CLINICAL REVIEW

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# CRANIOFACIAL SURGERY FOR NONMELANOMA SKIN MALIGNANCY: REPORT OF AN INTERNATIONAL COLLABORATIVE STUDY

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**Abstract:** *Background.* This study examined the efficacy of craniofacial surgery (CFS) in treating locally advanced nonmelanoma skin cancer (NMSC).

*Methods.* One hundred twenty patients who underwent CFS for NMSC were identified from 17 participating institutions. Patient, tumor, and treatment information was analyzed for prognostic impact on survival.

*Results.* Surgical margins were negative in 74%, close in 3%, and involved in 23% of patients. Complications occurred in 35% of patients, half of which were local wound problems. Operative mortality was 4%. Median follow-up interval after CFS was 27 months. The 5-year overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) rates were 64%, 75%, and 60%, respectively. Squamous cell histology, brain invasion, and positive resection margins independently predicted worse OS, DSS, and RFS.

*Conclusion.* CFS is an effective treatment for patients with NMSC invading the skull base. Histology, extent of disease, and resection margins are the most significant predictors of outcome.
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**Keywords:** skull base neoplasm; skull base/craniofacial surgery; skin cancer; head and neck; basal cell carcinoma; squamous cell carcinoma; treatment outcome; international collaboration

Skin cancer is the most common malignancy occurring in humans; 90% of these are nonmelanoma skin cancers (NMSCs).[1] Cutaneous basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), if diagnosed early and appropriately treated, have an excellent prognosis for cure. However, if neglected or undertreated, they can cause extensive local tissue destruction and occasionally disseminate, causing significant functional and aesthetic morbidity, and at times, death.[2,3] The head and neck region, which experiences a significant amount of solar exposure, is the predominant site of origin for these cancers. Head and neck NMSCs are notorious for extensive local subclinical spread along fascial planes, perichondrium, periosteum, vessels, and nerves. Embryonic fusion planes in the facial "H-zone" allow tumors to invade deeply and gain access to the skull base.[4] Skull base involvement complicates management, as surgical resection would then necessitate a combined craniofacial approach. Fortunately, craniofacial surgery (CFS) is seldom indicated for these tumors, but this also means that single institutional reports of outcomes are based on small numbers of patients that precludes meaningful statistical analysis. The International Collaborative Study on Craniofacial Surgery for skull base tumors[5] has provided a unique opportunity to examine the relevance of CFS in patients with tumors that ordinarily seldom require the operation. Herein, we present a detailed subgroup analysis of patients with NMSC treated with CFS for involvement of the skull base.

## PATIENTS AND METHODS

The collective report of the International Collaborative Study Group has been previously published, and the reader is referred to that source for details regarding study design.[5]

**Data Entry, Patient Exclusions, and Statistical Methods.** Of the 1307 eligible patients, 120 (9%) had undergone CFS for NMSC and were selected for this analysis. The follow-up interval was calculated in months from the date of CFS to the date of last follow-up or death, and the recurrence-free interval was calculated from the date of CFS to that of first recurrence. Overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) rates were calculated using the Kaplan–Meier method. Clinicopathological variables of significance were identified by the log-rank test and analyzed for independent effect by multivariate analysis using the Cox proportional hazards model.

**Patient Demographics.** Eighty-five patients were male (71%) and 35 were female (29%). The age range was 3 to 93 years (median age, 61 years). Medical comorbidity, including chronic obstructive pulmonary disease, cardiovascular disease, diabetes mellitus, and alcohol abuse, was reported in 17% of the 118 patients who had this data documented.

**Primary Tumor.** The anatomic attributes and extent of the primary tumor are listed in Table 1. Most tumors involved the anterior cranial fossa (104/120 or 87%). Only 7 patients had primary tumors involving the ear and temporal bone (7/120, 5%). Although BCC was the predominant histology (106/120 or 88%), in the subgroup of patients with ear and temporal bone tumors, SCC was more common (5/7, 71%). Because of the heterogeneity in reporting, no meaningful analysis of the individual categories of TNM staging was possible. However, only 2/116 (2%) patients had regional lymph node metastasis, both of whom had primary squamous cell cancers involving the temporal bone, and none had distant metastasis at presentation.

