Peer reviewed article

Staged surgical therapy of basal cell carcinoma of the head and neck region: an evaluation of 500 procedures[1]

Rolf Hüsler[a], *Fabian L. Schlittler*[a], *Janett Kreutziger*[b], *Markus Streit*[c], *Andrej Banic*[a], *Franziska Schöni-Affolter*[e], *Robert E. Hunger*[d], *Mihai A. Constantinescu*[a]

[a] Department of Plastic and Hand Surgery, University Hospital Inselspital, Berne, Switzerland
[b] Department of Anaesthesiology, University Hospital Inselspital, Berne, Switzerland
[c] Department of Dermatology, University Hospital Inselspital, Berne, Switzerland
[d] Department of Dermatology, Cantonal Hospital, Aarau, Switzerland
[e] Institution for Evaluative Research in Orthopaedic Surgery, University Hospital Inselspital, Berne, Switzerland

Summary

Questions under study/principles: The surgical therapy of basal cell carcinoma (BCC) is especially demanding in the facial area. This retrospective study was undertaken to evaluate the outcome of staged surgical therapy (SST) of BCC of the head and neck region performed on an interdisciplinary basis at our institution.

Methods: Patients treated for BCC in the head and neck area between 1/1/1997 and 31/12/2001 were included in the study. The lesions were histologically evaluated. Diameter of lesion, number of stages, defect coverage, operation time, recurrence and infection rates were analysed using descriptive and inferential statistical procedures.

Results: 281 patients were included in the study. SST was performed in two stages in 43.7%, in three stages in 12.9% and in four or more stages in 2.7%, depending on the type of tumour and the patient's pretreatment status. The total operating time per lesion averaged one hour. Defect coverage was achieved by direct closure (37.7%), by full thickness skin graft (39.5%), by split skin graft (1.1%), by local flaps (20.3%) or by composite grafts (1.1%). Median follow-up time was 58.5 months. Low rates of recurrence (3.6%) and infection (2%) were observed with this technique.

Conclusions: The staged surgical therapy of basal cell carcinoma evaluated here offers a series of advantages in respect of patient comfort and economy, while allowing precise histological safety with low infection rates and reliable long-term results.

Key words: staged surgical therapy; basal cell carcinoma; head and neck region; skin cancer

Introduction

Malignant cutaneous lesions of the face, head and neck area are of particular importance in the fields of plastic and reconstructive surgery, dermatology, ear, nose and throat (ENT), maxillo-facial and general surgery. Patients fear the lifelong stigmata associated with visible postoperative scars and deformities. Surgeons face the problem of removing sufficient tissue to ensure oncologically sound treatment [1], while avoiding an unnecessarily large excision with its avoidable sequel [2, 3]. Mohs' description of micrographic surgery was a milestone, especially in treating lesions of the face, in striking an optimal balance between sufficient resection and unnecessary trauma [2–4] via repetitive tangential excisions and immediate histological evaluation of the resection margins [5–7]. This approach requires, however, lengthy and unpredictable operating theatre time and the personnel resources of highly-trained specialists. Hence it becomes costly [8, 9] and remains limited to only a few specialised centres.

In theory, the staged surgical therapy (SST) approach offers similar advantages to Mohs' micrographic surgery (MMS) in terms of histological safety of the resection margins while allowing optimal planning of surgical procedures with little manpower and predictable operating theatre time allocation. The risk of wound infections is believed to be low in the well-vascularised region of the face, head and neck, which is thus particularly suitable for the staged surgical approach involving a period of open wound treat-

1 This study was presented in part at the annual meeting of the Swiss Association of Plastic, Aesthetic and Reconstructive Surgeons (SPGRAC) in Montreux, Switzerland 2007 and at the Day of Clinical Research at the University of Berne, Switzerland 2007.

No financial support to declare.

ment between excision of the lesion and closure of the defect [10].

SST of cutaneous lesions in the head and neck area has been opted for as an interdisciplinary approach at the Inselspital University Hospital over the last decade. This retrospective study was undertaken to evaluate the oncological and economic results obtained with this technique.

Patients and methods

The study was conducted on all patients treated surgically for basal cell carcinoma *(BCC)* of the face, head or neck at Inselspital University Hospital between January 1997 and December 2001. This retrospective time frame allowed an appropriate follow-up period. Exclusion criteria were incomplete records, genetically predisposing disorders with more than 5 BCCs, BCCs exceeding 6 cm in diameter and basosquamous lesions and radiation therapy. Additionally, patients with more than five lesions in the same body area were excluded since the distinction between recurrences and new primary lesions in the same body area is unreliable.

