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Evaluationen zur Therapie des spinozellulären Karzinoms der Gesichtshaut: Risikofaktoren für Lymphknotenmetastasen

und

Vergleich verschiedener Rekonstruktionstechniken bezogen auf die ästhetischen Ergebnisse

Dissertation

Zum Erwerb des Doktorgrades der Zahnmedizin
an der Medizinischen Fakultät der
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vorgelegt von Katharina Obermeier
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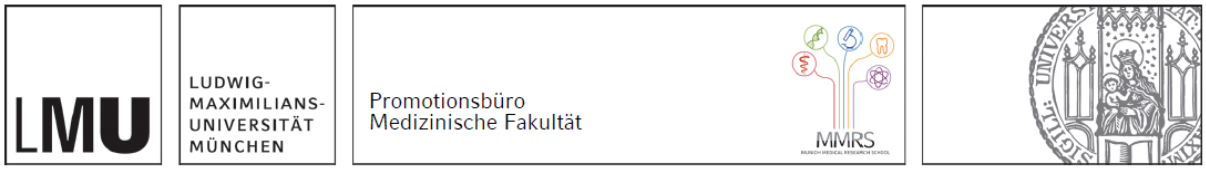
Bei der vorliegenden Dissertation handelt es sich um eine verkürzte Darstellung der wissenschaftlichen Forschungsergebnisse. Die ausführlichen Ergebnisse wurden bereits in folgenden Fachzeitschriften veröffentlicht.

1. **Risk factors for lymph node metastases of facial cutaneous squamous cell carcinoma**
   Katharina Obermeier, Matthias Tröltzsch, Michael Ehrenfeld, Wenko Smolka
   Journal of Cranio-Maxillo-Facial Surgery 45 (2017) 1138-1142.

2. **Comparison of aesthetic outcome of different facial reconstruction techniques after resection of cutaneous squamous cell carcinoma**
   Katharina Obermeier, Wenko Smolka
   Journal of Cranio-Maxillo-Facial Surgery 48 (2020) 117-121.

Eidesstattliche Versicherung



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Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

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München, 18.05.2021

Ort, Datum

K. Obermeier

Unterschrift Doktorandin

Inhaltsverzeichnis

Abkürzungsverzeichnis

CSCC	Cutaneous squamous cell carcinoma = spinozelluläres Karzinom
BCC	Basalzellkarzinom
G1	Histopathologisches Grading, gut differenziert
G2	Histopathologisches Grading, mäßig differenziert
G3	Histopathologisches Grading, schlecht differenziert

Publikationsliste

Englischsprachige Originalarbeiten

Obermeier K., Tröltzsch M., Ehrenfeld M., Smolka W. (2017)
Risk factors for lymph node metastases of facial cutaneous squamous cell
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Obermeier K., Smolka W. (2020)
Comparison of aesthetic outcome of different facial reconstruction techniques after resection of cutaneous squamous cell carcinoma
Journal of Cranio-Maxillo-Facial Surgery 48 (2020) 117-121.

Troeltzsch M., Probst FA., Rominger A., Müller-Lisse U., Probst M., **Obermeier K.**, Ehrenfeld M., Otto S.
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Journal of Oral-Maxillofacial Surgery 76(1) (2018) 190-198.

Kollmuss M., Kist S., **Obermeier K.**, Pelka AK., Hickel R., Huth KC.
Antimicrobial effect of gaseous and aqueous ozone on caries pathogen microorganisms grown in biofilms.
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Wissenschaftliche Vorträge

Smolka W., **Obermeier K.**, Ehrenfeld M.
Risikofaktoren für die Metastasierung bei kutanen Plattenepithelkarzinomen. 69. Kongress der Deutschen Gesellschaft für Mund-, Kiefer- und Gesichtschirurgie, 26. – 29. Juni 2019, Frankfurt, Deutschland

1. Eigenanteil

1.1 Beitrag zu Veröffentlichung I

PD Dr. Dr. Wenko Smolka konzipierte das Studiendesign und Zielpunkt der Studie. **Katharina Obermeier** rekrutierte die Patienten über die Datenbank der Klinik und Poliklinik für Mund-, Kiefer- und Gesichtschirurgie und wertete die Patientenakten retrospektiv aus. Die statistische Analyse wurde von Ruben Seyfried und **Katharina Obermeier** durchgeführt. Die Grafiken und Tabellen wurden von **Katharina Obermeier** erstellt. Dr. Dr. Matthias Tröltzsch half bei der Erstellung des Manuskriptes. **Katharina Obermeier** und PD Dr. Dr. Wenko Smolka erstellten das Manuskript. Professor Dr. Dr. Michael Ehrenfeld wirkte bei der Durchsicht des Manuskriptes mit und unterstützte durch intellektuellen Rat und Anregungen.

1.2 Beitrag zu Veröffentlichung II

PD Dr. Dr. Wenko Smolka konzipierte das Studiendesign und definierte die Zielsetzung der Studie. **Katharina Obermeier** rekrutierte die Patienten, sowie deren Fotografien über die Datenbank der Klinik und Poliklinik für Mund-, Kiefer-, und Gesichtschirurgie und wertete die Patientenakten retrospektiv aus. Die statistische Auswertung führte **Katharina Obermeier** durch, ebenso erstellte sie die Grafiken und Tabellen in der Publikation. **Katharina Obermeier** und PD Dr. Dr. Wenko Smolka erstellten gemeinsam das Manuskript. PD Dr. Dr. Wenko Smolka half bei der finalen Durchsicht des Manuskriptes mit und unterstützte durch intellektuellen Rat und Anregungen.

2. Einleitung

2.1 Epidemiologie und Pathogenese des spinozellulären Karzinoms

Das spinozelluläre Karzinom (CSCC) gilt nach dem Basalzellkarzinom als zweithäufigster bösartiger Tumor der Haut weltweit und macht insgesamt 20% aller nicht-melanozytären Hauttumoren aus (Leiter U. et al., 2017). Da besonders der Hals- und Kopfbereich erhöhter UV-Strahlung schutzlos ausgesetzt ist, sind spinozelluläre Karzinome zu 90% dort zu finden. Gleichzeitig handelt es sich bei diesem Bereich jedoch auch um den Teil des Körpers, der den Menschen als Individuum ausmacht (Stundzaite-Barsauskiene G. et al., 2019). Daher ist die Behandlung dieses Tumors besonders komplex für den Behandler und psychisch belastend für den Patienten.

Die Prognose des CSCC gilt bei frühzeitiger Erkennung und Behandlung bei einer Heilungsrate von über 95% als günstig (Stratigos A. et al., 2015). Für die Patienten, die nach oder vor Tumorresektion Metastasen entwickeln, verschlechtert sich jedoch die Prognose drastisch auf eine 2-Jahres-Überlebenszeit (Givi B. et al., 2011).

Laut Analyse der Deutschen Krebsregisterdaten beträgt der jährliche Anstieg der Fälle 6,7% (Rudolph C. et al., 2015). Dies ist auf die verbesserten Screening-Maßnahmen zurückzuführen und auf die bessere Datenerfassung der Krebsregister (Augustin M. et al., 2012). Besonders beim CSCC steigt mit zunehmendem Alter die Erkrankungswahrscheinlichkeit (Hollestein L.M. de Vries E. and Nijsten T., 2012). Als Hauptrisikofaktor für die Entstehung des CSCC gilt UV-Strahlung, daher werden die höchsten Inzidenzraten in Queensland, Australien angegeben (Raasch et al., 2002).

2.2 Risikofaktoren für die Entstehung von Metastasen

Für die Entstehung von Metastasen werden in der Literatur unter anderem die Risikofaktoren Immunsuppression, Komorbiditäten, Lokalisation, Infiltrationstiefe, Sicherheitsabstand, immunhistopathologische Marker und Infiltration in Nerven oder Blutgefäße beschrieben (Kelder W. et al., 2012, Brantsch KD. et al., 2008).

Seit Jahren weiß man, dass ein histopathologisches Grading G3, das einem Tumor mit schlecht differenziertem Gewebe entspricht, mit einer schlechteren Gesamtprognose einhergeht (Peat B., Insull P., Ayers R., 2011).

Allerdings liegen wenige Daten vor, ob ein G3-Tumor auch mit einem erhöhten Risiko für Metastasierung einhergeht. Obwohl nur 4% der Patienten im Krankheitsverlauf Metastasen entwickeln, sollte aber trotzdem ein besonderes Augenmerk auf diese Gruppe gerichtet werden. Grund hierfür ist die sich verschlechternde Prognose auf eine 2-Jahres Überlebenszeit (Givi B. et al., 2011). Ein Risiko-Score, der bestimmt, ab wann eine Entfernung des Wächterlymphknotens durchgeführt wird, oder wann eine Neck-Dissection indiziert ist, existiert für das spinozelluläre Karzinom bisher nicht. Andere Tumorarten, wie beispielsweise das maligne Melanom, haben diese Problematik seit Jahren in ihren Leitlinien zur Behandlung aufgenommen. Zu einer leitliniengerechten Standardtherapie zählt beim malignen Melanom die Entnahme des Wächterlymphknotens, die sogenannte Sentinel Lymph-Node Biopsie. Diese basiert auf dem Ergebnis der histopathologischen Untersuchung (McMasters KM. et al., 2001, Tas F. et al., 2004, Guitart J. et al., 2004). Insbesondere bei einer Tumordicke nach Breslow ab >1,0 cm, die als wichtigster prognostischer Parameter in der Melanombehandlung gilt, wird die Sentinel Lymph-Node Biopsie durchgeführt (Mays MP. et al., 2010). Ebenso bei anderen Tumorarten, wie vor allen Dingen beim Mamma-Karzinom gehört die Entfernung und histopathologische Untersuchung des Wächterlymphknotens zum Goldstandard (Lyman GH. et al., 2014).

