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ORIGINAL RESEARCH—SKULL BASE SURGERY

Extending the traditional resection limits of squamous cell carcinoma of the anterior skull base

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OBJECTIVES: Preliminary report to evaluate the efficacy of resection of squamous cell carcinomas that demonstrate intracranial invasion.

METHODS: A retrospective review of all cases of extracranial squamous cell carcinomas that extend intracranially treated by a single surgeon.

RESULTS: A total of 21 cases were reviewed. In 6 cases, there was noted to be overt brain invasion. Complete resection of the intracranial disease was achieved in each of the remaining 15 cases. There were no instances of CSF leak, meningitis, brain abscess, stroke, or other intracranial complication noted either acutely or secondarily. In follow-ups that ranged from 10 months (single patient died of disease at 10 months) to 6 years (average, 3.8 years), there were no instances of intracranial recurrence. There was a disease-free control rate of 67.7% at an average follow-up of 4.1 years.

CONCLUSIONS: Extending the resection of squamous cell carcinoma into the intracranial vault judiciously as outlined appears to be associated with acceptable outcomes in the treatment of advanced squamous cell carcinoma of the skull base.

Malignant involvement of the skull base remains a challenge for the surgeon. Historically, involvement of the skull base precluded curative surgical intervention and was deemed futile in this region. In fact, early attempts resulted in less than optimal results from both functional and oncologic perspectives. Over the last 30 years, the evolution of surgical technique and instrumentation has significantly improved the ability of surgeons to resect malignancy at the skull base. In addition, advances in radiographic imaging modalities have increased the accuracy of diagnostic imaging, surgical treatment planning, and postoperative monitoring associated with the skull base. In order to provide meaningful data, many reports within the literature related to surgical management of skull base malignancies combine varied histologic diagnoses in order to obtain sufficient numbers. This creates a considerable shortcoming in the attempt to define treatment parameters for specific malignant processes that afflict a given patient. It is well known that significant variance in treatment outcomes exists depending on the histologic diagnosis. For example, esthesioneuroblastoma has an excellent prognosis when compared with mucosal melanoma when the skull base is involved. These inherent differences also affect treatment algorithms to some extent. Therefore, it is important to obtain histologically specific information with respect to the treatment of skull base malignancies.

Traditionally, penetration of the skull base with dural involvement has been considered an ominous finding, if not a contraindication to surgical intervention. There exists a potential space between the superior limit of the deep cervical investing fascia and the dura of the cranial fossa that contains the osseous structure of the skull base and cervical soft tissue muscular origins. This space is traversed by the cranial nerves and vessels of the skull base and would not be expected to be a significant natural boundary to spread of carcinoma. Therefore, multiple investigators have evaluated the impact of dural involvement related to outcomes after resection of skull base malignancy.[1-3] Review of the anatomy of the skull base confirms the clinical observation that the multiple layers of the dura provide an important anatomic boundary from both an infectious and oncologic perspective. Recent investigations indicate that involvement of the skull base or dura may be less important to determine the feasibility of surgical resection than cranial nerve extension, widespread dural involvement, or frank parenchymal invasion.[2,3] As such, we have developed and used the treatment algorithm discussed here in an effort to more accurately determine the potential for surgical resection of malignant lesions that extend beyond the skull base into the cranial vault. The purpose of the present study is to report preliminary outcomes based on our experience related to surgical resection of anterior skull base squamous cell carcinoma and present the treatment algorithm currently in use at our institution. The effect of dural invasion or parenchymal involvement related to surgical technique and prognosis will be discussed.