Tumours were assessed under optimal operating-theatre lighting and 2.5x loupe magnification, and the clinical margin of the BCC was marked in ink. An appropriate excision margin of 3–5 mm was then drawn around the BCC area. The tumour was excised under local anaesthesia following the marked line. The specimens were oriented with a marker suture and fixated in formaldehyde for histological evaluation.

Histological examination was performed following ink marking by serial transverse blocking of the specimen, processing and embedding into wax blocks. Histology reports were issued with additional schematic line drawings for surgeon orientation. In cases with positive histological margins (incomplete BCC excision) surgery was performed again and the tissue specimen was analyzed as described above. Final defect closure or coverage was performed only following histological confirmation of tumour-free surgical margins. In the local health system, follow-up was performed both at the Inselspital University Hospital and by the referring dermatologist, who would re-refer the patient in the event of BCC recurrence, thus giving the patient the benefit of a close network of postoperative reassessment.

The data analysis included descriptive statistics of means (with standard deviation) or medians (with range), depending on the data distribution. Non-parametric tests (Wilcoxon or Kruskal-Wallis) were used to compare means. Differences in tumour diameters of different tumour types were assessed with linear models. The Bonferroni procedure was used to adjust for the problem of multiple comparisons. Homogeneity of variance for the groups was assessed by the Levene test.

Logistic procedures were used to analyse the following discrete data:

– Number of stages (Poisson distribution)
– Recurrences and infections (binary distribution)
– Pretreatment status (binary distribution).

In the Poisson model the numbers of stages were rescaled, starting with zero (equivalent to one stage, representing 40.9%). The models accounted for multiple lesions in a patient and were adjusted for age and gender. Statistical analysis was performed with SAS 9.1 [SAS Institute Inc., Cary, NC, USA] and the level of significance was set at 0.05 throughout the study.

Results

During the study period a total of 292 patients were treated surgically for BCC lesions in our unit. Of these, 228 patients' records met the inclusion criteria outlined above.

The gender distribution was equal, with 111 male and 117 female patients. The median age was 74 years (range: 26–97) with only 8% of the treated patients under 45 years of age at the time of the first excision. The patients' profession was recorded in 123 patients and was in most cases, surprisingly (86.2%), an indoor activity. In these patients, 281 basal cell carcinoma lesions were excised from the head and neck area. The majority of patients (83.3%) presented with only one basal cell carcinoma, while 11.4% presented with two lesions, 3.9% with three and only 1.3% with four or five (fig. 1).

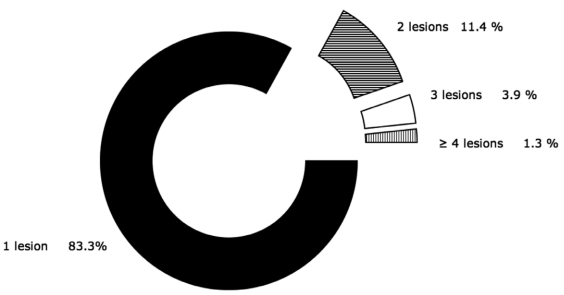


Figure 1

Incidence of BCC lesions in treated patients.

The mean tumour diameter was 11.32 mm (±8.43 mm). Surgical records showed the tumour diameter to be larger than 20 mm in only 9.8% of cases. The localisation was in the non-hair bearing areas of the head and neck in 97.5%, with a strong prevalence in the nasal (27.0%) and frontal (21.4%) areas. Other frequent localisations were the cheek (15.3%), eyelids (12.1%), ears (7.5%) and neck (7.5%), while the lips (5.3%), scalp (2.5%) and chin (1.4%) were less frequent sites of occurrence (fig. 2).

The histological types of basal cell carcinoma were solid in two thirds of cases (66.2%) and infiltrative in 17.1%, while 7.1% of the lesions were combined. In 9.6% of cases the histology report did not clearly specify the subtype of the lesion.

Figure 2

Tumour localisation according to the aesthetic areas of the head and neck.