Daher sollte in der vorliegenden Arbeit untersucht werden, ob es auch beim CSCC Faktoren gibt, die das Entstehen von Metastasen begünstigen. Patienten mit diesen Risikofaktoren würden von einer Behandlung der Lymphknoten profitieren.

2.3 Ästhetische Ergebnisse verschiedener Gesichtshautrekonstruktionen nach Tumorresektion

Doch nicht nur die Entwicklung von Metastasen, sondern auch die Rekonstruktion des Gesichts nach ausgedehnten Defekten durch Tumorresektionen stellt die Operateure vor eine große Herausforderung.

Aufgrund des einzuhaltenden Sicherheitsabstandes bei Tumorresektionen zur Vermeidung von Rezidiven entstehen oftmals große Defekte, die vor allen Dingen im Gesichtsbereich für den Patienten als störend und psychisch belastend angesehen werden. Besonders das Gesicht als individueller Teil des Menschen ist wesentlich für die Lebensqualität und sollte stets nach ästhetischen Aspekten rekonstruiert werden. Baker SR. et al. beschreiben 1990 in seinem Buch die verschiedenen Teile des Gesichts als ästhetische Gesichtseinheiten und orientieren sich unter anderem an den Langer-Gesichtsspannungslinien (Baker SR., 1990). Es werden die nasale Region, Stirnregion, zygomatische Region, infraorbitale, periorbitale und mandibuläre Region, sowie Kinnregion, Ober- und Unterlippenregion, Ohrregion und Schläfenregion als ästhetische Gesichtseinheiten beschrieben. Die Rekonstruktion des Gesichts bei Defekten, die sich über eine einzige ästhetische Gesichtseinheit erstrecken, ist oftmals schwierig. Aber besonders bei Defekten, die mehrere ästhetische Gesichtseinheiten betreffen, ist die Gesichtsrekonstruktion anspruchsvoll. Obwohl sowohl in Praxis als auch in Literatur verschiedene Rekonstruktionstechniken mit lokalen Lappenplastiken, als auch mit Fernlappenplastiken beschrieben und angewendet werden (Pepper JP., Baker SR., 2013), gelingt ein optimales ästhetisches Ergebnis oftmals nicht.

Lokallappen sind meistens technisch leichter anzuwenden und sind meist mit geringerer Operationszeit verbunden, auch die Hautfarbe passt zur Farbe der umliegenden Haut. Allerdings muss berücksichtigt werden, dass insbesondere Patienten mit ausgedehnten Tumordefekten unzureichend mit lokalen Lappenplastiken versorgt werden können, da das umliegende Gewebe nicht zur vollständigen Defektdeckung ausreicht (DColen UC., Koçer U., 2018).

Der Radialislappen und der Latissimus-dorsi-Lappen beispielsweise, die zu den Fernlappen zählen, sind dagegen indiziert, wenn Defekte groß sind und nicht mit lokalen Lappenplastiken gedeckt werden können. Fernlappenplastiken sind mit längeren Operationszeiten verbunden, aber das ästhetische Ergebnis ist oftmals wegen der unterschiedlichen Textur und Farbe der Haut nicht zufriedenstellend (Rao JK., Shende KS., 2016). In dieser Studie werden verschiedene Rekonstruktionstechniken zur Defektdeckung nach Resektion des CSCC mit lokalen Lappenplastiken und Fernlappenplastiken bezüglich des ästhetischen Ergebnisses verglichen.

3. Ziele dieser Arbeit

Alle oben genannten Faktoren zeigen, wie komplex und schwierig die Behandlung von Patienten mit einem spinozellulären Karzinom im Hals- und Kopfbereich ist. Es existieren zahlreiche Veröffentlichungen zu Risikofaktoren und Rekonstruktionsmöglichkeiten, aber kaum Studien, die die verschiedenen Faktoren zusammenbringen und vergleichen.

Diese Arbeit legt ihren Schwerpunkt sowohl auf die Erstellung eines Risiko-Scores für Entstehung von Lymphknotenmetastasen, als auch auf die verschiedenen Rekonstruktions-möglichkeiten des Gesichts bei Defekten nach Tumorresektionen bezüglich des ästhetischen Ergebnisses.

Die erste Studie zeigt den Einfluss von Risikofaktoren auf, der nach Auswertung von 99 Patientendaten der Klinik für Mund-Kiefer-Gesichtschirurgie LMU mittels eines logistischen Regressionsmodells berechnet wurde. Des Weiteren wurde hier besonders auf den Einfluss des histopathologischen Tumorgradings auf das Metastasierungsverhalten eingegangen. G2 Tumoren und G3 Tumoren und ihr Einfluss auf lymphogene Streuung wurden mittels eines Fisher-Tests ermittelt.

Die zweite Studie wertet postoperative Fotografien von Patienten nach Gesichtsrekonstruktionen mit lokalen Lappenplastiken und Fernlappenplastiken unter ästhetischen Gesichtspunkten aus. Für die Auswertung wurde ein 5-Punkte-System verwendet. Eine Jury bestehend aus drei Personen bewertete die postoperativen Aufnahmen hinsichtlich der Farbe, der Narbenbildung und der Struktur der unterschiedlichen Rekonstruktionen. Für die statistische Auswertung wurde hier ein Wilcoxon-Mann-Whitney-U-Test angewendet. Dieser Score soll die Wahl der Rekonstruktionsart künftig erleichtern.

4. Deutsche Zusammenfassung

Ziel der Studien war es zum einen, einen Risiko-Score für das Entstehen von Metastasen zu entwickeln und zum anderen die ästhetisch günstigste Rekonstruktionsart nach Tumorresektion zur Defektdeckung zu ermitteln, sowie Vor- und Nachteile der verschiedenen Lappenplastiken aufzuzeigen.

Für die Erstellung eines Risiko-Scores wurden nach Zusammentragen der Daten mittels eines logistischen Regressionsmodells die Risikofaktoren mit dem größten Einfluss auf das Entstehen von Metastasen ermittelt.

Als Hochrisikopatienten erwiesen sich Patienten mit schlecht differenziertem G3 Tumor: Das Risiko für Auftreten von Metastasen betrug hier 82,99%.

Bei R1-Resektion erhöht sich das Risiko auf 88,67% und bei Tumorlokalisation in der periorbitalen Region auf 47,17%.

Mit Hilfe des Ergebnisses aus dem logistischen Regressionsmodell ließ sich nun ein Risiko-Score für verschiedene Konstellationen berechnen.

So haben Patienten, die sowohl einen G3-Tumor haben, als auch R1-Resektion ein 99,74%-iges Risiko eine Metastase im Krankheitsverlauf zu entwickeln. Für Patienten mit allen drei oben genannten Risikofaktoren steigt das Risiko auf 99,99%. Das Ergebnis des Fisher-Tests zeigt auch, dass ein signifikanter Unterschied zwischen G2 und G3 Tumoren, die lymphogene Streuung betreffend, besteht. G3 Tumore sind somit mehr mit dem Auftreten von Metastasen assoziiert als G2 Tumore. Die Odds-Ratio Analyse errechnete ein 14-fach höheres Risiko für Metastasen bei Patienten mit einem schlecht differenzierten Tumor, als bei Patienten mit einem mäßig differenzierten Tumor. Daher sollte künftig überlegt werden, ob Patienten, die oben genannte Risikofaktoren aufweisen, von einer Behandlung der Halslymphknoten profitieren könnten. Ob dies in Form einer Wächterlymphknotenentfernung oder einer Neck-Dissection geschehen sollte, bleibt weiterhin zur Diskussion offen.

Zu beachten ist hier allerdings natürlich, dass es sich bei dem Patientengut um ausgewählte Patienten handelt, die auf Grund des bereits sehr fortgeschrittenen Befundes alle stationär in der Mund-Kiefer-Gesichtschirurgie der LMU behandelt worden sind.

Das zeigen auch die Defektgrößen nach der Tumorresektion: Defekte bis zu einer Größe von 10cm wurden plastisch gedeckt.

