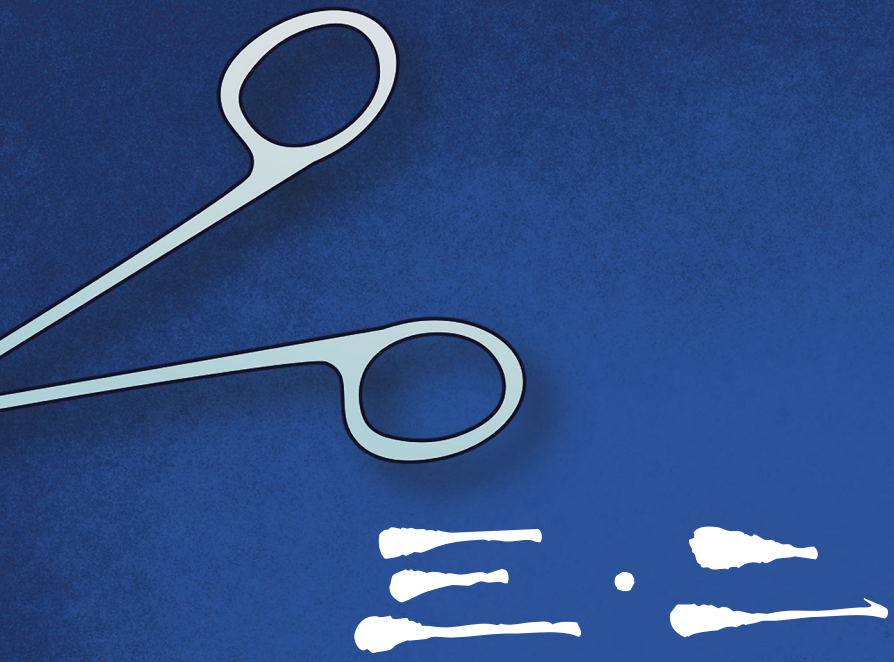

Aesthetic outcome and complications of simple interrupted versus running subcuticular sutures in facial surgery: A randomized controlled trial

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Introduction

Due to the rise in the incidence of skin cancer, facial surgery is performed with increasing frequency by dermatologists and plastic surgeons all over the world. Simple interrupted sutures (SIS) and running subcuticular sutures (RSS) are frequently used in dermatologic surgery. The suturing technique may influence the final aesthetic outcome. Currently, due to a lack of evidence, the choice of suturing technique is largely dependent on the surgeon's preference. Two earlier original studies have looked into this subject and found no difference in cosmetic outcome of wounds closed by SIS or RSS.(1, 2) However, long term evaluation is lacking in both studies. In addition, the occurrence of postoperative complications should also be taken into account when comparing both techniques. Earlier research on wounds following cardiac surgery suggested that RSS was associated with more infections than SIS although this was not the case in wound healing after appendectomies.(3-5) Literature addressing this topic in dermatologic surgery is not available. The goal of this study was to compare the long term aesthetic outcome and incidence of complications of facial wounds closed with SIS and RSS.

Method

Patients

This study was a randomized controlled, multi-center trial. Patients were recruited from the department of Dermatology of the Maastricht University Medical Center, the department of Dermatology of Catharina Hospital Eindhoven and the department of Plastic surgery of Zuyderland Medical Center, all situated in the Netherlands.

Adult patients receiving conventional excision or Mohs micrographic surgery (MMS) on the face with an expected primary closure of a defect larger than 4 millimeters were approached for participation. One lesion per patient was included. Excluded were patients with tumors located on the ears, nose, eyelids or mucosal parts of the lips and patients with hypertrophic or keloid scars in the past. The study protocol conformed to the guidelines of the Declaration of Helsinki and was approved by the Medical Ethical Committee of Maastricht University. All patients gave written informed consent prior to inclusion.

Patients were randomized into two groups: one receiving SIS and the other RSS. Randomization occurred by a computer generated list using random permuted blocks of six and was stratified by hospital. The allocation was generated and concealed until interventions were assigned, by a secretary not involved in the trial.

Interventions

In all procedures, local anesthesia was achieved with lidocaine hydrochloride 1% and epinephrine 1:100,000. In MMS, additional long lasting local anesthesia was achieved with bupivacaine 0.5%. All wounds were sutured in layers: for tension relieving deep sutures, absorbable synthetic braided (Vicryl®) or monofilament (Monocryl®, Caprosyn® or Biosyn®) material was used. The skin was closed with non-absorbable monofilament sutures (Ethilon® or Surgipro®). The brand of suturing material was dependent upon availability at the department. Sutured wounds were supported by adhesive closure strips and a clean pressure dressing. No occlusive dressing was used. Patients were advised to keep the wound dry until suture removal. No antibiotic prophylaxis was prescribed in the studied population.

Both SIS and RSS were removed one week post surgery. A high SPF sunscreen (Daylong Actinica®, Galderma S.A. Switzerland) was offered to all patients to be applied on the scar daily for three months after suture removal, to standardize postsurgical cosmetics usage. Patients were advised not to apply any other medication or cosmetics on the scar. None of the scars received any revision during the 12 month study period.

Outcome measures

The primary outcome in this study was the aesthetic outcome at 12 months after surgery as assessed by the overall impression on the Dutch Patient and Observer Scar Assessment Scale (POSAS) version 2.0. Secondary outcome measures were the incidence of complications and scores according to alternative methods for assessment of cosmetic outcome including the 4-point scale (excellent/good/fair/bad) and measurement with a colorimeter.

The cosmetic result was evaluated at three and twelve months post surgery. The patient completed the assessment according to the Patient Scar Assessment Scale (PSAS) and the 4-point scale. A researcher, blinded to the suturing technique, assessed the scars in person using the Observer Scar Assessment Scale (OSAS) and the 4-point scale.

The PSAS contained a 1 to 10 scale on six aspects: color, pliability, thickness, relief, itching and pain. Assessments with the OSAS were also based on six items including vascularity, pigmentation, pliability, thickness, relief and surface area. Each variable was scored 1-10 with 1 resembling normal skin and 10 the worst scar imaginable. The total PSAS and OSAS scores were calculated by summing the scores on all six items. The total score can vary from 6-60 with a higher score indicating a worse scar. In addition, both patients and observers gave an overall opinion of the scar on a scale of 1 to 10 with 10 indicating the worst scar imaginable.

The 4-point scale classified scars as "excellent" (no obvious scarring, atrophy or induration and slight or no redness or change in pigmentation compared with adjacent skin), "good" (no obvious scarring, atrophy or induration and/or moderate redness or increase in pigmentation compared with adjacent skin), "fair" (slight to moderate occurrence of scarring, atrophy, induration and/or significant redness or increase in pigmentation compared with adjacent skin) or "poor" (extensive occurrence of scarring, atrophy, induration and/or redness or increase in pigmentation compared with adjacent skin).

In addition to the two scales, the observer marked whether suture marks were present or absent.(6) Furthermore, an objective assessment of the scar was made with a colorimeter at 12 months post surgery (Minolta Chromameter CR-400, Minolta Camera co., Ltd) applying measure principles established by the International Commission on Illumination.(7, 8) The outcome was expressed in three parameters: L* which expressed the lightness of the scar with 0 being black and 100 being perfectly white, a* which indicated the erythema of the scar (positive values indicated red and negative green), and b* which indicated the pigmentation of the scar (positive values indicated yellow and negative blue). Two measurements were made consecutively and the average was reported. To compare the color of the scar with patient's own skin color, normal skin adjacent to the scar was measured. Before the measurements, the colorimeter was calibrated to a standard white plate (Minolta Camera co., Ltd).