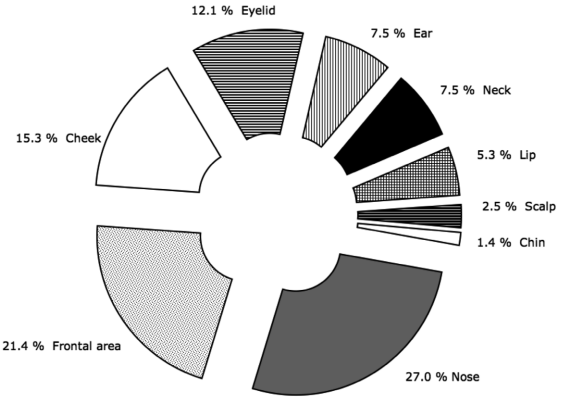
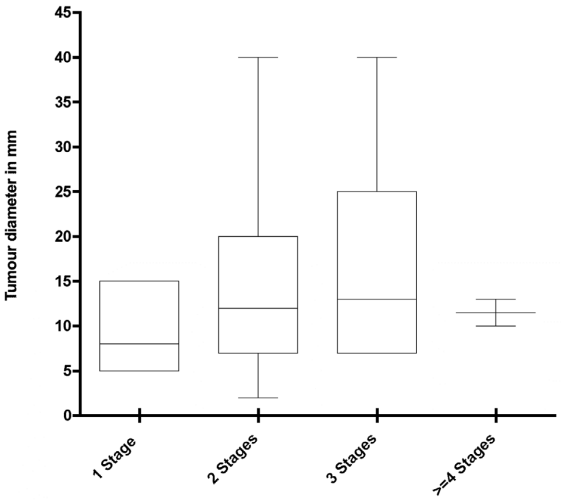


Figure 3

Surgical stages and measured initial tumour size



The tumour diameter did not vary significantly between different histological types of basal cell carcinoma (table 1).

Single stage procedures were performed in 40.9% of cases in situations where a primary temporary closure was possible without undermining the wound edges. Multiple stage surgical therapies were performed in two stages in 43.1%, required three procedures in 13.2% and were completed after four or more procedures in 2.8% of lesions. The resulting total of 500 procedures represents a mean of 1.8 procedures for each tumour, irrespective of the initial tumour diameter (fig. 3). In the logistic regression model, the combined tumour subtype required significantly more ($p = 0.021$) and the solid type significantly fewer ($p = 0.0330$) surgical excision stages than other subtypes (table 2).

The resulting defect had a median diameter of 2.5 cm following histologically proven complete excision. This finding is in agreement with the prevalent lesion diameter of 2 cm or below in 90% of cases. The recorded safety margins following staged excision reached a median of 2.45 mm (range: 1.8 to 4.3 mm).

Soft tissue defect coverage was performed by various techniques, in accordance with the steps of the reconstructive ladder in plastic surgery (table 1). No free flap transfer was necessary in these patients, in line with the explicit inclusion criteria of lesions less than 6 cm in diameter. The additional median operating time for each lesion was just above one hour (65 minutes, range: 23–146 minutes) and included the first excision, all necessary secondary excisions and the final reconstruction regardless of the degree of complexity.

The observed infection rate was low (1.3 % of patients or 2% of lesions) in spite of the necessary intermittent open wound treatment between surgical stages.

The recurrence rate was 3.6% (10 out of 281 lesions) and its incidence was equally divided among the various aesthetic units of the face. The ear showed the highest recurrence rate of 9.5%. The recurrent lesions measured only a median 5 mm in diameter, which underlines the success of careful follow-up by specialists. Immunosuppressed patients (3.9%) did not have a higher incidence of lesions ($p = 0.8235$, corrected for age and gender) or a higher recurrence rate ($p = 0.2792$). The duration of the immunosuppression preceding surgery (median 26 months) did not correlate significantly with the incidence of BCC lesions in this small group.

A second patient subgroup of particular interest was the "pretreated" group. These 49 patients (21.5%) had undergone a surgical procedure on a facial BCC lesion at least once (i.e., by the attending physician) prior to referral to our centre. The histological subtypes of BCC and the recurrence rates of this subgroup did not differ statistically

Table 1

Histological findings and surgical defect coverage techniques applied in the staged surgical therapy of BCC in the face, head and neck area.