Aufgrund der meist schon sehr ausgedehnten Befunde, waren in dieser Studie die Bedingungen für eine plastische ästhetisch ansprechende Rekonstruktion erschwert. Trotzdem war die Komplikationsratemit 8% sehr gering. Bei Anwendung des Wilcoxon-Mann-Whitney-U-Test ergab sich ein signifikanter Unterschied zwischen Textur und Hautfarbe bei lokalen Lappenplastiken und Fernlappenplastiken, wobei die Fernlappenplastiken deutlich schlechter abschnitten. Narben, die nach Rekonstruktion von lokalen Lappenplastiken entstehen, sind weniger sichtbar als Narben, die nach Fernlappenrekonstruktion entstehen.

Insgesamt schnitt bei der Auswertung, bezogen auf Textur, Hautfarbe und Narben, der Verschiebelappen mit einem Score von 1,4 am besten ab. Der Latissimus-dorsi-Lappen erhielt mit 4,16 den schlechtesten Score.

Zusammenfassend kann man sagen, dass lokale Lappenplastiken stets bevorzugt zur Gesichtsrekonstruktion eingesetzt werden sollten. Allerdings muss natürlich auch bedacht werden, dass größere Defekte, die beispielsweise ausgedehntere muskuläre oder knöcherne Defekte decken sollen, nicht mit einer lokalen Lappenplastik versorgt werden können. Ästhetische Einschränkungen, die sich für den Patienten postoperativ ergeben könnten, sollten künftig besser dem Patienten kommuniziert werden. Das ergibt auch eine Umfrage die Lee KS. et al. 2017 an Patienten zur Zufriedenheit über das ästhetische Ergebnis nach Tumorrekonstruktion durchführte.

Abschließend kann man als Fazit dieser Studien feststellen, dass ein Risiko-Score für die Tumor Vor- und Nachsorge Vorteile für das weitere Behandlungsvorgehen und die Prognose des Patienten mit CSCC haben könnte. Ebenso das Ranking der verschiedenen Rekonstruktionsmöglichkeiten könnte die Entscheidung und Planung der Defektdeckung durch den Operateur im Alltag erleichtern.

Allerdings sollte bei der Behandlung des Patienten stets berücksichtigt werden, dass jeder Patient ein Individuum ist und die Ergebnisse der Studie unter Umständen nicht auf alle Patienten projiziert werden können.

5. Englische Zusammenfassung

The aim of both publications was on the one hand to evolve a risk-score for developing metastases and on the other hand to determine the most aesthetic facial reconstruction after tumor resection. Also advantages and disadvantages of the different flap techniques should be revealed. To create a risk score using a logistic regression analysis the risk factors with the most important influence on lymph nodal spreading have been found. Patients with poor differentiated facial CSCC were proven to be high risk patients: The risk for developing metastases was 82.99%. An incomplete tumor resection R1 increased the risk to 88.67% and tumor localization in the periorbital region to 47.17%.

By means of this result of the logistic regression analysis a risk score for different constellations could be calculated:

Hence, patients with poor differentiated G3 tumor and R1-resection have a 99.74% high risk to suffer from lymph nodal spreading during course of disease. The probability of developing metastases for patients exhibiting all three risk factors rose up to 99.99%. The result of the Fisher's test showed a significant difference between moderate and poor differentiated tumors concerning lymph nodal spreading. Poor differentiated tumors are associated with a higher occurrence of lymph nodal spreading and have a 14-times higher risk of developing metastases compared to moderate differentiated tumors.

Therefore, it should be considered, if patients with those high-risk factors can benefit from treatment of the regional lymph nodes. It should be open for discussion and for other studies, whether performing a sentinel lymph node biopsy or a neck dissection is of benefit for patients with high risk factors.

It should be considered that there is a selection in the present group of patients. Only patients who were treated as impatient were included in this study. That is the reason for major tumor size and resulting major defect sizes in most patients: Defect sizes up to 10cm needed to be reconstructed.

Because of the extensive tumor sizes, the conditions for an aesthetic reconstruction after resection turned out to be hindered. However, complication rate with 8% was very low. After applying the Wilcoxon-Mann-Whitney-U-Test evaluation of the aesthetic outcome pointed out a significant difference concerning texture, color and scars between local flaps and distant flaps. The aesthetic result of the distant flaps was worse than the result of the local flaps. Scars

occurring after reconstruction using local flaps are slightly less visible than scars occurring after using distant flaps. Overall, the transposition flap showed the best result with a score of 1.4. The latissimus-dorsi-flap only achieved a score of 4.16.

In summary local flaps offer statistically better aesthetic results compared to distant flaps in terms of color and texture and they should be applied if possible. Indeed, it should be considered, that defects extending into bone and/or muscle, can often not be reconstructed with local flaps.

Henceforth, limitations concerning the aesthetic outcome should be discussed with patients before surgery. This has been shown in a survey by Lee KS. et al. 2017, who asked patients about their satisfaction of the aesthetic outcome after surgery.

Concluding, these investigations proof, that a risk score in the treatment of patients with CSCC has advantages for further aesthetic outcome and prognosis of patients. Alike the ranking of different reconstruction options could be helpful in the decision for planning of facial reconstruction.

Nevertheless, it must be taken into consideration, that every patient is an individual and the result might not be applicable for all patients.

6. Veröffentlichung I

Risk factors for lymph node metastases of facial cutaneous squamous cell carcinoma
2017

Katharina Obermeier, Matthias Tröltzsch, Michael Ehrenfeld, Wenko Smolka

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Abstract

Purpose: Determining the risk factors for lymph node metastases of facial cutaneous squamous cell carcinoma and identifying their value for predicting nodal spread.

Patients and Method: Data of 99 patients was examined retrospectively. Conditions such as tumor staging, tumor thickness, location, histological grading, R1-resection, local recurrence, lymph node metastases, neurovascular and lymphovascular invasion were evaluated. Statistical analysis was performed using a logistic regression analysis and Fisher Test.

Results: Logistic regression analysis indicates that poor differentiation, R1-resection and periorbital location are high risk factors for nodal spread in facial cutaneous squamous cell carcinoma.

Conclusion: Patients that show poorly differentiated facial cutaneous squamous cell carcinoma and/or have had previous R1-resection might benefit from treatment of regional lymph nodes

Key words: cutaneous squamous cell carcinoma, lymph node metastases, risk factors

Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer and mostly found in sun exposed areas. Head and neck are affected in approximately 90% of the cases (Brantsch KD. et al., 2008).

The prognosis of CSCC is generally good with very high rates of local control and cure rates of 95% after surgery (Stratigos A.et al., 2015). However, in case of nodal spread the prognosis detereorates dramatically. The approximate life expectancy of patients showing lymph node metastases is about 2 years (Givi B. et al., 2011).

Only 4% of patients suffering from CSCC develop metastasis of the cervical lymph nodes (Brantsch KD. et al., 2008). However, there are high risk factors like perineural invasion, desmoplastic type, tumor thickness and diameter as well as poor differentiation that increase the risk for developing lymph node metastases (Kelder W. et al., 2012). In high risk patients the rate of nodal spread is significantly increased and reaches up to 35% (Sweeny L. et al., 2014).

The aim of this study was to determine the risk factors for lymph node metastases of facial CSCC and to find out their value for predicting nodal spread. This would have an impact on tumor staging, treatment and patients' follow-up.

Patients and Methods

This study was approved by the institutional review board of the University Hospital of Munich, Germany (Munich, Germany; UE Nr 138-14). It included 99 patients who underwent surgical treatment of facial CSCC between 2007 and 2014. Sixty-seven patients were male and 32 female. The mean age of the patients at surgery was 79.8 years, ranging from 25 to 103

years. None of the patients was immunosuppressed. The follow-up time, defined as the interval between surgery and the latest follow-up examination, ranged from 6 months to 84 months with a mean of 34.

Only patients with facial CSCC, who underwent treatment as inpatients, were included in this study. The different locations of facial CSCC are shown in Fig. 1. All patients were classified according to the UICC TNM classification as shown in Fig. 2. Primary tumor resection was performed in 87 patients. Six of these patients needed further resection because of incomplete tumor removal during primary surgery. Twelve patients were sent to our department because of previous incomplete tumor resection which had been performed elsewhere. All 18 patients with incomplete tumor resection during primary surgery underwent re-resection. Tumor free margins could be achieved after one, two and three further resection procedures in 10, 6 and 2 cases, respectively.

All patients underwent computed tomography examination (CT) for preoperative tumor staging. Because of radiologically suspicious lymph nodes 53 patients underwent neck dissection. Patients developed nodal recurrence in 12 cases. The time-period between primary tumor resection and appearance of lymph node metastases was between 3 months and 48 months (mean range 18.2 months). Four patients suffered from lymph nodal spreading at the time of their initial diagnosis of CSCC.

Patient records and all available documents and radiographs were reviewed. Data were collected on local recurrence, lymph node metastases, histopathological grading, desmoplastic type, neurovascular invasion, lymphovascular invasion, tumor thickness and maximum diameter. In 12 patients some histopathological data were missing. In these cases we re-evaluated the pathological specimen under a light microscope to gain the missing information.

The computer software program “R” (Free software Foundation, Boston, MA 02110-1335) was used for statistical analysis. Statistical analysis was performed using a logistic regression analysis to determine the risk factors for locoregional lymph node metastases in cases of facial CSCC. Statistical significance was defined as $p<0.05$. Fisher’s Test was used to test the significance of histopathological grading on the development of nodular tumor spread. Statistical significance was defined as $p<0.05$.