The following complications were recorded: hemorrhage, surgical site infection, wound dehiscence and hyper-or hypoesthesia. At one week, 3 months and 12 months post surgery, patients were questioned about complications and their files were checked for verification. Hemorrhage had to occur within seven days post surgery and required pressure dressing, coagulation or suturing. Surgical site infection had to occur within 30 days and required incision/ drainage or antibiotics. Dehiscence of the wound was recorded by the research assistant at suture removal.

Statistical analysis

In our earlier study, a mean score of 3.7 with a standard deviation of 1.6 was observed on the overall opinion of the OSAS.(6) To enable detection of a clinically relevant difference of minimal 1 point with a power of 90% and a significance level of 5% (two-sided), a total of 108 patients were required. An allocation ratio of 1:1 indicated recruitment of 54 per group. Inclusion of a minimum of 120 patients (60 per group) was planned to account for a loss-to-follow-up of 10%.

Differences between randomized groups were tested for statistical significance using the Chi-square test for categorical variables. For continuous variables the t-test for indepen-

dent samples was used for normally distributed variables or the Mann-Whitney U test for not-normally distributed variables. Both intention-to-treat (ITT) and per-protocol (PP) analyses were performed. P-values ≤0.05 were considered to indicate statistical significance. Analysis was performed using IBM SPSS Statistics version 20.0.0.1.

Results

From 1st April 2014 to 1st April 2015, 204 patients met the inclusion criteria (Figure 1) and 142 consented to participate. Sixty-two patients did not want to participate mainly because of a preference for one of the suturing techniques or refusal to make the extra visits to the hospital at 3 and 12 months as required by the study. Of the 142 randomized patients 73 were assigned to SIS and 69 RSS.

Baseline characteristics are shown in Table I. All patients assigned to the SIS group received SIS. Three of them received a re-excision and the wounds were closed again with SIS. Of the 69 patients assigned to the RSS group, 61 received RSS. The other 8 patients received SIS because adequate wound approximation could not be achieved with RSS. Five of these patients had a tumor located on the cheek; two had a tumor located on the chin and one on the forehead. In addition, two of the 61 patients who received RSS initially, received SIS sutures later due to wound dehiscence and re-excision. Thirteen patients were lost to follow-up in the studied period.

Few examples of the scars with their corresponding POSAS scores are shown in Figure 2.

The cosmetic results at twelve months after surgery are shown in table II. The median scores on the overall opinion of the OSAS (3.0) and PSAS (2.0) were identical in both groups. Total OSAS (9.0 for SIS and 10.0 for RSS) and PSAS scores (8.0 for both groups) were also very similar. According to the 4-point scale, the distribution of the scores showed no significant differences between SIS and RSS although a slightly greater proportion of patients and observers rated the scar as excellent/good in the SIS group. The results of the ITT analyses were analogous to those of the PP analyses. In a subgroup of patients who received SIS (16.4% ITT and 16.0% PP) a permanent suture mark was left. Permanent suture marks were more frequently observed in patients with Fitzpatrick skin type I (23.1% vs. 5.3%) and in patients with operations done in the frontal area (30.8% vs. 16.4%). When comparing the subgroup of patients receiving SIS with visible suture marks with those without, we observed a higher median scores of the observer's overall impression (4.0 vs. 2.0) and total OSAS (12.0 vs. 8.0). On the other hand, patients did not score their scars differently whether or not suture marks were present. In the SIS group,

color difference between normal skin and scar measured by the colorimeter had a mean value of-0.4 (SD 5.3) on the L* parameter (black/whiteness), 1.4 (SD 2.9) on the a* parameter (erythema) and -4.0 (SD 2.9) on the b* parameter (pigmentation). These values were -1.3 (SD 3.4), 1.1 (SD 2.9) respectively -3.8 (SD 2.5) in the RSS group.

Figure 1. Flow chart of inclusion and randomization. SIS: simple interrupted suture. RSS: running subcuticular suture.

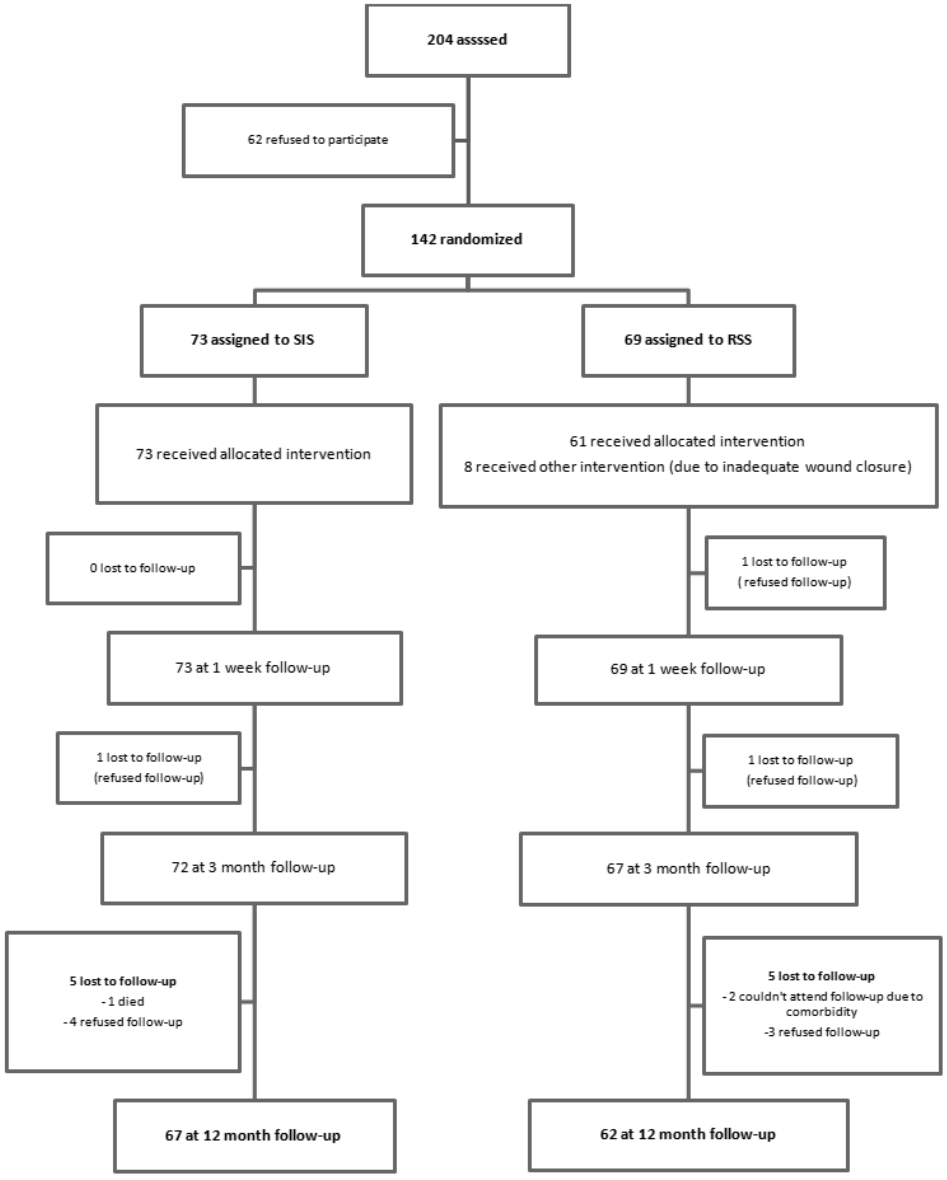
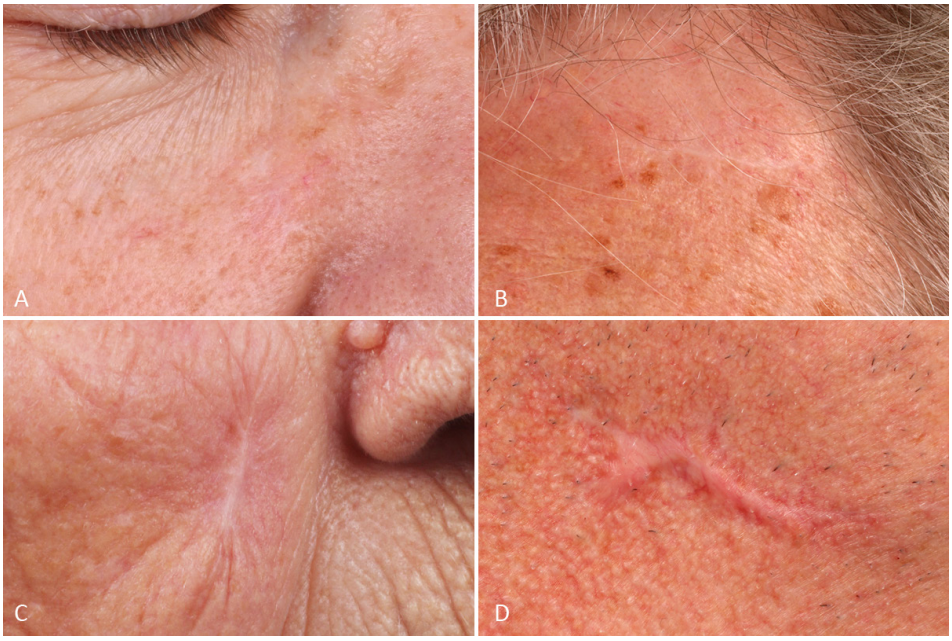