	Basal cell carcinoma subtype				
	Solid	Infiltrative	Combined	Undefined	Total
Number of lesions (%)	186 (66.2)	48 (17.1)	20 (7.1)	27 (9.6)	281
Diameter of tumour mm (mean, SD)*	10.66 (± 7.81)	13.76 (± 11.25)	12.41 (± 7.48)	10.86 (± 7.24)	11.32 (± 8.43)
Number of stages performed (mean, SD)	1.63 (± 0.73)	1.92 (± 0.77)	2.80 (± 1.15)	2.00 (± 0.92)	1.8 (± 0.84)
Defect coverage techniques:					
Direct closure	86 (81%)	11 (10%)	4 (4%)	5 (5%)	106 (37.7%)
Full thickness skin graft	62 (56%)	24 (21.5%)	11 (10%)	14 (12.5%)	11 (39.5%)
Local flap	35 (61.5%)	10 (17.5%)	4 (7%)	8 (14%)	57 (20.3%)
Composite graft	1 (33.3%)	2 (66.6%)	0	0	3 (1.1%)
Split thickness graft	1 (33.3%)	1 (33.3%)	1 (33.3%)	0	3 (1.1%)
Secondary healing	1	0	0	0	1 (0.3%)

* There were no statistically significant differences between the initially measured tumour diameters of the different histological BCC subtypes ($p = 0.275$; Levene Test)

Table 2
Parameter estimates of variables for the number of staged surgery.

	Estimate	Standard error	P-value
Intercept	0.3403	0.611	0.5776
Tumour diameter	0.0116	0.0073	0.1107
Age	0.0001	0.0045	0.9784
Gender (ref. = "female")	–0.0247	0.1308	0.8504
Immunosuppression (ref. = "no")	0.1007	0.4513	0.8235
Pretreatment (ref. = "no")	0.4474	0.139	0.0013
Type of tumour			
Combined	0.5954	0.258	0.021
Infiltrative	–0.1973	0.2309	0.3928
Solid	–0.4624	0.2169	0.033

Note: The undefined group was set to value zero for statistical comparison between the various groups

from those in the overall patient group. This group represents two thirds of all patients undergoing three or more surgical stages. The Poisson model showed that these patients required significantly (p = 0.0013) more stages for complete surgical therapy than patients treated primarily at our institution (table 2).

Discussion

The worldwide rise in the incidence of malignant cutaneous lesions [11, 12] calls for medically and oncologically appropriate treatment for these growing patient numbers at a time of downward pressure on health expenditures, when all treatment costs are subject to close cost accounting and specialised personnel are becoming scarce. Although Mohs' micrographic surgery [7] is known to strike a perfect balance between sufficient tissue excision and limited collateral damage, especially in the visible areas of the face, head and neck, similar cost effective treatment modalities like the staged surgical therapy presented here should be evaluated with respect to their efficacy in tumour treatment [8, 13, 14].

The current study shows that staged surgical therapy is very similar to MMS in terms of oncological safety [15], while offering significant advantages in operative planning, cost and resource availability [8], elements essential for smaller centres and varied surgical disciplines.

The technique evaluated is not new and must be clearly differentiated from single surgical excision with immediate closure [2, 16–18]. The most frequently performed comparative studies have focused on MMS versus surgical excision with immediate wound closure [19], without a knowledge of histological safety margins. There are inherent issues surrounding surgical closure over an incompletely excised lesion with a subsequently higher rate of recurrence due to iatrogenic spread of malignant cells.

The oncologically important issue of tumour free excision margins prior to defect closure is addressed in the staged surgical technique, in which risks of iatrogenic spread are minimised by leaving the wound open with appropriate wound care until final histology reveals clear safety margins and defect coverage can be performed. Both the oncological and the cosmetic advantages of SST over single stage surgical excision with immediate closure become evident if one compares the resection safety margins [2] and the outcome in terms of recurrence [20], not to mention the need for revision of closed wounds in the case of incomplete excisions [3, 8].

A possible drawback of SST when compared to other therapies [3, 8] could lie in the open wound therapy required throughout the treatment from the first surgical step of lesion excision to the final step of defect coverage. Hence an important parameter for risk/benefit calculation in the assessment of SST is the rate of infection, which was observed in only 2% of lesions treated. None of the patients with infections needed to undergo larger excisions or additional surgery, since the wounds were open and could easily be treated topically or through systemic antibiotic coverage. The resultant delay in treatment has never exceeded one week in any of these four patients. This positive finding might well be explained by the particularly good perfusion pattern of the soft tissues of the head and neck area, which also allow excellent healing in older or even immunosuppressed patients.

An interesting sidelight from the data presented in this study is the high incidence of BCC in patients with an indoor occupation compared to patients with an outdoor occupation. Possible explanations for this are either the fall in the percentage of persons performing outdoor jobs in recent decades, optimised protection in outdoor jobs or – the most likely explanation – that the data refer to the UV-irradiation toll of outdoor hobbies in patients with indoor jobs.