Results

Twenty-four patients were staged as T1, 27 were staged as T2, 34 patients had T3 CSCC and 14 patients had T4 primaries. The average diameter of all tumors was 2.7 cm, ranging from 0.6 cm to 10.5 cm. In four cases patients staged T1 had lymph nodal spreading, in 10 cases staged T2, in 13 cases staged T3 and in 7 cases staged T4. Fourty-three patients suffered from multiple CSCC and 30 patients suffered from CSCC in combination with basal cell carcinoma (BCC). 10 patients (23,2%) with multiple CSCC developed lymph node metastases and 9 patients (30%) with BCC and CSCC suffered from metastatic disease.

Tumor thickness was determined by histopathological examination. The average tumor thickness was 13 mm, ranging from 1mm to 55 mm. According to Brantsch KD. et al., there is no risk of lymph node metastases if the tumor thickness is less than 2 mm (Brantsch KD. et al., 2008). There is a low risk if the tumor thickness is between 2.01 mm and 6 mm and a high risk if the tumor thickness exceeds 6 mm (Brantsch KD. et al., 2008). The number of patients with a tumor thickness of up to 2 mm, with a tumor thickness of 2.01 mm to 6 mm and a tumor thickness greater than 6 mm is shown in Table 1.

Local recurrence occurred in 35 patients after a mean time-period of 19.8 months ranging from 3 months to 204 months. 85.8% (30 patients) presented with tumor thickness > 6 mm.

Tumor diameters > 20 mm were found in 25.7% of the patients (9 patients). 7 patients (20%) had a desmoplastic type. Poor histological differentiation was present in 19 patients (54.3%). Perineural invasion occurred in 13 patients (37.1%) and R1-resection was found in 10 patients (28.6%).

On histopathological examination perineural invasion was detected in 27 specimen of primary facial CSCC. Twelve patients (44.4%) with perineural invasion developed lymph node metastases. Infiltration of the cartilage was present in 11 cases and bone infiltration was found in 21 cases. In 18 patients CSCC infiltrated the orbit. The parotid gland was affected by cancer in 15 cases. Histopathological examination also revealed a desmoplastic type in 12 patients. Six of these patients developed lymph node metastases.

Nine patients had CSCC of the ear and five of these patients had metastases. All nine patients with involvement of the periorbital region developed lymph node metastases. Of the 20 patients with CSCC of the forehead region, only two developed metastases. One metastasis occurred in seven patients with CSCC of the upper lip, six in 27 patients with CSCC of the lower lip, and four in 20 patients with CSCC of the cheek. Three of the nine patients with involvement of the temporal region, and had four of the seven patients with involvement of the nose had lymph node metastases.

R1-resection was found in 18 patients. Of these patients 67% (12 patients) had lymph node metastases during their follow-up.

On histopathological grading, well differentiated (G1) CSCCs were determined in 14 patients. Moderate differentiation (G2) was found in 45 patients and poor differentiation (G3) was present in 40 patients. Patients with G1 did not develope any metastases. In cases of moderate differentiation (G2) 6 patients developed nodal spread. A total of 28 patients with G3 presented with lymph node metastases. For statistical analysis Fisher's Test was used to find out if there is a difference between the development of lymph node metastases in patients

with G2 and G3. The null hypothesis revealed p-value of P = 2.80607. Hence, G3 is associated with a higher occurrence of lymph node metastases. Odds ratio analysis revealed that patients with G3 have a 14-time higher risk to develop nodal metastases than patients, who suffer from G2 CSCC.

A total of 37 patients received radiotherapy. Thirty-four patients were treated with postoperative adjuvant radiotherapy. Three patients received radiation therapy preoperatively. The mean dose was 47,4 Gray (Gy) ranging from 10 Gy to 70,6 Gy.

Chemoradiotherapy was admitted to eight patients of 34 who received postoperative radiotherapy, and in two cases chemotherapy without radiation was administered. In seven cases 5-fluorouracil (5-FU) was used, in 1 case bleomycin and in one further case mitomycin (MMC). In one patient cetuximab was given during radiation.

Overall, 34 patients suffered from metastatic disease before, during or after the first diagnosis. Most patients had only one affected lymph node, i.e. 26 patients suffered from N1. Seven patients suffered from N2 and one patient from N3. None of the patients developed distant metastases.

Logistic regression analysis was used to determine the risk factors for the development of lymph node metastases in cases of facial CSCC. As no lymph node metastasis appeared in the patients with histological grading G1, this group of patients was not included in the logistic regression analysis. This meant that 85 patients were included in the statistical analysis. The logistic regression analysis indicated that histological grading G3, R1-resection and periorbital location are high risk factors for lymph node metastases in facial CSCC (Table 2).

In the present patient group, the risk for lymph node metastases in patients with G3 as the only high risk factor was 82.99%. It was 88.67% in patients with R1-resection as the only high risk factor. Patients who had CSCC of the periorbital region had a 47.17% risk for developing lymph node metastases. If patients had both G3 and R1-resection, the risk for nodal spread was 99.74%. If patients with periorbital CSCCs had also G3 or R1-resection, the risk for lymph node metastases was 97.79% and 98.61%, respectively. The risk for lymph node metastases in patients with all three high risk factors (G3, R1-resection, periorbital location) was 99.99% in the present patient group.

Discussion

The majority of patients with facial CSCC can be treated successfully with surgical resection. Using 3D histology-guided surgery, local control of the disease of 97% can be achieved (Häfner HM. et al., 2011). On the other hand, prognosis for patients with lymph node metastases is poor. Five-years survival rates in patients with proven lymph node metastases can drop down to 25% overall survival (Szewczyk M. et al., 2015).

Only approximately 5% of regional lymph node metastases occur in patients with CSCC (Kelder W. et al., 2012). However, high risk factors such as perineural invasion, desmoplastic type, tumor thickness and diameter as well as poor differentiation increase the risk for developing lymph node metastases up to 35% (Sweeny L. et al., 2014).

In our study, 34% of all patients with facial CSCC developed lymph node metastases. One or more high risks factor were a prime cause of the high incidence of metastases in the present patient group. In this study, only patients who had been treated as in patients were included. This might be the reason for the high number of patients with large tumors and advanced stage of disease.

Tumor diameters ≥ 20 mm had been determined as a relative risk factor for developing lymph node metastases in a retrospective case control study of 170 patients with CSCC of the head and neck (Peat B. et al., 2011). In this study the predictive factors for lymph node metastases had been identified by a statistical regression analysis. Moderate histological differentiation and Clark Level V had also been determined as relative risk factors. If all three relative risk factors are present, the incidence of metastases is 37%. If only two relative risk factors or one relative risk factor are present the incidence drops down to 5% and 0.3%, respectively. In a large review article the lesion size has been mentioned as an indication for nodal spread in case of CSCC of the head and neck (Veness MJ., 2007). But it was concluded that tumor size alone is probably a weak indication. Rowe et al. reported an incidence of metastases of 30% for tumor diameters ≥ 20 mm versus 9% for tumor diameters < 20 mm (Rowe RJ. et al., 1992). In the present study, the incidence of metastases was 40% for tumor diameters ≥ 20 mm versus 16% for tumor diameters < 20 mm (Rowe RJ. et al., 1992). However, no correlation between tumor diameter and lymph node metastases was determined by using logistic regression analysis.

It has been postulated that patients with multiple CSCC and patients with CSCC of the head and neck with previous treated facial BCC are at higher risk to develop lymph node metastases (Szewczyk M.et al., 2015). In our study lymph node metastases occured in 23% of patients with multiple facial CSCC. Nine patients (30%) with facial CSCC and previous treated facial BCC also showed metastatic disease. However, a logistic regression analysis revealed no statistical relevance for these risk factors.

Tumor thickness has been identified as important in predicting for nodal spread in patients with CSCC. In a prospective study of 615 patients performed by Brantsch KD. et al. the incidence of lymph node metastasis was 0% in patients with tumor thickness of less than 2 mm (Brantsch KD.et al., 2008). In cases of tumor thickness between 2 mm and 6 mm the incidence for developing lymph node metastases was 4% and 16% for patients with tumor thickness > 6 mm.

Similar results were found in the present study. Only one metastasis occurred in the group of patients with tumor thickness of less than 2 mm. Whereas 10 patients with lymph node metastases were present in cases with tumor thickness between 2 mm and 6 mm and 23 were found in patients with thickness > 6 mm. Still, no correlation was proven between tumor thickness and lymph node metastases using logistic regression analysis.

Perineural invasion occurs in approximately 5% of CSCC cases (Veness MJ., 2007). It has been reported that patients with perineural invasion have a significant increase in lymph node metastases compared to those without for perineural invasion (Breuninger H. et al., 1990). Similar results had been reported by Moore BA. et al. in a prospective study of 193 patients with CSCC of the head and neck (Moore BA. et al., 2005). Perineural and lymphovascular invasion had also been stated to be an absolute risk factor for metastases of CSCC of the head and neck with a predicted incidence of metastases of 37% (Peat B. et al., 2011). In our study, 44.4% of patients with perineural invasion developed lymph node metastases. Nevertheless, no correlation between perineural invasion and the presence of lymph node metastasis could be found when performing logistic regression analysis.