Table I. Baseline characteristics according to randomization.

		SIS group		RSS group	
Gender	Male	45	61.6%	47	68.1%
	Female	28	38.4%	22	31.9%
Age (mean ±SD)		67 (±12.5)		67 (±15.0)	
Skin type	I	7	9.6%	3	4.3%
	II	60	82.2%	59	85.5%
	III	6	8.2%	4	5.8%
	IV	0	0.0%	2	2.9%
Immunosuppression	Yes	4	5.5%	3	4.3%
	No	69	94.5%	65	94.2%
Anticoagulants	Yes	27	37.0%	28	40.6%
	No	46	63.0%	40	58.0%
Sun exposure*	Chronic	27	37.0%	28	40.6%
	Intermittent	33	45.2%	28	40.6%
	Seldom	13	17.8%	11	15.9%
Smoking	Active	12	16.4%	13	18.8%
	Quit	42	57.5%	38	55.1%
	Never	19	26.0%	17	24.6%
Alcohol	Regularly	51	69.9%	45	65.2%
	Occasionally	7	9.6%	10	14.5%
	Never	15	20.5%	13	18.8%
Tumor size (mean ±SD)	Length (in millimeter)	7.2 (±3.9)		8.0 (±3.8)	
	Width (in millimeter)	6.6 (±3.5)		7.4 (±3.5)	
Type of tumor	Malignant	53	72.6%	53	76.8%
	Benign/pre-malignant	20	27.4%	16	23.2%
Location	Frontal	18	24.7%	9	13.0%
	Temporal	20	27.4%	18	26.1%
	Cheek	30	41.1%	30	43.5%
	Peri-occular	1	1.4%	4	5.8%
	Peri-oral	4	5.5%	8	11.6%
Specialty	Dermatology	55	75.3%	52	75.4%
	Plastic surgery	18	24.7%	17	24.6%
Total		73		69	

SIS: simple interrupted suture. RSS: running subcuticular suture.
SD: standard deviation.
*sun exposure was defined as chronic if one had outdoor work or had lived in tropical area's for at least five years, as intermittent if one had indoor work but spend vacations out in the sun and as seldom if one rarely sunbath.

Figure 2. Examples of scars at 12 months and their corresponding POSAS scores.



2A: 55-yo female, right cheek.
OSAS: overall opinion 1, total score 7. PSAS: overall opinion 2, total score 9.
2B: 72-yo male, left frontal area.
OSAS: overall opinion 3, total score 10. PSAS: overall opinion 1, total score 6.
2C: 79-yo female, right cheek.
OSAS: overall opinion 4, total score 11. PSAS: overall opinion 3, total score 12.
2D: 46-yo male, chin.
OSAS: overall opinion 8, total score 20. PSAS: overall opinion 8, total score 35.
yo: year old, OSAS: Observer Scar Assessment Scale, PSAS: Patient Scar Assessment Scale.

Table III showed the scores at three months after surgery. No statistically significant differences between the SIS and RSS group were observed. The scores on cosmetic outcome at twelve months were slightly better than at three months post surgery indicating improvements of the scars over time.

Complications of both suturing techniques were presented in table IV. The frequency of hemorrhage, infection or wound dehiscence was similar in both groups. The RSS group did tend to have more patients with hyper-or hypoesthesia of their scars at 12 months (12.9% ITT, 11.1% PP) compared with the SIS group (4.5% ITT, 6.7%PP), although not statistically significant. Two patients developed a hypertrophic scar, one in each group.

Table II. Cosmetic results at 12 months.

		Intention to treat		
		SIS	RSS	p
Observer				
Overall opinion (median + range)		3.0 (1-8)	3.0 (1-8)	0.19
Total OSAS (median + range)		9.0 (6-30)	10.0 (6-23)	0.12
4-point scale (n/%)				0.58
	Excellent	25/67 (37.3%)	19/62 (30.6%)	
	Good	32/67 (47.8%)	28/62 (45.2%)	
	Average	9/67 (13.4%)	14/62 (22.6%)	
	Poor	1/67 (1.5%)	1/62 (1.6%)	
Patient				
Overall opinion (median + range)		2.0 (1-7)	2.0 (1-8)	0.65
Total PSAS(median +range)		8.0 (6-34)	8.0 (6-47)	0.13
4-point scale (n/%)#				0.15
	Excellent	17/66 (25.8%)	19/61 (31.1%)	
	Good	46/66 (69.7%)	33/61 (54.1%)	
	Average	3/66 (4.5%)	8/61 (13.1%)	
	Poor	0/66 (0.0%)	1/61 (1.6%)	
Difference between scar and normal skin measured by the colorimeter(mean +SD)				
L*		-0.4 (5.3)	-1.3 (3.4)	0.24
A*		1.4 (2.9)	1.1 (2.9)	0.83
B*		-4.0 (2.9)	-3.8 (2.5)	0.63

SIS: simple interrupted suture. RSS: running subcuticular suture.
SD: standard deviation.
For two patients the assessment of the scar was only made by the researcher and not the patient.

		Per protocol		
		SIS	RSS	p
Observer				
Overall opinion (median + range)		3.0 (1-8)	3.0 (1-8)	0.41
Total OSAS (median + range)		9.0 (6-23)	10.0 (6-22)	0.55
4-point scale (n/%)				0.99
	Excellent	26/75 (34.7%)	18/54 (33.3%)	
	Good	35/75 (46.7%)	25/54 (46.3%)	
	Average	13/75 (17.3%)	10/54 (18.5%)	
	Poor	1/75 (1.3%)	1/54 (1.9%)	
Patient				
Overall opinion (median + range)		2.0 (1-7)	2.0 (1-8)	0.73
Total PSAS(median +range)		9.0 (6-38)	8.0 (6-47)	0.77
4-point scale (n/%)#				0.12
	Excellent	17/74 (23.0%)	19/53 (35.8%)	
	Good	52/74 (70.3%)	27/53 (50.9%)	
	Average	5/74 (6.8%)	6/53 (11.3%)	
	Poor	0/74 (0.0%)	1/53 (1.9%)	
Difference between scar and normal skin measured by the colorimeter(mean +SD)				
L*		-0.6 (5.2)	-1.1 (3.4)	0.25
A*		1.4 (2.8)	1.1 (3.0)	0.68
B*		-4.0 (2.9)	-3.8 (2.6)	0.84

One patient in the SIS group was diagnosed with progressive dementia and could not make the assessment adequately; one patient in the RSS group was admitted to hospital at the time of assessment and was not willing to fill in the questionnaire.