The limitations of this study should be noted. It was conducted as a single Swiss centre retro-

spective analysis and therefore data availability was limited and no direct comparison of different techniques could be performed. Nevertheless, this evaluation of the staged surgical technique affords insight into the oncological outcome – reflected in the low recurrence rate – and economic aspects – reflected in the short overall operative procedure times – of this approach.

The comparison of oncological safety and cost effectiveness of SST and MMS can be conducted only indirectly, assessing the available literature for comparison of overall operative procedure times and costly complication and recurrence rates. The patients' age, gender and lesion types observed in the present study compare well with the Mohs' therapy groups assessed by Julian and Bowers in two British centres [21]. The number of tumours treated, the observed mean lesion size, the mean number of layers or stages and the number of pretreated lesions were very similar in both study groups, as was the oncological outcome, showing comparable overall recurrence rates for the two techniques, viz. 3.8% following MMS and 3.6% following SST at 5-year follow-up.

In terms of cost effectiveness and patient comfort, the results of the present study are paralleled by a comparative evaluation of surgical therapy and MMS performed by Essers et al. in a European centre [3, 8]. In that analysis the authors conclude that surgical therapy is less costly than MMS, thanks in particular to shorter operative procedure times and reduced personnel costs, findings which are also supported by the results of the current patient series. Finally, the possibility of entirely non-surgical therapy to BCC lesions has also to be addressed with a view to cost effectiveness. Non-surgical therapy has certainly its indication in superficial and small BCC lesions, in which the course of the therapy can be well assessed by inspection. Various therapeutic forms, including topical chemotherapy [22], cryotherapy [11, 22, 23], photodynamic therapy [24] and even radiotherapy [12, 25–28] showed recurrence rates of approximately 10%, which are significantly higher than the presented SST excision results and hence associated with high costs resulting from repeated treatment and follow-up outpatient appointments, with subsequent reduction of patient comfort. The frequently evoked cosmetic superiority of results in non-surgical therapy should be set against much larger and more stigmatising surgical procedures if lesions recur.

Two final aspects of SST are, firstly, timely involvement of the patient in the decision-making process regarding the choice of reconstruction, which can be planned well in advance in order to secure the optimal cosmetic result, and, secondly, optimisation of operating theatre resources thanks to predictable time management with final histology available preoperatively.

Conclusions

Staged surgical therapy is a simple and reliable surgical approach able to achieve oncologically therapeutic results similar to the "state of the art" Mohs' micrographic surgery for patients with BCC of the head and neck area. Staged surgical therapy can be adopted by varied surgical disciplines in small hospital centres thanks to its ready availability, low costs and predictability of operative duration and resource planning, warranting broad clinical use for the benefit of the patient in need.

Correspondence:
Mihai Adrian Constantinescu
Consultant Plastic Surgeon
Department of Plastic and Hand Surgery
University Hospital, Inselspital
CH-3010 Berne
Switzerland
E-Mail: mihai.constantinescu@insel.ch

References

1 Fleischer AB Jr, Feldman SR, Barlow JO, et al. The specialty of the treating physician affects the likelihood of tumor-free resection margins for basal cell carcinoma: results from a multi-institutional retrospective study. J Am Acad Dermatol. 2001;44:224–30.
2 Bisson MA, Dunkin CS, Suvarna SK, Griffiths RW. Do plastic surgeons resect basal cell carcinomas too widely? A prospective study comparing surgical and histological margins. Br J Plast Surg. 2002;55:293–7.
3 Kumar P, Watson S, Brain AN, et al. Incomplete excision of basal cell carcinoma: a prospective multicentre audit. Br J Plast Surg. 2002;55:616–22.
4 Lawrence CM. Mohs' micrographic surgery for basal cell carcinoma. Clin Exp Dermatol. 1999;24:130–3.
5 Vuyk HD, Lohuis PJ. Mohs micrographic surgery for facial skin cancer. Clin Otolaryngol Allied Sci. 2001;26:265–73.
6 Bartley GB. Mohs surgery: proclamation, proof, principles, and promise. Ophthalmology. 2004;111:615–6.
7 Mohs F. Chemosurgery, a microscopically controlled method of cancer excision. Arch Surg. 1941;42:279–95.
8 Smeets NW, Krekels GA, Ostertag JU, et al. Surgical excision vs Mohs' micrographic surgery for basal-cell carcinoma of the face: randomised controlled trial. Lancet. 2004;364:1766–72.
9 Essers BA, Dirksen CD, Nieman FH, et al. Cost-effectiveness of Mohs' Micrographic Surgery vs Surgical Excision for Basal Cell Carcinoma of the Face. Arch Dermatol. 2006;142:187–94.
10 Lodde JP, Grangier Y, Le Roux P, Fabre E. Sclerodermiform basal cell carcinoma. Apropos of a study of 83 cases. Ann Chir Plast Esthet. 1998;43:373–82.