In a prospective study of 594 CSCCs desmoplastic CSCCs were found to metastasize 6 times more often than non-desmoplastic CSCCs (Breuninger H. et al., 1997). Therefore, the authors concluded that desmoplasia is a highly significant prognostic factor for CSCC and is associated with the occurrence of lymph node metastases. Half of the patients with desmoplasia in the present study had lymph node metastases. However, the group of patients with a histological desmoplastic type was too small and therefore not used as a variable in the logistic regression analysis.

CSCC located on the ear had been reported to be a high risk factor for developing regional lymph node metastases (Mourouzis C. et al., 2009). In a retrospective study of 194 patients with CSCC of the head and neck Mourouzis C. et al. found 6 patients with CSCC on the ear that showed lymphatic spread into regional lymph nodes. Despite the small number of patients, a correlation between CSCC located on the ear and the development of metastases was found

on logistic regression analysis. On the other hand, other authors reported the lip as primary site to be a risk factor for metastases in CSCC (Vartanian JG. et al., 2004). In contrast, in our study there was a correlation between periorbitally located CSCCs and lymph node metastases using logistic regression analysis.

Incomplete surgical resection of CSCC will lead to locoregional recurrence with increased risk of lymph node metastases in about 50% of patients (Veness MJ., 2007). In a previous study of 194 patients with CSCC of the head and neck incomplete excision margins had been reported to be a statistically proven high risk factor for the development of lymph node metastases (Mourouzis C. et al., 2009). This result can be confirmed by the present study, as R1-resection was found to have a correlation with occurrence of metastases.

Poor differentiation is known to be a strong indication for developing lymph node metastases in patients with CSCC. It has been stated to be an absolute risk factor by Peat B. et al. with a predicted incidence of nodal metastases of 37% (Peat B. et al., 2011). Mourouzis C. et al. also reported that patients with poorly differentiated CSCC are at greater risk to develop lymph node metastases (Mourouzis C. et al., 2009). Cherpelis BS. et al. had shown that 44% of patients with metastatic CSCCs had poorly differentiated lesions (Cherpelis BS. et al., 2002). In the present study, a correlation between poorly differentiated lesions and the development of lymph node metastases was proven using logistic regression analysis. It has also been shown that patients with G3 have a 14-times higher risk to develop metastases than patients with G2. Therefore, poor differentiation is a strong indication for nodal spread in CSCC.

In the present study, the risk for developing lymph node metastasis in patients with G3 or R1-resection was 82.98% and 88.67%, respectively. In patients, who had both, G3 and R1-resection, the risk for nodal spread was increased by up to 99.74%. Hence, G3 as well as R1-resection is a strong indication for the development of nodal metastases in facial CSCC. As such a high risk for lymph node metastases was found in patients with facial CSCC that are poorly differentiated and have had R1-resection, treatment of lymph nodes should be taken into consideration in these selected cases.

According to the European consensus-based interdisciplinary guideline elective neck dissection is not recommended in facial CSCC because of the low incidence (Stratigos A. et al., 2015). Sentinel lymph node biopsy (SLNB) in CSCC has been investigated in several studies. However, the therapeutic value of SLNB has not been confirmed yet (Ross As. and Schmults CD., 2006). Several authors proposed elective neck dissection in patients with high risk factors (Maher NG. and Hoffman GR., 2014; Szewczyk M. et al., 2015; Wermker K. et al., 2015).

Conclusion

Based on the results of the present study, we conclude that patients with facial CSCC that show poorly differentiated and/or have had previous R1-resection might benefit from treatment of the regional lymph nodes.

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Tables

Table 1: Tumor thickness and metastases

Tumor thickness	>2mm	2,0-6mm	>6mm
No. of patients	6 patients	33 patients	60 patients
No. of patients with metastases	1 patient	10 patients	23 patients

Table 2: Correlation between lymph node metastases and risk factors (n=85)

	Correlation coefficient	P-value
G3	3.9024	0.00000461
R1-Resection	4.3762	0.000432
Periorbital Location	2.2053	0.036160

Figure legends

Fig. 1: Locations of facial CSCC

Fig. 2: UICC TNM classification of 99 patients with CSCC

Figures

Fig. 1

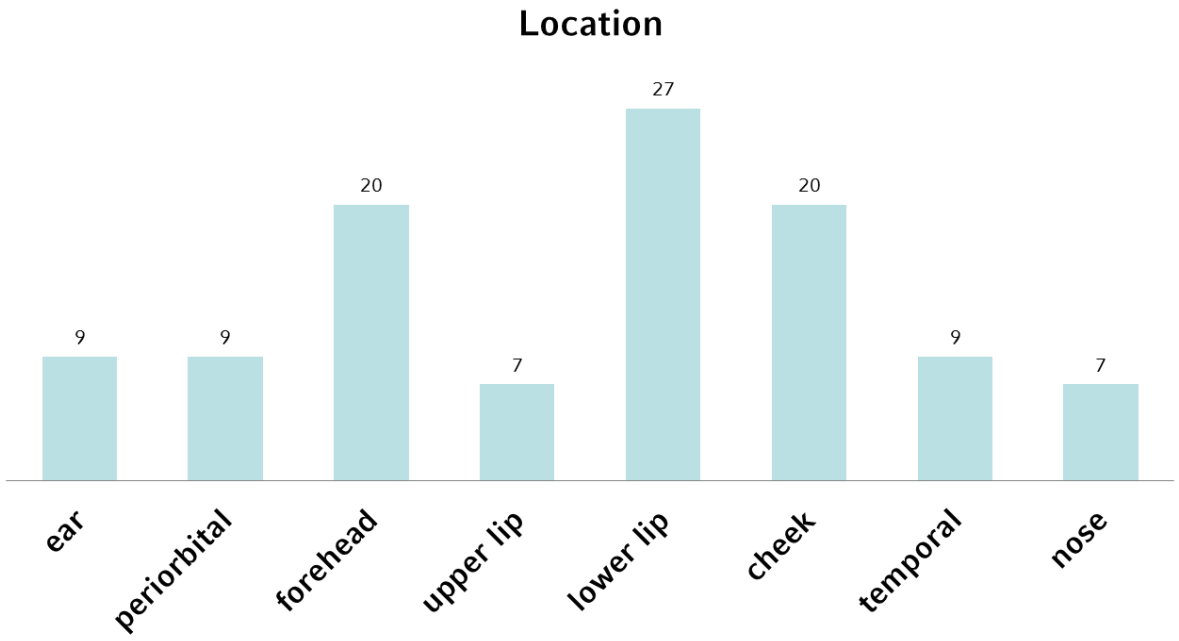
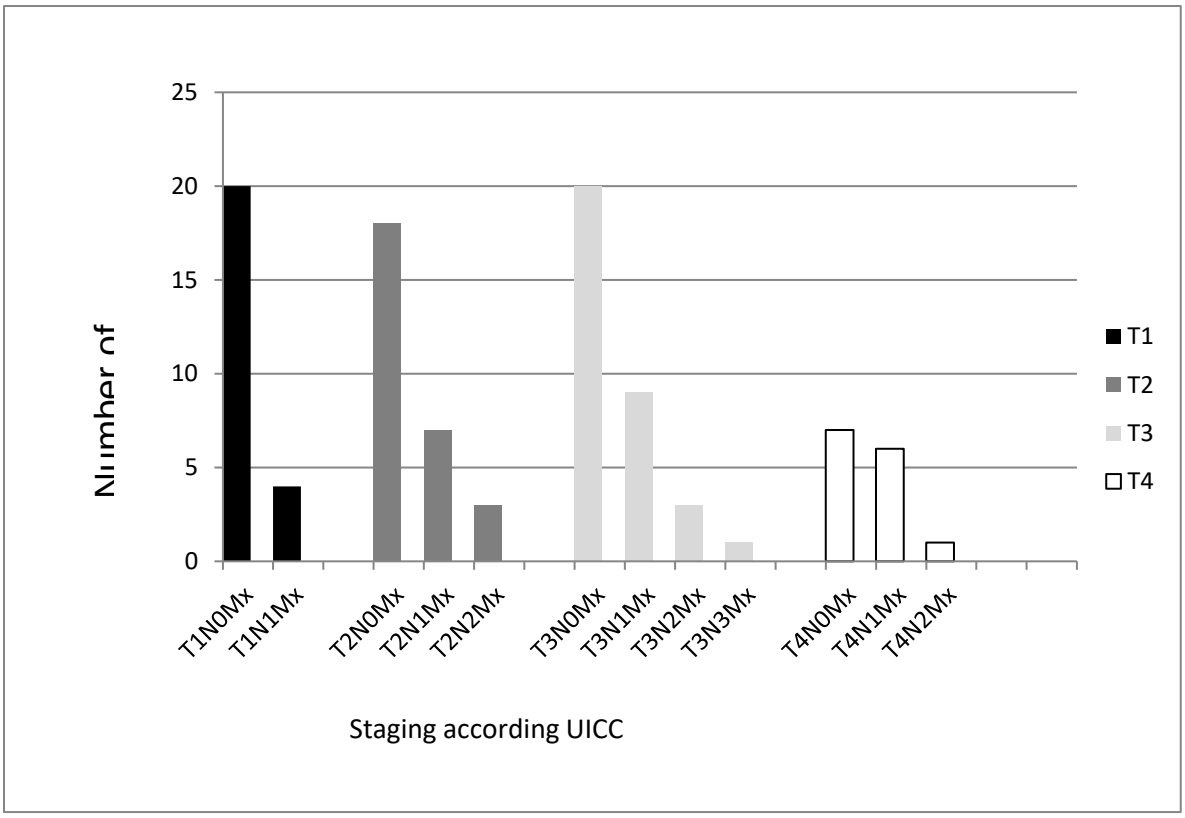


Fig. 2



7. Veröffentlichung II

Comparison of aesthetic outcome of different facial reconstruction techniques after resection of cutaneous squamous cell carcinoma

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Abstract

Purpose: The aim of the study was to compare local and distant flaps for facial reconstruction after resection of cutaneous squamous cell carcinoma.