Table III. Cosmetic results at 3 months.

		Intention to treat		
		SIS	RSS	p
Observer				
Overall opinion (median + range)		3.5 (1-8)	4.0 (1-8)	0.60
Total OSAS (median + range)		11.0 (6-23)	12.0 (6-22)	0.29
4-point scale (n/%)				0.78
	Excellent	17/72(23.6%)	12/67 (17.9%)	
	Good	30/72 (41.7%)	32/67 (47.8%)	
	Average	23/72 (31.9%)	22/67 (32.8%)	
	Poor	2/72 (2.8%)	1/67 (1.5%)	
Patient				
Overall opinion (median + range)		2.0 (1-8)	2.0 (1-8)	0.52
Total PSAS (median +range)		10.0 (6-32)	12.0 (6-47)	0.51
4-point scale (n/%)				0.78
	Excellent	16/72 (22.2%)	15/67 (22.4%)	
	Good	49/72 (68.1%)	43/67 (64.2%)	
	Average	7/72 (9.7%)	9/67 (13.4%)	
	Poor	0/72 (0.0%)	0/67 (0.0%)	

SIS: simple interrupted suture. RSS: running subcuticular suture.
SD: standard deviation.

Table IV complications in both groups.

	Intention to treat		
	SIS	RSS	p
Hemorrhage	4/73 (5.5%)	3/68 (4.4%)	0.77
Infection	1/73 (1.4%)	2/68 (2.9%)	0.52
Wound dehiscence	4/73 (5.5%)	4/68 (4.4%)	0.77
Hyper-or hypoesthesia at 3 months	6/72 (8.3%)	5/67 (7.5%)	0.85
Hyper-or hypoesthesia at 12 months	3/67 (4.5%)	8/62 (12.9%)	0.09

SIS: simple interrupted suture. RSS: running subcuticular suture.

		Per protocol		
		SIS	RSS	p
Observer				
Overall opinion (median + range)		4.0 (1-8)	3.0 (1-8)	0.64
Total OSAS (median + range)		11.0 (6-30)	11.5 (6-23)	0.56
4-point scale (n/%)				0.55
	Excellent	18/81 (22.2%)	11/58 (19.0%)	
	Good	32/81 (39.5%)	30/58 (51.7%)	
	Average	29/81 (35.8%)	16/58 (27.6%)	
	Poor	2/81 (2.5%)	1/58 (1.7%)	
Patient				
Overall opinion (median + range)		2.0 (1-8)	2.0 (1-8)	0.08
Total PSAS (median +range)		12.0 (6-35)	11.5 (6-47)	0.69
4-point scale (n/%)				0.68
	Excellent	16/81 (19.8%)	15/58 (25.9%)	
	Good	55/81 (67.9%)	37/58 (63.8%)	
	Average	10/81 (12.3%)	6/58 (10.3%)	
	Poor	0/81 (0.0%)	0/58 (0.0%)	

	Per protocol		
	SIS	RSS	p
Hemorrhage	4/80 (5.0%)	3/61 (4.9%)	0.98
Infection	1/80 (1.3%)	2/61 (3.3%)	0.41
Wound dehiscence	4/80 (5.0%)	3/61 (4.9%)	0.98
Hyper-or hypoesthesia at 3 months	8/81 (9.9%)	3/58 (5.2%)	0.31
Hyper-or hypoesthesia at 12 months	5/75(6.7%)	6/54 (11.1%)	0.37

Discussion

This randomized controlled trial showed that 12 months after surgery, both the observer and the patient rated the aesthetic outcome of SIS and RSS equally. RSS was associated with a slight higher rate of hyper-or hypoesthesia, while other postoperative complications occurred at a similar frequency in both groups.

Our study confirmed the results of two earlier studies, finding a similar aesthetic outcome of both suturing techniques.(1, 2) Orozco-Covarrubias et al. compared the cosmetic result of facial linear scars using a self developed 3-point scale (excellent, good or poor) while Blouin et al. applied the 100-point visual analog scale, 5-point Stony Brook Scar evaluation scale and 6-point wound evaluation scale. Follow-up in these studies was limited to three months and six months, respectively. In addition to the evidence already available, we have shown that this finding is still persistent at long term follow-up assessed by POSAS, 4-point scale and the colorimeter. Although in our study a slightly larger proportion of the scars were rated as excellent/good on the 4-point scale in the SIS group by both the observer and the patient, this difference was not statistically significant.

The evaluation of aesthetic outcome has always been challenging, as no gold standard exist. Patients tended to evaluate their scars as better than the observers in this study, indicated by the lower median scores on overall opinion and a lower total score of the PSAS compared with the OSAS. In addition, several earlier studies have shown that patients weight various aspects of the scar quite differently than the observers.(6, 9-11) For example, itch and pain can negatively contribute to the overall opinion of the patient while these factors are not visible to the observer. While most assessment scales are designed for an objective appraisal of the aesthetic appearance of the scar by the observer, the patient's perspective (including aspects which are not strictly aesthetic) is also of great importance.(12)

Color is one of the important characteristics of scars.(6, 9, 10) According to the POSAS, color is assessed as a whole by the patient and as pigmentation and vascularity by the observer. A more objective method to assess the different aspects of color is the Minolta Chromameter as shown in an earlier study.(13) No color differences were observed between both suturing techniques as measured with the colorimeter at 12 months post surgery.

Permanent suture marks are one of the reasons some surgeons prefer RSS in facial surgery.(14) We observed persistence of suture marks in 16% of the patients in the SIS group. While observers consider scars with suture marks less cosmetically acceptable than those without, patients did not score their scar differently whether or not suture marks were

present. Apparently, patients regard other aspects of the scar as far more important than the presence of suture marks. This could be subjective and dependent upon the personal background and culture of the patient. Although incorporated in different scar assessment scales such as the SBSES(15) and SCAR scale(16), the clinical relevance of suture marks for patients remains debatable. It has to be said, that despite the persistence of suture marks in a certain subgroup of patients receiving SIS, the overall cosmetic appearance of SIS and RSS were equally rated. This could indicate that SIS might have even resulted in better cosmesis if suture marks were totally absent.

This study is the first randomized controlled trial evaluating postoperative complications of RSS and SIS in facial surgery. A recent Cochrane review concluded that superficial wound dehiscence might be reduced by RSS although this was based on limited evidence and studies of non-dermatological surgery such as abdominal and open-heart surgery.(17) We have found similar proportions of patients who have experienced wound dehiscence, infection or hemorrhage in both groups while more dysesthesia occurred in the RSS group. According to literature, the use of occlusive dressing could promote wound healing and reduce complications.(18) We did not apply an occlusive dressing in the current study.

Several limitations of this study need to be mentioned. First, one single observer did all the assessments of cosmetic outcome. Although the same observer evaluated all scars in both groups at 12 months, the adoption of multiple observers would have increased the reliability of the assessment and might increase the potential to detect subtle differences between the suturing techniques. However, objective measurements on the color aspect of the scars with a colorimeter did not reveal differences. Second, treatment crossover occurred in eight of the patients from the RSS group. To assess the impact of these crossovers, PP analysis was performed and showed similar results as the ITT analysis. Finally, due to availability in different hospitals, various brands of suture materials were used. Ideally, one and the same suture material should be applied, but this was not feasible. Therefore, stratification by hospital was used to ensure an even distribution of types of suture material in both groups.