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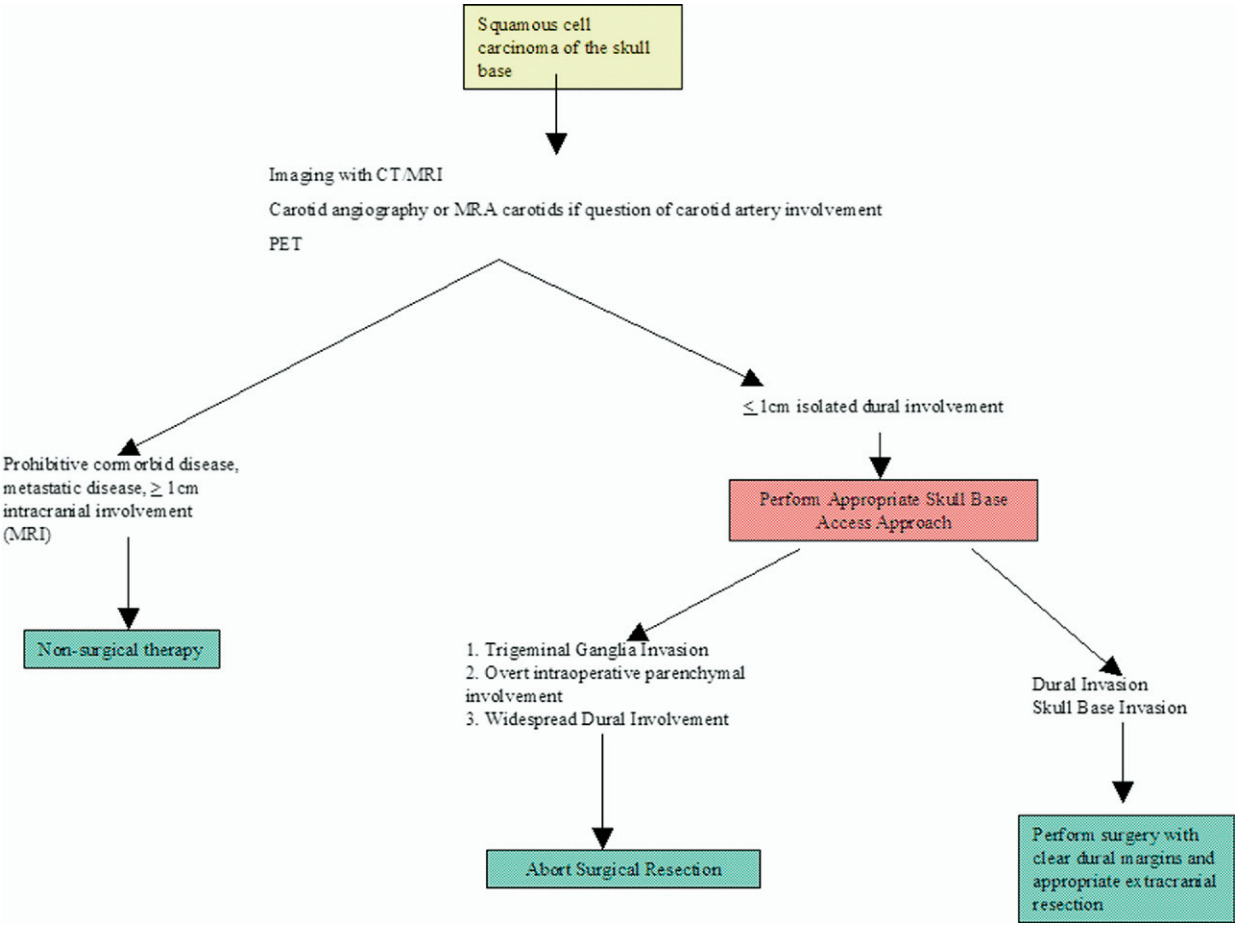

Figure 1 Algorithm for surgical resection of advanced stage skull base malignancy with intracranial extension.

METHODS

This study is a retrospective medical record review of patients treated by the senior author (Y.D.) from August 1997 to July 2005 for skull base malignancy with a minimum follow-up of 12 months. The study was approved by the institutional review board at our institution. All patients underwent appropriate evaluation including clinical examination with fiberoptic nasopharyngoscopy as well as contrast-enhanced computed tomography (CT)/magnetic resonance imaging (MRI) of the primary lesion and brain. Metastatic evaluation included CT of the neck, chest, and abdomen as well as routine laboratory studies. Recently (within the last 3 years), positron emission tomography (PET) scanning has been added to the metastatic evaluation of patients with skull base malignancies at our institution in advanced lesions and when approved by insurance.