Patients and Method: Fifty patients with facial CSCC and subsequent facial reconstruction were retrospectively analysed. All complications such as wound infection, wound dehiscence, flap necrosis, partial or total flap loss were recorded. The aesthetic outcome was evaluated using colour prints of patients' photographs of different flaps in terms of skin, colour, texture and scars by three judges. To compare the aesthetic outcome of distant and local flaps a Wilcoxon-Mann-Whitney-U-Test was applied.

Results: The overall complication rate was low. Colour and texture of local flaps presented with statistically significant better results compared to distant flaps. There were no statistically significant differences between scars of local flaps and distant flaps ($p=0.528$). A slight tendency was found showing scars of local flaps to be less visible than scars of distant flaps in defects extending in more than one facial aesthetic unit.

Conclusion: Local flaps show statistically significant better aesthetic results compared to distant flaps in terms of colour and texture. Scars of local flaps seem to be slightly less visible compared to distant flaps in cases where defects were bridging more than one facial aesthetic unit.

Key words: aesthetic facial units, facial reconstruction, cutaneous squamous cell carcinoma

Introduction

Surgery is still the first line treatment for cutaneous squamous cell carcinoma (CSCC)of the head and neck. Low rates of relapse and high cure rates of 95% can be obtained (Obermeier K. et al., 2017). However, ablative surgery can lead to large facial defects requiring extensive reconstruction (van Leeuwen AC. et al., 2015). Especially the face as part of human identity and is vital for a person's life and should be reconstructed considering aesthetic aspects. Therefore, preservation of facial aesthetic units such as nasal, forehead, zygomatic, infraorbital, periorbital, mandibular, chin, lower lip, upper lip, nasal, ear and temple is an important part in facial reconstruction (Baker SR., 1990). Often more than one facial aesthetic unit is affected after tumor resection requiring in more complex reconstruction strategies.

A variety of local and distant flaps for covering facial defects have been developed (Pepper JP. and Baker SR., 2013; Chen WL. et al., 2017). Microvascular flaps are an option in case of large defects. However, these flaps often include poor colour match and bulky tissue (Rao JK. and Shende KS., 2016). Local flaps are easier to handle and the surgical procedure is often faster. Furthermore, the colour of the flaps matches the circumjacent skin. Local flaps are, however, limited to smaller and medium size defects (Dölen UC. And Koçer U., 2018).

The aim of this study is to evaluate and compare different local and distant flaps for facial reconstruction after resection of CSCC. Local and distant flaps are compared regarding complication rates and aesthetic outcome.

Material and Methods

This study was approved by the institutional review board of the University Hospital of Munich, Germany (Munich, Germany; UE Nr 138-14). The present retrospective study includes 50 patients, who underwent surgical resection and reconstruction of facial CSCC between 2007 and 2014.

Twenty-six patients were male and 24 female. The mean age of the patients at time of reconstructive surgery was 83.2 years, ranging from 53 to 105 years. Only patients with facial CSCC and subsequent facial reconstruction were included. In 35 patients only one aesthetic facial unit was affected (8 forehead, 3 nose, 6 orbital, 13 lower lip, 3 upper lip and 2

mandibular aesthetic facial unit). In 15 patients the defect after tumor resection extended into more than one aesthetic facial unit. In 11 patients 2 aesthetical facial units were affected, in 3 patients 3 and in one patient 5. (Table 1)

Patient records and all available documents, radiographs and photographs were reviewed retrospectively. Data were collected on maximum defect size after resection, defect-site, affected facial aesthetic unit and kind of reconstruction. Moreover complications such as wound infection, wound dehiscence, flap necrosis and partial or total flap loss were recorded. In addition further information about secondary surgical interventions after the primary reconstruction was collected.

Postoperative photographs are available in all 50 patients. The photographs were taken after a mean time of 143 days after surgery (range: 12 days – 805 days). The aesthetic outcome was evaluated using colour prints of patient's photographs in terms of skin colour, scars and texture by three judges. These judges rated the photographs in random order. To evaluate the aesthetic outcome in terms of skin colour, scars and texture of the reconstruction a 5-point scoring system (1 = very good; 2 = good; 3 = fair; 4 = poor; 5 = very poor) was applied. (Fig. 1) Patients were divided into two groups, those with local and those with distant flap reconstruction. (Table 2) Eleven different flaps were used. The aesthetic outcome in both groups in terms of skin colour, scars and texture was compared. Additionally, the mean score of all three parameters (colour, scar and texture) was determined for each kind of flap that was used more than once.

Statistical analysis

Statistical analysis was conducted using SPSS® 24 version 4.0 (SPSS Inc., Chicago, IL, USA). To compare the aesthetic outcome of distant and local flaps a Wilcoxon-Mann-Whitney-U-Test was applied. This test was used because data were scaled in an ordinal scaling system. Before applying the statistic test median values were calculated for each criteria: texture, colour and scar appearance. Statistical significance was defined as $p<0.05$.

In order to avoid distinctly visible scars closure lines are placed at the junction of facial aesthetic units. (Robinson JK., 2004). A Wilcoxon-Mann-Whitney-U-Test was used to compare scars of reconstructed defects that were limited to a single facial unit with those extending into more than one facial aesthetic unit. Statistical significance was defined as $p<0.05$.

Further, it was investigated whether there is a difference in the appearance of scars in local versus distant flaps in cases of reconstructed defects that extended into more than one facial aesthetic unit. However, no statistical analysis was performed for the distant flap group due to the small number of samples (n=4). Instead, box plots were used for exploratory data analysis.

Results

Forty local flaps (10 rotation flaps, 10 transposition flaps, 9 bilateral advancement flaps, 4 paramedian forehead flaps, 4 Bernard/Burrow cheek advancement flaps, one Abbé flap, one Dieffenbach flap and one advancement flap) and 10 distant flaps (6 radial forearm flaps, 2 latissimus dorsi flaps and 2 split skin flaps) were used for reconstruction of facial defects after resection of cutaneous squamous cell carcinoma. (Table 2) The affected aesthetic facial unit and the kind of flap used for reconstruction is displayed in Table 3.

The mean maximum defect size after tumor resection was 3.7 cm, ranging from 0.6 cm to 11 cm. In 6 cases the tumor infiltrated the orbit and an exenteration of the orbit had been performed.

The overall complication rate was low. Wound dehiscence occurred in 3 local flaps (2 Bernard/Burrow cheek advancement flaps, one transposition flap) and one distant flap (split skin flap). Neither no flap necroses, nor partial or total flap losses were recorded. Secondary surgical procedures after the primary reconstruction were reported in 3 patients. Two patients with latissimus dorsi flap reconstruction required volume reduction of the flap. One patient with Bernard/Burrow cheek advancement flap reconstruction received secondary intervention in terms of restoration of the vermillion of the lip.

The aesthetic outcome in terms of colour, texture and scar appearance of distant flaps compared to local flaps was evaluated using a Wilcoxon-Mann-Whitney-U-Test. There were statistically significant differences between the two groups (distant flaps vs. local flaps) regarding colour and texture ($p<0.05$). Colour and texture of local flaps exhibited with statistically significantly better results compared to colour as well as texture of distant flaps. There were no statistically significant differences between scars of local flaps versus scars of distant flaps ($p=0.528$). Box plots are displayed in Fig. 2 for better visualisation of the results.

There were no statistically significant differences between the appearance of scars of reconstructed defects limited to a single facial unit and those extending into more than one facial aesthetic unit ($p=0,07$).

The rating of the scar appearance in local and distant flaps in cases of reconstructed defects extending into more than one facial aesthetic unit are shown in bow plot in Fig. 3. Scars in local flaps score slightly lower than those in distant flaps. Hence, scars of local flaps seem to be less obvious than scars of distant flaps in the examined subgroup.