11 Kokoszka A, Scheinfeld N. Evidence-based review of the use of cryosurgery in treatment of basal cell carcinoma. Dermatol Surg. 2003;29:566–71.
12 Woerle B, Heckmann M, Konz B. Micrographic surgery of basal cell carcinomas of the head. Recent Results Cancer Res. 2002;160:219–24.
13 Eberle FC, Schippert W, Trilling B, et al. Cosmetic results of histographically controlled excision of non-melanoma skin cancer in the head and neck region. J Dtsch Dermatol Ges. 2005;3:109–12.
14 Lawrence CM, Comaish JS, Dahl MG. Excision of skin tumours without wound closure. Br J Dermatol. 1986;115: 563–71.
15 Lalloo MT, Sood S. Head and neck basal cell carcinoma: treatment using a 2-mm clinical excision margin. Clin Otolaryngol Allied Sci. 2000;25:370–3.
16 Leibovitch I, Huilgol SC, Selva D, et al. Basosquamous carcinoma: treatment with Mohs micrographic surgery. Cancer. 2005;104:170–5.
17 Griffiths RW, Suvarna SK, Stone J. Do basal cell carcinomas recur after complete conventional surgical excision? Br J Plast Surg. 2005;58:795–805.
18 Friedrich RE, Giese M, Li L, et al. Diagnosis, treatment and follow-up control in 124 patients with basal cell carcinoma of the maxillofacial region treated from 1992 to 1997. Anticancer Res. 2005;25:1693–7.
19 Blomqvist G, Eriksson E, Lauritzen C. Surgical results in 477 basal cell carcinomas. Scand J Plast Reconstr Surg. 1982;16: 283–5.
20 Silverman MK, Kopf AW, Bart RS, et al. Recurrence rates of treated basal cell carcinomas. Part 3: Surgical excision. J Dermatol Surg Oncol. 1992;18:471–6.
21 Julian CG, Bowers PW. A prospective study of Mohs' micrographic surgery in two English centres. Br J Dermatol. 1997; 136:515–8.
22 Bath-Hextall F, Bong J, Perkins W, Williams H. Interventions for basal cell carcinoma of the skin: systematic review. BMJ. 2004;329:705.
23 Motley RJ, Gould DJ, Douglas WS, Simpson NB. Treatment of basal cell carcinoma by dermatologists in the United Kingdom. British Association of Dermatologists Audit Subcommittee and the British Society for Dermatological Surgery. Br J Dermatol. 1995;132:437–40.
24 Rhodes LE, de Rie M, Enstrom Y, et al. Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. Arch Dermatol. 2004;140:17–23.
25 Thissen MR, Neumann MH, Schouten LJ. A systematic review of treatment modalities for primary basal cell carcinomas. Arch Dermatol. 1999;135:1177–83.
26 Petit JY, Avril MF, Margulis A, et al. Evaluation of cosmetic results of a randomized trial comparing surgery and radiotherapy in the treatment of basal cell carcinoma of the face. Plast Reconstr Surg. 2000;105:2544–51.
27 Wilson AW, Howsam G, Santhanam V, et al. Surgical management of incompletely excised basal cell carcinomas of the head and neck. Br J Oral Maxillofac Surg. 2004;42:311–4.
28 Fleming ID, Amonette R, Monaghan T, Fleming MD. Principles of management of basal and squamous cell carcinoma of the skin. Cancer. 1995;75:699–704.

Established in 1871

Formerly: Schweizerische Medizinische Wochenschrift

Swiss Medical Weekly

The European Journal of Medical Sciences

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW is a peer-reviewed open-access journal
- SMW's impact factor has been steadily rising. The 2007 impact factor is 1.310.
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of professional statisticians for every article with statistical analyses

- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts:	submission@smw.ch
Letters to the editor:	letters@smw.ch
Editorial Board:	red@smw.ch
Internet:	http://www.smw.ch

EMH FMH Schwabe
Editores Medicorum Helveticorum

Official journal of the Swiss Society of Infectious Diseases, the Swiss Society of Internal Medicine and the Swiss Respiratory Society

Supported by the FMH (Swiss Medical Association) and by Schwabe AG, the long-established scientific publishing house founded in 1488