Primary surgical resection was offered to all patients deemed appropriate candidates based on clinical examination, CT/MRI findings, and overall medical condition. Included in the review were all patients with biopsy-confirmed squamous cell carcinoma (SCC) that involved the anterior cranial fossa/skull base who underwent surgical resection of the primary tumor as the principal treatment modality. Patients with overt brain parenchymal involvement (as defined by greater than 1 cm extension beyond the dural margin) were not considered for surgical resection and therefore were excluded from the study. Patients who had evidence of metastatic disease or who were deemed inappropriate surgical candidates based on medical condition were also excluded from the review. Patients who selected radiotherapy or chemoradiotherapy as the primary treatment modality were also excluded from this review. The patients in this study were previously untreated.

Surgical resection of the tumor was executed with standard skull base resection techniques via the coronal approach. Techniques included combined anterior cranial fossa, temporal, fronto-temporal craniotomy, as well as orbitozygomatic/orbitocranial approaches as previously described by the senior author.[4,5] Neurosurgical consultation was obtained in all cases with appropriate operative assistance when indicated. Intraoperative evaluation of the tumor after appropriate surgical exposure was then performed and surgical resection was achieved with the algorithm shown in Figure 1. It should be stated that although this report concerns advanced squamous cell carcinoma of the skull base, we currently apply the treatment algorithm as outlined in Figure 1 for a variety of histologic diagnoses. In addition, it is our opinion that resection of skull base melanoma re-

mains a viable option for some patients, but given the universally poor long-term prognosis, extensive preoperative counseling is warranted.

Management of dural involvement is performed in the following manner. Dural incisions are performed approximately 1 to 2 cm from the suspected site of dural involvement as determined by the preoperative MRI scan. If overt parenchymal involvement of the brain is suspected, frozen section biopsy is performed. If frozen section biopsy is positive, then no further attempts at oncologic resection are made. This is due to the fact that outcomes in terms of survival and locoregional control are generally unchanged and undue surgical morbidity is inflicted on the patient when resection of the extracranial portion of the tumor is completed. It should be noted that if preoperative imaging studies confirm frank parenchymal involvement with malignancy, surgical resection is not an option offered to the patient. It is only in cases in which MRI scanning shows focal dural or parenchymal enhancement less than 1 cm that this staging procedure is performed. (See discussion.)

In the event that isolated dural involvement is discovered, the dura is resected with a surgical margin of >1 cm preferred. Intraoperative frozen section analysis of the resected dural margins is performed with further resection of the dura completed if the surgical margins are found positive for malignancy. The involved portion of the osseous skull base is resected via the intracranial approach with a >1 to 2 cm margin preferred. Involved neural foramina falling within this margin are sacrificed. The carotid artery is released and subsequently translocated from the carotid canal if it falls within the 1 to 2 cm margin of resection but is not grossly involved with malignancy. Overt malignant involvement of the carotid artery requires judicious tumor excision with positive margins that require postoperative radiotherapy. In the case of malignant invasion of the major divisions of the trigeminal nerve, as is often observed with infratemporal or pterygopalatine fossae involvement, the trigeminal ganglion is identified. Any and all divisions in proximity to tumor at the extracranial level are at this point sacrificed and a clean margin sought distal to the trigeminal ganglion. If the margin involves the ganglion itself, the procedure is aborted for reasons already given (Fig 1).