In conclusion, this randomized controlled trial showed similar aesthetic outcome of simple interrupted and running subcuticular sutures in facial dermatologic surgery. Hyper-or hypoesthesia occurred more frequently in running subcuticular sutures, possibly favoring the choice for simple interrupted sutures.

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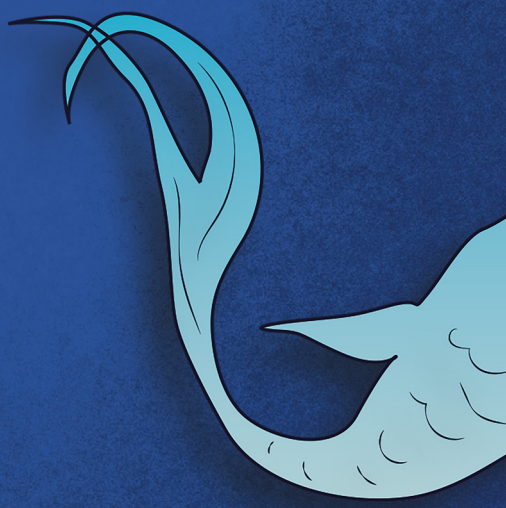
第四章

Discussion and Valorisation



Discussion and Valorisation

Cutaneous surgeries are routinely carried out by dermatologists, plastic surgeons and general practitioners. Mainly due to the rise of skin malignancies, the absolute number of annually performed skin surgery is on the rise.(1, 2)Although not hazardous by definition, these procedures can cause functional limitations and cosmetic concerns. In addition, complications such as haemorrhage and surgical site infections (SSI) occasionally occur.(3-5) Together, these factors could pose a burden on the patient's quality of life.(6) Knowledge gaps and practice differences exist among doctors in delivering optimal care in dermatologic surgery. For example, surveys reveal variations in the management of antithrombotic medication prior to surgery and the prescription of antibiotic prophylaxis.(7-12) In addition, many continue to debate which suturing method and other perioperative management would provide the most cosmetic appealing results as sound evidence is lacking. This thesis provides evidence on several of these topics and contributes to tailored clinical decision making in order to deliver optimal patient centred care in dermatologic surgery.

Complications of dermatologic surgery

Risk of bleeding and the management of antithrombotic medication

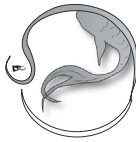
In Section 2.1, we have shown that the risk of haemorrhage was increased in patients on antithrombotic medication compared with patients not on these drugs. However, cessation of the medication had only minor effects on the risk of bleeding, while two severe vascular events were reported in the group discontinuing their medication. Balancing both risks, favours the continuation of antithrombotics in dermatologic surgery.

Today, approximately 40% of patients presenting for dermatologic surgery is on one or more antithrombotic medication.(13-15) Although stopping all antithrombotic medication prior to any surgery used to be common practice, many recent data suggest that this practice should be abandoned.(16) Currently, it is advice to continue all antithrombotic unless there is a significant risk of severe haemorrhage due to either procedure related or medication related characteristics. This is also recommended in a recent guideline published by a German group of dermatologists.(17)

Although we advocate against routine cessation of antithrombotic medication, we do think that blood's clotting tendency should be measured preoperatively in patients on Vitamin K antagonists, especially in patients with larger defects and/or complicated reconstructive procedures. The international normalized ratio (INR) is used for this purpose. For most

patients, the therapeutic range is targeted between an INR of 2.5 and 3.5. It can however, be challenging to maintain this range due to abundant interactions of the medication and genetic polymorphisms in metabolisms of patients.(18) In dermatologic surgery, only one study has compared the severity and frequency of haemorrhage in patients with different preoperative INR values.(19) Results of this study showed that excessive bleeding, defined as haematoma or persistent bleeding unrelieved by pressure dressings or manual pressure, occurred much more often in patients with an INR >3.5 compared with those with an INR<3.5.(19) We have not documented INR in our study but do think that future research should focus to define the INR threshold above which the risk of excessive haemorrhage would be too high to perform surgery. In the author's personal opinion, elective dermatologic surgery should be postponed when the INR is beyond the therapeutic range.

Another important topic for future research is the risk of haemorrhage in patients on newer anticoagulant and antiplatelet medication. The efficacy of novel anticoagulant medication, such asdabigatran, rivaroxaban and apixaban, has been shown to be equal or superior to the traditional Vitamin K antagonists for several indications such as non-valvular atrial fibrillation and venous thromboembolism.(20-25) In contrast to Vitamin K antagonists, these newer medications have very predictable pharmacokinetics. Therefore, routine laboratory monitoring of coagulation time is not required, although monitoring can be done when a high risk of excessive bleeding is suspected. In the case of direct thrombin inhibitors (such as dabigatran), ecarin clotting time (ECT) and dilute thrombin time(TT) can be measured to assess the risk of bleeding.(26) For direct factor Xa inhibitors such as rivaroxaban and apixaban, monitoring can be done by measuring anti-factor Xa activity calibrated for the specific drug of the patient.(27, 28) It has to be noted, that no antidotes exist for these medications to reverse their effect in the event of haemorrhage or overdose. One study has studied the risk of bleeding after cutaneous surgery in patients on novel anticoagulants and identified mild bleeding in one of 27 patients (41 surgeries) while on dabigatran, and no complications in 4 patients (5 procedures) on rivaroxaban. (29) Thus far, only one retrospective study has compared the risk of bleeding in patients receiving skin surgery (Mohs micrographic surgery) who were on traditional anticoagulants with those on novel anticoagulants.(30) It showed that the novel anticoagulants were associated with a significantly higher risk for postoperative haemorrhage although the complications were mild in severity. Regarding the current antiplatelet therapy, acetylsalicylic acid remains the corner stone by inhibiting thromboxane A2 production. Clopidogrel, which is often given in combination with acetylsalicylic acid, inhibits the platelet $P2Y_{12}$ adenosine diphosphate (ADP) receptor and therefore inhibits aggregation of platelets. Novel therapies such as prasugrel and ticagrelor inhibit the same platelet ADP receptor as clopidogrel but have a more rapid onset of inhibition. The magnitude of risk of haemorrhage in dermatological patients on these kinds of medication has not



been studied so far. A recently published review on pharmacokinetics, pharmacodynamics and side effects of traditional and novel oral anticoagulant and antiplatelet therapies in dermatologic surgery recommends managing the novel therapies in a similar way as the traditional medication, until the specific risks of these drugs are established.(31)

Surgical site infection and antibiotic prophylaxis

In Section 2.2 we have evaluated the independent effect of patient, surgery and lesion related factors on the risk of acquiring SSIs. We have shown that this risk is significantly increased in patients receiving procedures on the ears, with larger defects and in whom surgical wounds were closed by flaps or secondary intention. Whether an individual patient will develop an infection post surgery depends on an interplay of different risk factors. Therefore, all potential risk factors should be taken into account in the risk prediction of a patient. We have developed the first prediction model in literature in Section 2.3 for this purpose and have shown its adequate performance in our study population.

Considering the low incidence of SSI in dermatologic surgery, routine prescription of antibiotic prophylaxis should be strongly discouraged. Also, the presence of one risk factor in a patient rarely justifies antibiotic prophylaxis. In our net benefit analysis, we have shown that antibiotic prophylaxis will only be beneficial in a small subgroup of patients on the condition that one is willing to treat eight or more patients in order to prevent one SSI. This applies for patients with a significantly increased risk of SSI calculated based on the location, size and closure method of the wound. If one is willing to treat less than eight patients in order to prevent one SSI, no prophylaxis should be considered in dermatologic surgery.