**Treatment.** A majority of patients (63%) had undergone some form of treatment prior to CFS, many of whom had received multiple treatment modalities. Seventy-two patients (60%) had previous surgery, and 29 patients (24%) had received previous radiation therapy (range, 2880–7540

**Table 1.** Location, extent, and pathology of the primary tumor.

| | No. of patients (%) |
|---|---|
| Involvement of skull base | |
| Anterior cranial fossa | 104 (86.7) |
| Middle cranial fossa | 15 (12.5) |
| Anterior and middle cranial fossae | 1 (0.83) |
| Orbital invasion | |
| None | 35 (29.7) |
| Periosteum | 21 (17.8) |
| Bone | 10 (8.48) |
| Intraorbital contents | 52 (44.1) |
| Data not reported | 2 |
| Intracranial extension | |
| None | 40 (33.9) |
| Bone invasion | 51 (43.2) |
| Dural invasion | 23 (19.5) |
| Brain invasion | 4 (3.39) |
| Data not reported | 2 |
| Cranial nerve deficits | |
| None | 91 (77.1) |
| Present | 27 (22.9) |
| Data not reported | 2 |
| Tumor histology | |
| Basal cell carcinoma | 106 (88.3) |
| Squamous cell carcinoma | 14 (11.7) |

**Table 2.** Details of craniofacial resection.

| | No. of patients (%) |
|---|---|
| Type of approach ($n = 117$) | |
| Anterior fossa | 99 (84.6) |
| Middle fossa | 16 (13.7) |
| Anterior and middle fossae | 2 (1.71) |
| Margins of resection ($n = 105$) | |
| Close | 3 (2.86) |
| Negative | 78 (74.3) |
| Positive | 24 (22.8) |
| Reconstruction ($n = 119$) | |
| No | 10 (8.40) |
| Yes | 109 (91.6) |
| Reconstruction type ($n = 109$) | |
| Autologous nonvascularized tissue | 12 (11.0) |
| Cadaveric or bovine tissue | 1 (0.92) |
| Free flaps | 30 (27.5) |
| Galeal/pericranial flaps | 63 (57.8) |
| Multiple flaps | 2 (1.84) |
| Nonvascularized bone | 1 (0.92) |

cGy; median dose, 5586 cGy). Only 3 patients had been treated with prior chemotherapy.

Table 2 lists the details of CFS, reconstruction, and margin status. Twenty-four patients (23%) had histologically positive margins of surgical resection. Adjuvant postoperative external beam radiation therapy (PORT) was administered to 23 patients (range, 4500–7400 cGy; median, 5700 cGy). One patient received adjuvant postoperative chemotherapy as well.

**Follow-Up.** The follow-up interval ranged from 1 to 279 months with a median of 27 months. The period of follow-up was longer than 5 years in 31 patients (26%).

## RESULTS

Forty-two patients (35%) suffered a postoperative complication, most commonly surgical wound-related (24%). The postoperative mortality rate was 4%. With a median follow-up of 27 months (range, 1–279 months), the 5-year OS and DSS rates, calculated using the Kaplan–Meier method, were 64% and 75%, respectively. The median time to recurrence was 18.5 months (range, 1–143 months) and the 5-year RFS was 60%. Information on the patterns of failure was not available for analysis. The median survival for patients with positive margins of surgical resection was 39 months, as opposed to 147 months for those with clear margins ($p < .0001$). Squamous cell histology and presence of brain invasion were independently significant predictors for worse RFS, DSS, and OS (Tables 3–5). Positive margins of surgical resection independently predicted worse RFS and DSS (Tables 3 and 4).

## DISCUSSION

Current literature on CFS largely consists of single-institution retrospective reports, which are difficult to interpret and extrapolate from. Because of the rarity of skull base malignancies, single-center experiences are relatively small, and by necessity, different tumor histologies have often been analyzed collectively irrespective of well-known differences in their biologic behavior. This problem is well exemplified by cutaneous cancers, which aside from a few published reports,[6–8] are generally under-represented in most series on CFS for malignant tumors.[9–11] Furthermore, all SCCs, whether mucosal or cutaneous, are often indistinctively grouped together in these series. This bias in reporting may have occurred in this series as well; only 14/120 (12%) cases included in this report had squamous cell histology. Additionally, a selection bias of contributing institutions may have also been responsible to an extent for the low representation of squamous cell tumors in this study, i.e., patients with advanced SCC of the skin may have been excluded more readily than those with BCC, since the latter group is generally perceived to suffer from a more