The results of the evaluation of the aesthetics are evaluated in terms of colour, scar appearance and texture for each flap. The results for all the flaps that were used more than once are shown in Fig.4. Furthermore, the mean score of all three parameters (colour, scar appearance and texture) was determined for each kind of these flaps. The flap with the best aesthetic results in colour, scar appearance and texture shows the transposition flap with an average score of 1.4. The Bernard/Burrow cheek advancement flap achieved the second-best result (average score 1.75), followed by the rotation flap (average score 1.91) and the bilateral advancement flap (average score 2.07). The average score of the split skin-flap was 2.57, of the paramedian forehead flap 3.08, of the radial forearm flap 3.6 and of the latissimus dorsi flap 4.16.

Discussion

Free flap reconstruction of the face is usually the first choice in case of large defects (Rao JK. and Shende KS., 2016). However, the main disadvantage of free flaps is that colour, texture

and thickness often do not match the skin. Therefore, local flaps still play a substantial role in the reconstruction of facial defects (Lee RG. and Baskin JZ., 2006). Interestingly, overall complication rates between local and distant flaps have been demonstrated to be similar. In a retrospective study Heth JA. et. al. evaluated 67 patients with local or distant flaps for skull base reconstruction (Heth JA. et al., 2002). Wound complications occurred in 28% of all patients with similar rates for local and distant flaps. Free flaps were associated with early wound complications, whereas local flaps often come along with late wound breakdown complications.

In the present study, complications such as wound dehiscence were found in only 8% of the patients. Furthermore, wound dehiscence mainly occurred in local flaps as an early complication and was therefore rather related to unfavourable wound closure tension.

Postoperative flap necrosis with partial or total flap loss is a major complication in locally pedicled as well as in distant flaps (Smolka W. and Iizuka T., 2005). Fortunately, the success rate of free tissue transfer has been reported to range from 91% to 99% (Suh JD. et al., 2004). However, no flap necrosis and partial or total flap loss was found in the present study.

One of the main advantages of local flaps for facial reconstruction is a similar colour and texture of the flap and the region to be reconstructed (Lee KS. et al., 2017). However, the tissue does not match the facial skin in colour and texture and in distant flaps they therefore often appear as a mismatched patch within the normal facial skin (Menick FJ., 1998, Fernandes R. and Clemow J., 2012). In the presents study local flaps were proven to offer statistically significantly better results compared to distant flaps in terms of colour and texture.

Whenever possible, scars resulting from facial reconstruction should be hidden and therefore lie along a boundary of a facial aesthetic unit (Omidi M. and Granick MS., 2004). Defects bridging facial aesthetic units should, therefore, be segmentally repaired with combinations of flaps in order to place scars at the junction of facial aesthetic units (Robinson JK., 2004). However, in the present study, all defects were reconstructed with a single flap even in cases were defects extended into more than one facial aesthetic unit. Interestingly, there was no statistically significant difference between the appearance of scars of reconstructed defects

limited to a single facial unit and those bridging more than one facial aesthetic unit. However, scars of local flaps seem to be less visible than scars of distant flaps in cases where defects are bridging more than one facial aesthetic unit.

Lee et al. evaluated patients' satisfaction after facial reconstruction with local and distant flaps using a scoring system (Lee KS. et al., 2017). Satisfaction of patients having underwent facial reconstruction was rated higher with local flaps. The results of the present study are with accordance to the findings of Lee et al. Regarding aesthetics, local flaps showed better results than distant flaps in terms of skin colour and texture in reconstructing natural appearance. Scars resulting from local flaps seem to be slightly less visible than scars of distant flaps in defects extending into more than one facial aesthetic unit.

In the present study, transposition flaps achieved the best aesthetic outcome whereas latissimus dorsi flaps had the worse. However, each facial defect requires individual reconstruction approaches as defects differ in size, depth and location of a defect (Fernandes R. et al., 2012). For example large and deep defects require a bulky flap such as a distant microvascular free flap. In cases of total defects of the lip a reconstruction of the ring muscle is indicated. Furthermore, an incision for local flap repair, which is not well hidden under a skin tension line, will result in an insufficient scar (Lee KS. et al., 2017). Hence, the results of the present study must be interpreted on the basis of common sense standards for facial reconstruction.

Conclusion

Local flaps offer statistically significantly better aesthetic results compared to distant flaps in terms of colour and texture. Scars of local flaps seem to be slightly less visible than distant flaps in cases where defects are bridging more than one facial aesthetic unit. However, these results should be interpreted on the basis of common-sense standards for facial reconstruction.

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Tables

Table 1: Patients with more than one aesthetical face unit affected by tumor resection

patients	number of aesthetic facial unit affected	kind of aesthetic facial unit
1	2	zygomatic, mandibular
2	2	zygomatic, mandibular
3	2	zygomatic, mandibular
4	2	zygomatic, mandibular
5	2	zygomatic, mandibular
6	2	zygomatic, mandibular
7	2	lower lip, chin
8	2	zygomatic, orbital
9	2	zygomatic, temple
10	2	Zygomatic, temple
11	2	temple, orbital
12	3	nose, orbital, upper lip
13	3	orbital, temple, zygomatic
14	3	ear, zygomatic , mandibular
15	5	orbital, nose, temple, zygomatic, lower lip

Table 2: Kind and number of local and distant flaps.

local flaps (number)	distant flaps (number)
rotation flap (10)	radial forearm flap (6)
paramedian forehead flap (4)	latissimus dorsi flap (2)
transposition flap (10)	split skin flap (2)
bilateral advancement flap (9)	
Bernard/Burrow cheek advancement flap (4)	
Abbé flap (1)	
Dieffenbach flap (1)	
advancement flap (1)	

Table 3: Affected aesthetic units and kind of reconstruction

Patient No.	Kind of reconstruction	Affected aesthetic unit
1	rotation flap	forehead
2	rotation flap	zygomatic, mandibular
3	rotation flap	zygomatic, orbital
4	rotation flap	forehead
5	rotation flap	orbital, temple, zygomatic
6	rotation flap	forehead
7	rotation flap	temple, orbital
8	rotation flap	forehead
9	rotation flap	zygomatic, mandibular
10	rotation flap	forehead
11	transposition flap	orbital
12	transposition flap	mandibular
13	transposition flap	mandibular
14	transposition flap	orbital
15	transposition flap	zygomatic, mandibular
16	transposition flap	zygomatic, mandibular
17	transposition flap	lower lip
18	transposition flap	zygomatic, temple
19	transposition flap	lower lip
20	transposition flap	zygomatic, mandibular
21	bilateral advancement flap	lower lip
22	bilateral advancement flap	lower lip
23	bilateral advancement flap	lower lip
24	bilateral advancement flap	lower lip
25	bilateral advancement flap	lower lip
26	bilateral advancement flap	upper lip

27	bilateral advancement flap	lower lip
28	bilateral advancement flap	lower lip
29	bilateral advancement flap	nose
30	radial forearm flap	orbital
31	radial forearm flap	zygomatic, mandibular
32	radial forearm flap	forehead
33	radial forearm flap	orbital
34	radial forearm flap	zygomatic, temple
35	radial forearm flap	orbital
36	Bernard/Burrow	lower lip
37	Bernard/Burrow	lower lip
38	Bernard/Burrow	lower lip
39	Bernard/burrow	upper lip
40	latissimus dorsi flap	lower lip, chin
41	latissimus dorsi flap	orbital, nose, temple, zygomatic, lower lip
42	splitskin flap	forehead
43	splitskin flap	ear, zygomatic, mandibular
44	paramedian forehead flap	nose
45	paramedian forehead flap	orbital
46	paramedian forehead flap	nose
47	paramedian forehead flap	nose, orbital, upper lip
48	Abbé-flap	upper lip
49	Dieffenbach	lower lip
50	advancement flap	forehead

Figure legends

Fig. 1: Clinical example of local flap (A, B). Intraoperative view of rotation flap (A) and postoperative view (B). Radial forearm flap as an example for a distant flap (C).

Fig. 2: Box plots showing aesthetic outcome in terms of colour, texture and scar of distant flaps compared to local flaps.

Fig. 3: Box plots showing the appearance of scars in local versus distant flaps in cases of reconstructed defects that extended into more than one facial aesthetic unit.