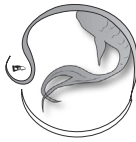
In addition to how many patients a doctor is willing to treat, there are several other important aspects of antibiotic prophylaxis to be addressed. The selection and dosing of the drug, the timing of administration and duration of prophylaxis are important issues that will be discussed here.

In the selection of antibiotics, the drug should be effective against the targeted bacteria while collateral damage to endogenous flora and potential bacterial resistance should be kept to a minimum.(32) In the Netherlands, narrow spectrum penicillins such as flucloxacillin are used as first line treatment in SSIs. Therefore, these drugs should rather not be used prophylactically.(33) First and second generation cephalosporins are preferred as they are effective against skin flora (staphylococci and streptococci), the most common cause of SSI.(34, 35) In addition, *Escherichia coli*, which could colonize intertriginous areas, is usually sensitive to cephalosporins as well.(36) First and second generation cephalosporins are not effective against *Pseudomonas* species, which are sometimes present

in moist areas. However, a SSI is rarely caused by *Pseudomonas*. Therefore, only under exceptional circumstances, there is an indication for prophylactic antibiotic treatment against *Pseudomonas* species.

Another important modality to consider is timing of prophylaxis. Adequate tissue levels of the antibiotics should be reached at the time of incision to prevent SSI. The optimal window is therefore considered to be within 1-2 hour before the incision depending on the drug and method of administration.(32, 37-39) Prophylaxis starting after the incision is much less effective and should be avoided.(40) Because skin surgery is usually short in duration, one single dose prior to incision is the most effective method of prophylaxis. In a recent randomized controlled double-blind trial, orally administered cephalexin 2g 40-60min prior to dermatologic surgery has shown to reduce the risk of SSI in patients receiving complex closure on the nose and ears.(41) As a rule of thumb, when the procedure takes longer than two half-lives of the substance used, a repeated dosing is recommended.(37, 42) Once the wound is closed, contamination of bacteria from adjacent skin or mucosa ceases. Although many clinicians tend to prescribe antibiotics for a prolonged period after surgery, this practice lacks evidence in the literature.(43) In addition, a prolonged course of 5-7 days of oral antibiotics equals a normal therapeutic course instead of an intended prophylactic one. One recent Cochrane review studied the application of topical antibiotic after the wound has been closed, once or several times until suture removal, and concluded that it could possibly reduce the risk of SSI although no recommendation could be made due to small sample sizes.(44)

There are several other control measures that can be taken in the prevention of SSI. The recent WHO guideline for the prevention of SSI, has formulated several recommendations including taking a bath/shower prior to surgery, treatment of known nasal carriage of *Staphylococcus aureus* and not removing hairs in the surgical area prior to surgery.(39) Other common practices, such as the usage of sterile drapes and gloves are recommended although evidence is lacking. The effects of these measurements in specific dermatological procedures should be studied in the future.(40)



Outcome of dermatologic surgery

Evaluation of surgical outcome

To adequately assess the cosmetic outcome after dermatologic surgery, we have compared two commonly applied scales in the assessment of linear facial scars, the Patient and Observer Scar Assessment Scale (POSAS) and the 4-point scale, in Section 3.1. We have shown that observers do not weigh individual scar characteristics equally to arrive to an

overall opinion, which challenges the assumption that calculating a total POSAS score by summing of the scores on the individual items is a valid approach.

To overcome this problem, a weighted scoring system is necessary. The exact weight given to each sub-item is however highly subjective and therefore debatable. In our view, no one-size-fits-all principle could apply here as every individual observer and patient will prioritize their sub-items differently. Therefore, in the evaluation of scars, it is important to regard a scoring system as a whole with all scores on the sub-items presented. A mere mathematical sum of all scores might by insufficient for this purpose.

Great aesthetic outcome after surgery does not always equal patient satisfaction. Patient reported outcome measures (PROMs) are developed to quantify outcomes through the eye of the patient. PROMs could be valuable in dermatologic surgery to better understand the patient's perspective and expectations.(45, 46) In addition to outcome measurement, expectation management prior to surgery is also of great importance.(47) When patients have very low expectations, they might be very satisfied with mediocre outcome, while patients with inappropriately high expectations might be unhappy with the best care possible. Future studies evaluating the aesthetic outcome should take this into account and preferably incorporate a presurgical questionnaire next to the postsurgical assessment. This could also help physicians identifying the specific problems and concerns a patient might have to provide him or her with tailored information.

Suturing technique and outcome of surgery

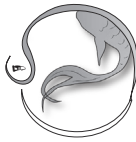
In Section 3.2 we have compared the aesthetic outcome and complications in patients receiving closure by simple interrupted sutures(SIS) and running subcuticular sutures (RSS) in a randomized controlled trial. Both methods yield similar cosmetic results at 12 months post surgery rated by both patients and observers. Dysesthesia occurred more frequent in the RSS group while the occurrence of other postoperative complications was comparable. Based on our results, SIS might be preferred in facial surgery. However, there are several issues that need to be addressed before final conclusions can be drawn.

Suturing material is one of those issues. To adequately compare both suturing methods, non-absorbable sutures were used in both groups in our study. This is not always the case in daily practice, as absorbable sutures are commonly applied in RSS. In addition, although tradition teaches us to use non-absorbable material for SIS, some studies claim that absorbable material might perform equally well.(48, 49) Moreover, the application of absorbable material would make suture removal redundant which could save time and money in healthcare. Therefore, a comparison of both suturing methods using absorbable material would be very interesting in analogy with our study.

A fascinating finding of our study is the evaluation of suture marks. In the eye of most dermatologists, the ideal scar is a fine barely visible line without suture marks which blends into the relaxed skin tension lines.(50) However, in our study, patients seem to rate their scars with or without suture marks equally cosmetically appealing. In addition, while the observer does consider scars with suture marks less beautiful than those without, the overall cosmetic appearance of SIS and RSS were rated equally. As our results are based on observations made by one single observer, the importance of suture marks remains an interesting topic for future studies. Furthermore, the cause of suture marks is variable and not per se dependent on the suturing technique. These marks can occur due to re-epithelialization and scarring of the skin at which the suturing material pierces the skin. Some, however, states that they can also occur due to high tension regardless of the suturing technique.(51) The exact mechanism of suture marks and efforts to avoid them remain interesting topics for future studies.

Finally, there are still many other factors that could influence the aesthetic appearance of scars. Many dermatologists have their own preference and standards in suturing techniques. Heterogeneity exists in the degree of undermining, number of tension relieving dermal sutures and other varieties of suturing methods. Finally, postsurgical measures such as occlusive wound dressing and topical scar treatments are other interesting topics to be addressed in subsequent studies.(52, 53)

Conclusions and future perspectives



Considering current evidence, all anticoagulant and antiplatelet therapies should be continued for the large majority of patients undergoing dermatologic surgery, although preoperative monitoring might be necessary in patients with larger defects and/or complicated reconstructive procedures. Discontinuation of the antithrombotic medication must be done with caution as this can put patients at risk for thromboembolism. Evidence on the risk of bleeding for novel antithrombotic medication is still lacking. Future studies addressing this topic will be very important for formulating clinical guidelines on this topic.

The routine prescription of antibiotic prophylaxis should be strongly discouraged in dermatologic surgery. Only when one is willing to treat more than eight patients in order to prevent one SSI, antibiotic prophylaxis can be considered. Application of our prediction model adequately identifies patients at risk for SSI who might benefit from prophylaxis, although external validation is required before this model can be widely applied. Considering the office setting of most dermatologic procedures, a single dose of 2g cephalexin

orally administered one hour prior to incision appears to be the most practical and effective method of prophylaxis for most patients. Prolongation of the course postsurgery, as well as initiation of the course after surgery should be discouraged for the purpose of prophylaxis.