**Table 3.** Prognostic predictors of recurrence-free survival.

| Covariate | No. of patients | % 5-year RFS | Univariate analysis, log-rank test | Multivariate analysis relative risk (95% confidence intervals) |
|---|---|---|---|---|
| Age, y | | | | |
| ≤50 | 30 | 58.3 | NS | – |
| ≥51 | 90 | 60.7 | | |
| Sex | | | | |
| Female | 35 | 62.1 | NS | – |
| Male | 85 | 58.3 | | |
| Medical comorbidity | | | | |
| None | 98 | 60.6 | NS | – |
| Present | 20 | 56.0 | | |
| Anatomic location | | | | |
| Anterior cranial fossa | 104 | 61.2 | | |
| Middle cranial fossa | 15 | 59.4 | NS | – |
| Both | 1 | 0.0 | | |
| Orbital involvement | | | | |
| None | 35 | 49.1 | | |
| Periosteum | 21 | 62.3 | NS | – |
| Bone | 10 | 36.0 | | |
| Intraorbital contents | 52 | 71.6 | | |
| Intracranial involvement | | | | |
| None | 40 | 78 | | Reference |
| Bone | 51 | 51.8 | .015 | NS |
| Dura | 23 | 51.7 | | NS |
| Brain | 4 | 0.0 | | 12.7 (1.1–141.8), $p = .039$ |
| Histology | | | | |
| Basal cell carcinoma | 106 | 63.1 | .0009 | Reference |
| Squamous cell carcinoma | 14 | 28.6 | | 4.7 (1.0–21.4), $p = .046$ |
| Surgical margins | | | | |
| Negative/close | 81 | 73.4 | <.0001 | Reference |
| Positive | 24 | 39.0 | | 7.4 (2.8–19.7), $p < .0001$ |
| Previous radiation | | | | |
| No | 91 | 59.6 | NS | – |
| Yes | 29 | 60.3 | | |

*Abbreviations: RFS, recurrence-free survival; NS, not significant.*

indolent and hence controllable disease. The lack of distinction between BCC and the more ominous cutaneous malignancies, if and when skin cancers are analyzed and reported separately, may bias interpretation of results and lead to false conclusions. It is well recognized that treatment outcomes depend significantly on the histologic type of the primary tumor. Therefore, the current study, which is based on information on the largest number of patients accumulated in a single report, was designed to specifically address CFS for cutaneous BCC and SCC. The pros and cons of such a collaborative endeavor are significant.[5] While a large population becomes available for examining outcomes of relatively uncommon tumors and treatments, it necessitates accepting a heterogeneous study population. Specifically, although the details of surgical management are similar between the groups, there are likely to be differences in patient selection, adjuvant treatment, and data collection, and while these differences reduce the effect of less significant events on the data, they allow the results to be more universal in their applicability.

Regional lymph node metastasis is uncommon in patients with BCC relative to SCC. Only 2 patients in this series had regional nodal disease, both of whom had SCC of the temporal bone. Neither patient survived beyond 3 months despite having undergone CFS with negative margins of resection. For the subgroup of patients with regional metastasis from cutaneous SCC, survival remains poor despite aggressive multimodality therapy.[12] Contrastingly, patients with massive, recurrent BCC involving the skull base are at low risk for metastatic disease and generally enjoy better survival outcome depending on the ability to achieve local tumor control.