Fig. 4: Overview of all flaps evaluated after the 5-point-score system

Fig. 1 A

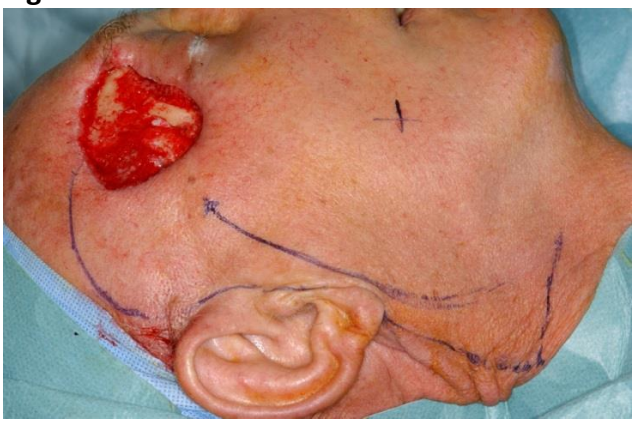


Fig. 1 B

Fig. 1 C

Fig. 2

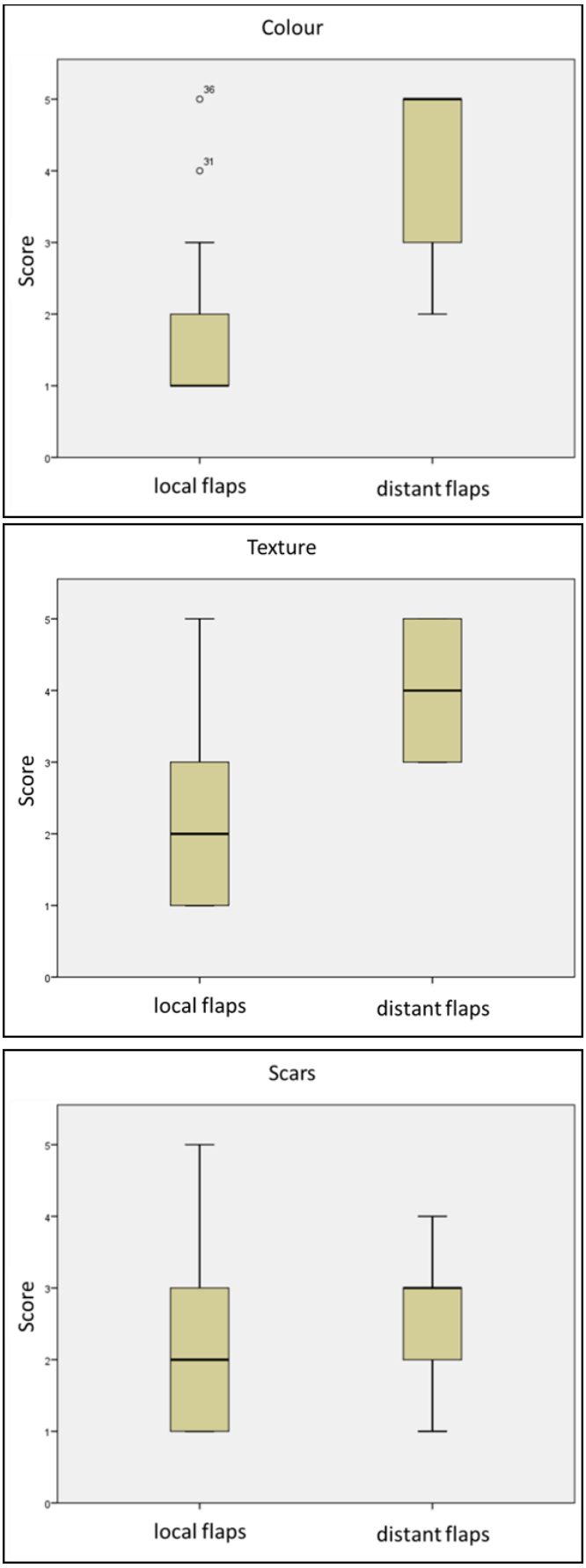

Colour
Score
36
31
local flaps
distant flaps
Texture
Score
local flaps
distant flaps
Scars
Score
local flaps
distant flaps

Fig. 3

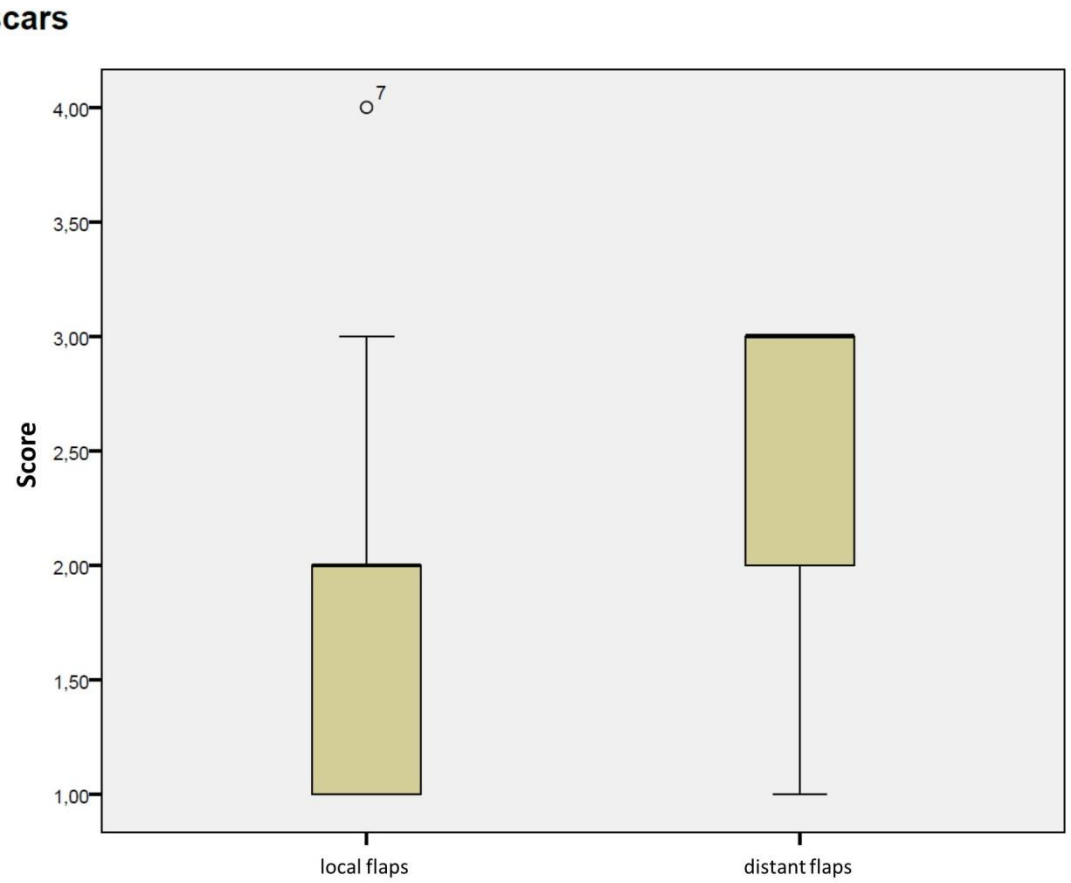
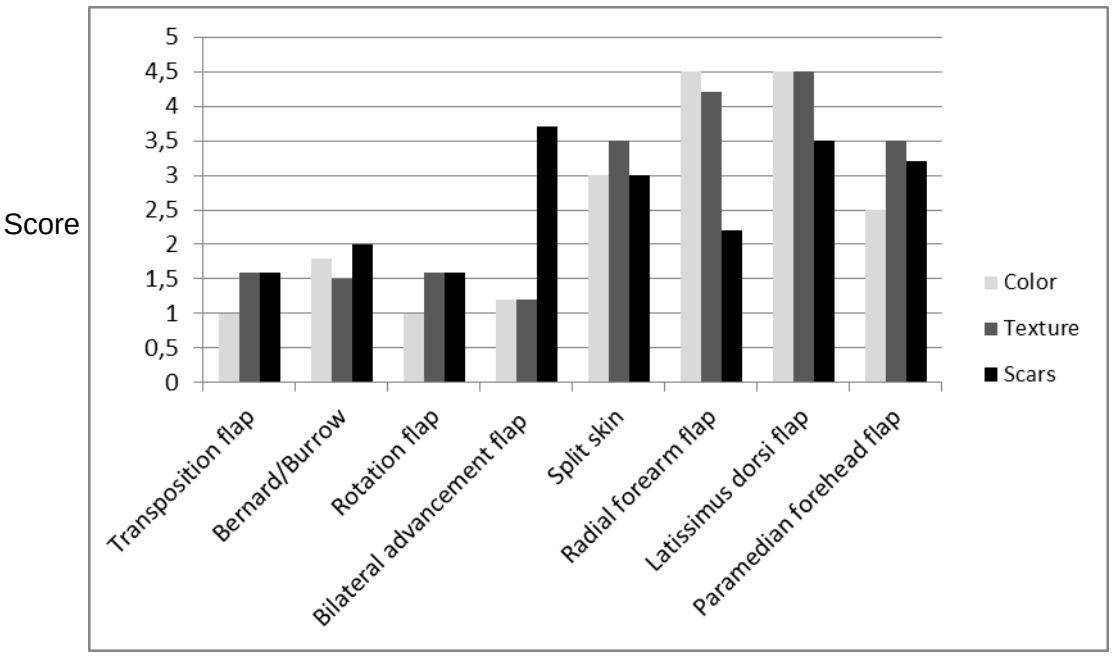

scars
Score
4,00
3,50
3,00
2,50
2,00
1,50
1,00
7
local flaps
distant flaps

Fig. 4


Score
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
Color
Texture
Scars
Transposition flap
Bernard/Burrow
Rotation flap
Bilateral advancement flap
Split skin
Radial forearm flap
Latissimus dorsi flap
Paramedian forehead flap

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