The evaluation of aesthetic outcome after dermatological surgery is a challenging task as patients and observers tend to weigh individual scar characteristics differently. PROMs and preoperative expectation management might contribute to better tailor making of care.

In facial surgery, SIS seems the preferred method of suturing as it resulted in comparable cosmetic results compared to RSS, and was less often associated with dysesthesia. Future studies on the impact of various factors on the aesthetic outcome of facial scars should focus on different suturing methods using absorbable material as well as other surgical and postoperative measures such as type of wound dressings and topical scar treatments.

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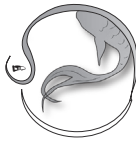

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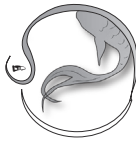

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第五章

Summary

Summary

Dermatologic surgery is incorporated into the daily practice of dermatologists, mostly because of the rising incidence of skin cancer. Furthermore, plastic surgeons and general practitioners perform skin surgery on a regular basis. Although widely performed, evidence based practice is sparse and guidelines based on good quality research are desired. The first part of this thesis addresses complications of dermatologic surgery, such as surgical site infections (SSIs) and postoperative haemorrhage, together with strategies for their prevention. The second part focuses on the evaluation and optimisation of aesthetic outcome of dermatologic surgery to deliver the best patient centred care.

Chapter 1 provides a general introduction on dermatologic surgery underlining potential complications and measurements of cosmetic outcome after surgery.

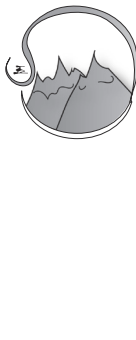
Chapter 2 provides studies concerning the two major complications of dermatologic surgery: postoperative haemorrhage and SSI. In **Section 2.1** we retrospectively evaluated the risk and severity of postoperative bleeding in patients who received Mohs micrographic surgery and were on antithrombotic medication. The study goal was to evaluate the relative risk (RR) of postoperative haemorrhage and thrombotic events in patients who temporarily stopped taking antithrombotic medication. In 423 procedures, 18 haemorrhages occurred (4.3%). No life-threatening bleeds were reported. The RR of haemorrhage in patients discontinuing their antithrombotic medication when compared to controls, patients not on any antithrombotic medication, was 3.52 (95% confidence Interval (CI) 0.93–13.38). This RR was similar to that in patients continuing their medication compared to the same group of control patients (3.84, 95% CI1.13–12.98). Two thrombotic events occurred, both in patients who discontinued their medication. We thereby concluded that, balancing both risks (bleeding versus vascular thrombosis), continuation of anticoagulants is favoured during dermatologic surgery.

In **Section 2.2 and 2.3,** the emphasis is laid on SSI after dermatologic surgery. To identify risk factors for acquiring an infection, we collected data on patient, procedure and lesion related characteristics in all patients receiving skin surgery during a one-year period. None of the patients received antibiotics in the perioperative period. In 1977 procedures, 79 cases (4.0%) had clinical symptoms of an infection. This was confirmed by culture in 38 (1.9% of all procedures) of them. Using the most stringent definition of SSI (clinical symptoms confirmed by a positive culture), a significantly higher risk of SSI was found in surgeries performed on the ear (odds ratio (OR) 6.03, 95% CI 2.12–17.15), in larger defects (OR 1.08 per cm^2 increase, 95% CI 1.03–1.14), and following closure with flaps (OR 6.35, 95% CI1.33–30.28) or secondary intention healing (OR 3.01, 95%CI 1.11–8.13). These characteristics were also associated with a higher risk of clinically suspected SSI regardless of culture results, although associations were slightly

weaker. Based on these risk factors, we developed a prediction model to estimate the risk of SSI in individual patients (**Section 2.3**). After internal validation, the overall performance of the model was good, with an area under the curve of 84.1%. Decision curve analysis showed that the model was potentially useful if one was willing to treat more than eight patients with antibiotic prophylaxis to avoid one infection. For those who preferred more restrictive use of antibiotics, a default strategy of treating no patients at all with prophylaxis would be the best choice. Considering the rising antibiotic resistance and potential side effects of antibiotics, the routine prescription of antibiotics for the prevention of SSI in dermatologic surgery should be strongly discouraged.

Chapter 3 discusses cosmetic outcome of dermatological surgery. In **Section 3.1** the reliability of the most commonly applied grading scales, the Patient and Observer Scar Assessment Scale (POSAS) and the 4-point scale, is evaluated. Fifty patients with facial linear surgical scars were included. The intraclass correlation coefficient (ICC) was used as a measure of reliability. In terms of reliability, the overall opinion and the 4-point scale were superior to the total POSAS score or the sub-items. Observers did not weigh individual scar characteristics equally, to arrive at an overall opinion, which challenged the assumption that calculating a total POSAS score by summing of the scores on the individual items is a valid approach. Therefore, in the evaluation of scars, it is important to regard a scoring system as a whole, with all scores on the sub-items presented. A mere mathematical sum of all scores is insufficient for this purpose. **Section 3.2** presents the results of a multicentre randomized controlled trial. One hundred and forty-two adults receiving dermatologic surgery in the face were randomized to wound closure with either simple interrupted sutures (n=73) or running subcuticular sutures (n=69). Twelve months post surgery, the overall cosmetic assessments according to the patient and the observer as well as colour measurements were similar in both groups leading to the conclusion that both methods result in a comparable aesthetic outcome. Although not statistically significant, hyper-or hypoesthesia was less frequently reported in the group receiving simple interrupted sutures. For this reason, this method might be preferable as method of suturing.

Finally, a discussion and valorisation of the results are provided in **Chapter 4**.



Appendix

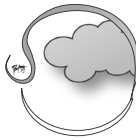
Samenvatting

Samenvatting

Dermatochirurgie is een essentieel onderdeel van de dermatologie en behoort tot de dagelijkse bezigheden van dermatologen, mede door de stijgende incidentie van huidkanker. Naast dermatologen voeren ook plastisch chirurgen en huisartsen veel dermatologische ingrepen uit. Ondanks de gangbaarheid van deze ingrepen, ontbreekt het aan eenduidige richtlijnen. Het eerste gedeelte van dit proefschrift gaat over complicaties van dermatochirurgie, zoals postoperatieve bloedingen en wondinfecties, met daarbij maatregelen die genomen kunnen worden om deze complicaties te voorkomen. Het tweede gedeelte legt de nadruk op het meten en optimaliseren van de cosmetische resultaten na dermatochirurgie om de beste patiëntgerichte zorg te kunnen leveren.

Hoofdstuk 1 bevat een algemene introductie van dermatochirurgie, met nadruk op de veel voorkomende complicaties en uitkomstmaten.

In **hoofdstuk 2** worden onderzoeken besproken waarin aandacht werd besteed aan de twee meest voorkomende complicaties van dermatochirurgie: postoperatieve bloeding en wondinfectie. **Paragraaf 2.1** betreft een retrospectieve studie waarin het risico op en de ernst van postoperatieve bloeding werden geëvalueerd, in patiënten die antistolling gebruikten en vervolgens Mohs micrografische chirurgie ondergingen. Het doel was om na te gaan in welke mate het tijdelijk staken van antistolling voorafgaand aan de ingreep de kans op een postoperatieve bloeding zou verminderen en in hoeverre er complicaties zouden optreden als gevolg van het staken van de antistolling. In 18 van de geïncludeerde 423 ingrepen (4,3%) trad er een nabloeding op. Er werd geen levensbedreigende bloeding gezien. Bij vergelijking van patiënten die hun antistolling hadden gecontinueerd tijdens de operatie met patiënten die geen antistolling gebruikten voorafgaand aan de operatie (controlegroep) was het relatieve risico (RR) op een nabloeding 3,84 (95% betrouwbaarheidsinterval (BI): 1,13–12,98). Patiënten die hun antistolling tijdelijk hadden gestaakt hadden een RR op nabloeding van 3,52 (95% BI 0,93–13,38) vergeleken met de controle groep. Na het staken van antistolling kregen twee patiënten een vasculaire thrombose. Vanwege de geringe daling in het RR op nabloeding na tijdelijk staken van antistolling en de geobserveerde kleine kans op trombose concluderen we dat, alleen bij hoge uitzondering het noodzakelijk is antistolling te staken voor dermatologische ingrepen.