**Table 4.** Prognostic factors for disease-specific survival.

| Covariate | No. of patients | % 5-year DSS | Univariate analysis, log-rank test | Multivariate analysis relative risk (95% confidence intervals) |
|---|---|---|---|---|
| Age, y | | | | |
| ≤50 | 30 | 65.4 | NS | – |
| ≥51 | 90 | 77.8 | | |
| Sex | | | | |
| Female | 35 | 71.2 | NS | – |
| Male | 85 | 76.8 | | |
| Medical comorbidity | | | | |
| None | 98 | 76.7 | NS | – |
| Present | 20 | 60.3 | | |
| Anatomic location | | | | |
| Anterior cranial fossa | 104 | 76.3 | | |
| Middle cranial fossa | 15 | 74.3 | NS | – |
| Both | 1 | 0.0 | | |
| Orbital involvement | | | | |
| None | 35 | 64.4 | | |
| Periosteum | 21 | 75.5 | NS | – |
| Bone | 10 | 100.0 | | |
| Intraorbital contents | 52 | 77.1 | | |
| Intracranial involvement | | | | |
| None | 40 | 88.7 | | Reference |
| Bone | 51 | 69.8 | .0029 | NS |
| Dura | 23 | 66.5 | | NS |
| Brain | 4 | 0.0 | | 39.2 (2.6–593.7), $p = .008$ |
| Histology | | | | |
| Basal cell carcinoma | 106 | 79.3 | <.0001 | Reference |
| Squamous cell carcinoma | 14 | 28.6 | | 20.2 (3.3–122.3), $p = .001$ |
| Surgical margins | | | | |
| Negative/close | 81 | 82.0 | .0008 | Reference |
| Positive | 24 | 46.1 | | 8.2 (2.5–26.8), $p = .001$ |
| Previous radiation | | | | |
| No | 91 | 77.0 | NS | – |
| Yes | 29 | 66.4 | | |

*Abbreviations: DSS, disease-specific survival; NS, not significant.*

Single-institution reports have yielded conflicting results regarding outcome for patients undergoing CFS for salvage versus those undergoing primary treatment. Some series have reported similar survival between these 2 groups,[9,13] while others have noted improved outcome in the previously untreated setting.[6,8,14] In the Brazilian series, in which skin cancers constituted 51% of the tumors, salvage surgery portended worse prognosis. Whether or not patients had received previous therapy had no impact upon disease specific survival in this collaborative study.[6] This may perhaps be explained by the larger proportion of patients with cutaneous SCC in the former report, whereas BCC far outnumbered SCC in our collective experience. Regardless, a multidisciplinary forum is crucial for discussing various benefits and limitations of both surgical and nonsurgical treatment options, on a case by case basis, to arrive at a suitable treatment plan without undue delay.

The threshold for addition of PORT to the treatment plan is generally lower in patients undergoing CFS because of the inherent anatomic difficulty in obtaining wide surgical margins of clearance. Adjuvant PORT was administered in 19% of patients in the current study, and this figure may have been limited by the fact that as many as 24% of patients had been treated with external beam radiation therapy prior to referral for CFS. Another important contributing factor may have been related to geographic differences in the patterns of practice. Most of the patients in this series were from institutions in South America (92/120, 77%). Postoperative radiation therapy was only delivered to 16% of these patients.

**Table 5.** Prognostic factors for overall survival.

| Covariate | No. of patients | % 5-year OS | Univariate analysis, log-rank test | Multivariate analysis relative risk (95% confidence intervals) |
|---|---|---|---|---|
| Age, y | | | | |
| ≤50 | 30 | 56.2 | NS | – |
| ≥51 | 90 | 66.5 | | |
| Sex | | | | |
| Female | 35 | 61.6 | NS | – |
| Male | 85 | 65.4 | | |
| Medical comorbidity | | | | |
| None | 98 | 66.5 | NS | – |
| Present | 20 | 47.6 | | |
| Anatomic location | | | | |
| Anterior cranial fossa | 104 | 67.4 | | |
| Middle cranial fossa | 15 | 45.7 | NS | – |
| Both | 1 | 0.0 | | |
| Orbital involvement | | | | |
| None | 35 | 54.6 | | |
| Periosteum | 21 | 67.8 | NS | – |
| Bone | 10 | 100.0 | | |
| Intraorbital contents | 52 | 63.0 | | |
| Intracranial involvement | | | | |
| None | 40 | 81.9 | | Reference |
| Bone | 51 | 58.1 | .005 | NS |
| Dura | 23 | 50.4 | | NS |
| Brain | 4 | 0.0 | | 6.8 (1.0–45.8), $p = .048$ |
| Histology | | | | |
| Basal cell carcinoma | 106 | 71.0 | <.0001 | Reference |
| Squamous cell carcinoma | 14 | 14.3 | | 9.6 (3.4–27.1), $p < .0001$ |
| Surgical margins | | | | |
| Negative/close | 81 | 65.4 | NS | – |
| Positive | 24 | 46.1 | | |
| Previous radiation | | | | |
| No | 91 | 63.3 | NS | – |
| Yes | 29 | 66.4 | | |

*Abbreviations: OS, overall survival; NS, not significant.*

Because of the small proportion of patients treated with postoperative radiation therapy and the unclear selection criteria used, we cannot derive any meaningful conclusion as to any beneficial role from adjuvant radiation therapy in this series.