Paragrafen 2.2 en 2.3 bevatten studies over risicofactoren voor postoperatieve wondinfecties na dermatologische chirurgie. De eerste studie evalueerde de associaties tussen de kans op wondinfectie en patient-, operatie- en tumorgebonden eigenschappen in alle patiënten die dermatochirurgie ondergingen in één jaar. Geen van de geïncludeerde patiënten gebruikte antibiotica in de studieperiode. In totaal werden 1977 ingrepen geïncludeerd, waarbij in 79

gevallen (4,0%) klinische symptomen van een wondinfectie optraden. In 38 gevallen (1,9%) werd dit bevestigd met een positieve kweek. Bij handhaving van de striktste definitie van een wondinfectie (klinische verdenking bevestigd met een positieve kweek), werd er een significant verhoogd risico op het optreden van een wondinfectie gevonden voor ingrepen die op het oor werden uitgevoerd (*odds ratio* (OR) 6,03, 95% BI 2,12–17,15), bij grote defecten (OR 1,08, 95% BI 1,03–1,14 per cm^2 toename oppervlakte), en bij wonden die gesloten werden met plastieken (OR 6,35, 95% BI 1,33–30,28)of secundaire granulatie (OR 3,01, 95%CI 1,11–8,13). Deze risicofactoren waren ook positief geassocieerd met de kans op puur een klinische verdenking op een infectie, ongeacht de uitslag van de wondkweek. Echter waren de associaties minder sterk. Gebaseerd op deze bevindingen werd er een predictiemodel ontwikkeld en beschreven in **paragraaf 2.3** om de kans op een wondinfectie in een individuele patiënt te voorspellen. Na interne validatie van het model bleek het model goed onderscheid te kunnen maken tussen patiënten met en zonder een wondinfectie (bevestigd met een positieve kweek) met een oppervlakte onder de *receiver operating characteristic* (ROC) curve van 84,1%. Eenvoudige besliskundige modellen (*decision curve analysis*) lieten zien dat het predictiemodel van toegevoegde waarde is in de klinische praktijk, mits men bereid was om acht of meer patienten te behandelen om één wondinfectie te voorkomen. Wanneer men niet bereid was om zoveel patienten te behandelen om één wondinfectie te voorkomen, verdiende een strategie waarbij in principe nooit antibioticum profylaxe wordt voorgeschreven de voorkeur. Het routinematig voorschrijven van antibiotica met het doel wondinfecties te voorkomen dient afgeraden te worden in de dermatochirurgie gezien de toenemende resistentie vorming en potentiele bijwerkingen van antibiotica.

Hoofdstuk 3 legt de nadruk op de uitkomst van dermatochirurgie. De aandacht gaat hierbij uit naar de beoordeling en mogelijke optimalisatie van cosmetische resultaten na dermatochirurgie. In **paragraaf 3.1** worden de twee meest gebruikte schalen voor de beoordeling van littekens, namelijk de *Patient and Observer Scar Assessment Scale* (POSAS) en een eenvoudige 4-punts schaal, met elkaar vergeleken. Vijftig patiënten met lineaire ilttekens in het gelaat werden geïncludeerd. Als maat voor de reproduceerbaarheid van beoordelingen van de cosmetische aspecten van de littekens werd de *intraclass correlation coefficient* (ICC) gebruikt. De belangrijkste conclusie was dat de reproduceerbaarheid van zowel de beoordelingen van de algemene indruk op de POSAS schaal als de eenvoudige 4 punts schaal beter waren dan de totale score op de POSAS schaal. Daarbij werd ook gezien dat verschillende beoordelaars andere waardes hechtten aan de verschillende karakteristieken van een litteken. Derhalve is een simpele optelsom van de sub scores geen valide beoordelingsmethode van een litteken. Voor een volledige en betrouwbare beoordeling dienen alle scores als geheel gepresenteerd te worden. **Paragraaf 3.2** beschrijft een multicenter, gerandomiseerde, enkelblinde trial waarin 142 volwassen patiënten werden gerandomiseerd naar transcutane (n=73) versus intracutane (n=69) hechttechniek na dermatochirurgie in het gelaat. Twaalf maanden postoperatief werd het cosmetisch resultaat beoordeeld door de patiënt en de arts. Tevens werd de kleur van het

litteken met een colorimeter gemeten. Over het algemeen gaven patiënten hun littekens een betere beoordeling dan hun arts. In beide gerandomiseerde groepen waren de beoordelingen en meetingen vergelijkbaar. In de groep met transcutane hechtingen werd iets minder vaak (hoewel statistisch niet significant) dysesthesie gezien wat ervoor zou kunnen pleiten dat dit de voorkeursmethode van hechten betreft.

Ten slotte worden de resultaten en hun toepasbaarheid bediscussieerd in **hoofdstuk 4**.

Dankwoord

Dankwoord

Zonder deelnemende patiënten zou niet alleen dit proefschrift, maar elk klinisch onderzoek onmogelijk zijn. Hierbij wil ik dan ook als eerste iedereen die heeft deelgenomen aan mijn onderzoeken bedanken voor hun tijd en inspanning.

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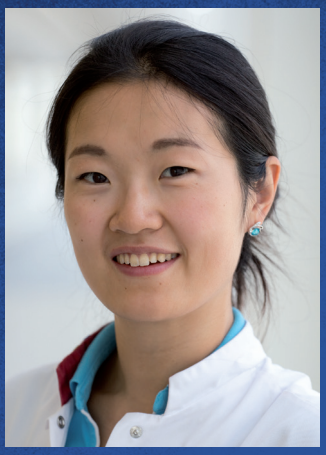
CURRICULUM VITAE



Xiaomeng Liu (刘潇萌) werd geboren op 4 februari 1987 in het noorden van China (Harbin). Nadat ze in 1999 naar Nederland was verhuisd behaalde ze haar vwo-gymnasium diploma aan het Van Maerlantlyceum te Eindhoven. In 2005 begon ze aan de geneeskundestudie aan de Universiteit Utrecht. Tijdens de studie werd ze geselecteerd voor het Excellent Traject, als voorbereiding op een wetenschappelijke verdieping naast het reguliere geneeskunde curriculum. Daarbij heeft ze onderzoek gedaan naar intracerebrale bloedingen en diagnostiek van pinda-allergie. Tevens publiceerde ze een Cochrane review over de behandeling van schizofrenie. Na het versneld behalen van haar artsenexamen begin 2011, startte ze in het aansluitende academisch jaar met de opleiding tot dermatoloog in het Maastricht Universitair Medisch Centrum, waar haar interesse in wetenschappelijke onderzoek zich snel verder ontwikkelde. Deze wetenschappelijke interesse gecombineerd met haar passie voor de dermatologische chirurgie, vertaalde zich in het starten van dit promotietraject al in een vroeg stadium van haar specialisatie. Sinds 2016 werkt ze als dermatoloog in het Flevoziekenhuis in Almere.