As in the current study, most individual series of CFS with significant numbers have reported postoperative complications in approximately 35% to 50% of patients.[9,11] The ranging values likely represent institutional differences in patient selection and reporting criteria for CFS. The postoperative mortality rate in the current collaborative study was 4%. Age, or medical comorbidity, did not appear to be significant confounding factors for various outcome measures in this study. Only 17% of patients in this study were reported to have other medical ailments. This may indicate overall stringent patient selection criteria, or that patients with locally advanced skin cancers are generally healthier in comparison to patients with other malignant histologies. Also noteworthy is that the surgical defects of 27% of patients in this series underwent reconstruction with free tissue transfer. The availability of technical expertise in free tissue transfer has significantly enhanced our ability to resect components of the facial and cranial anatomy while preventing significant complications such as cerebrospinal fluid leaks, brain herniation, and life-threatening infections. The majority of complications in this series were related to local wound problems, which generally resolved with conservative management and did not cause undue prolongation of postoperative recovery.

In this collaborative report on CFS for NMSC tumor histology, extent of brain invasion, and margin status were evident as significant predic-

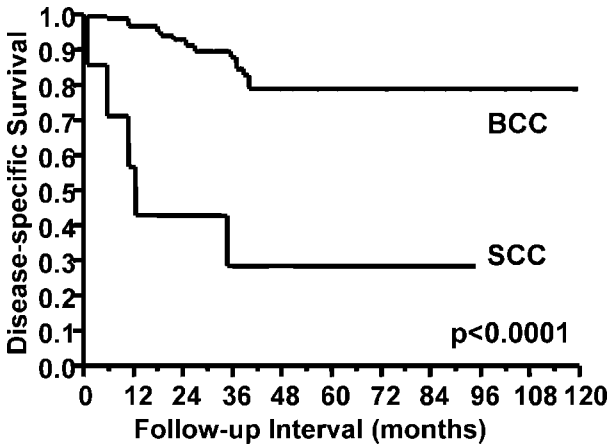


**FIGURE 1.** Disease-specific survival by histology. BCC, basal cell carcinoma, SCC, squamous cell carcinoma.

tors of local failure and disease-related mortality. This is in keeping with smaller single-institution studies such as Backous et al.[15] Patients with cutaneous SCC have a 20-fold greater risk of cancer-related death compared with those with BCC, and a 5-year DSS of only 29% after CFS (Figure 1). Unlike the experience reported from Canada,[7] squamous cell histology clearly portended worse survival outcomes. Brain invasion is an ominous finding and uniformly fatal. None of the 4 patients with brain invasion survived beyond 2 years. Although a number of authors report dural invasion as being a significant negative prognosticator for survival,[9,16–18] it did not impact upon survival outcomes in this subgroup of patients with NMSC. This may be reflective of the difference in biological behavior between BCC, which constituted the majority of cases in this study, and the more aggressive tumor histologies included in the above-cited series. This hypothesis is consistent with the skull base experience of centers with a large proportion of skin cancer patients.[6] The importance of "histologically" complete resection of malignant tumors in improving local control and disease-specific survival cannot be overemphasized. Fifty percent of patients with positive surgical margins die of disease within 5 years of treatment.

Cancers of the skin are among the commonest of human malignant tumors, and are generally easy to treat if diagnosed at an early stage. Reasonable locoregional control of the disease can be expected with timely and appropriate therapy and regular posttreatment surveillance. Unfortunately, in a small fraction of patients the disease progresses to necessitate a major surgical procedure such as CFS. Progressive disease with involvement of the face and skull can be not only aesthetically unpleasing and functionally debilitating, but also nonsalvageable despite aggressive surgery. Treatment decisions should be made on an individual basis with careful consideration of the histology of the tumor, its local extent, and the feasibility of complete surgical resection.

## CONCLUSION

Our data validate the use of CFS as an effective treatment modality in patients with NMSC invading the skull base. Selection and prognostication is similar to CFS in general, with tumor histology, extent of tumor at presentation, and adequacy of surgical resection being the most significant predictors of outcome.

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