At this point in the procedure, resection of the extracranial tumor is performed with the use of a standard technique. Appropriate management of the neck, including formal neck dissection if warranted, is performed at this time. Dural incisions/defects are repaired with xenograft material such as absorbable bovine collagen sheeting and sealed with fibrin glue. Reconstruction of the defect is then performed with the primary objectives being separation of the intracranial and extracranial compartment and restoration of the facial skeleton if indicated. Separation of the intracranial compartment from the paranasal sinuses and pharynx (and aerodigestive tract flora) is essential to prevent cerebrospinal fluid leakage, meningitis, and to provide cerebral support as well as protect neural and vascular structures exposed during surgical resection. Reconstruction is performed with a variety of techniques including regional (temporalis, pericranial, pectoralis) or microvascular (latisimus, radial forearm, rectus) flaps as previously described.[6,7]

All patients received either preoperative (n = 6) or postoperative (n = 9) radiation therapy (5500 to 7000cGy) that extended from the area of intracranial involvement through the primary site and into the draining lymph nodes. Adjunctive chemotherapy was only variably provided in 8 patients. The most common agents administered were cisplatin and 5-fluorouracil.

RESULTS

A total of 21 cases were reviewed. There were 15 males and 6 females with an average age of 62.6 years. In 6 cases, there was noted to be overt brain involvement or trigeminal ganglion invasion as documented on initial craniotomy and biopsy as outlined in the treatment algorithm. Definitive resection was not performed in this subset of patients. The remaining 15 patients had involvement, alone or in combination, of the bone of the skull base/widening neural foramina (11), intracranial neural involvement of trigeminal nerve below the level of the trigeminal ganglion (9), limited dural involvement (6), and overt (full thickness) dural involvement (4). Primary sites included ethmoid sinus (7), maxillary sinus (9), and facial skin (5). Complete resection of the intracranial disease was achieved in each of the latter 15 cases. Although all cases had significant anterior fossa involvement, 8 patients had lateral extension into the infratemporal fossa and half of these required carotid mobilization. There were no instances of CSF leak, meningitis, brain abscess, stroke, or other major intracranial complications noted either acutely or secondarily. There were 3 cases of delayed skin atrophy and temporal bone exposure in patients undergoing postoperative radiation therapy. All of these had had temporalis flap harvest for skull base reconstruction and hydroxyapatite cement cranioplasty.

Definitive resection of the disease below the level of the skull base was achieved in each case with gross clearance of disease. Patients who required carotid mobilization did not have adverse effects on survival as compared with those who did not require mobilization. Complete resection is important. On follow-ups that ranged from 10 months (earliest death was at 10 months in a single patient who died of disease) to 6.4 years (mean, 4.1 years; median, 4.3 years), there were no instances of intracranial recurrence. There were a total of 5 recurrences, 1 local (extracranial) and 4 distant (lung n = 3; widely disseminated n = 1) yielding a disease-free control rate of 67.7% at a mean follow-up of 4.1 years. Three of 4 patients with full thickness dural involvement developed distant metastatic disease at an average of 1.2 years postoperatively. Two patients died of unrelated causes with no evidence of disease. Four of the recurrences were in patients who had received preoperative

radiation therapy, including the local failure in the extracranial compartment. Patients who had aborted procedures based on our algorithm fared universally poorly with palliative chemoradiation, all succumbing to their disease; the longest survived 13.5 months.

DISCUSSION

Surgery for malignant neoplasms of the skull base has changed dramatically over the last 30 years. Numerous advances such as the development of combined craniofacial surgical approaches, endoscopic instrumentation and surgical technique, image guidance technology, and an extensive array of reliable reconstruction techniques have improved the ability of the oncologic surgeon to resect malignant tumors of the skull base.[7-9] Improved radiologic imaging techniques such as high resolution CT and MRI have resulted in a paradigm shift in the ability to accurately stage skull base malignancy and plan appropriate surgery and radiation therapy.[10,11] These advances coupled with significant progress related to adjuvant radiotherapy and chemotherapy have improved outcomes in terms of locoregional control and disease-free survival for patients afflicted with these malignancies.[12]

The majority of the currently available reports with respect to the surgical management of skull base malignancies often combine a variety of tumor histologies, stages, and treatment regimens.[13,14] These heterogeneous data hinder the surgeon when making decisions related to patients who present with a specific diagnosis and stage of malignancy. It is well known that the histologic type of tumor has a significant effect on outcomes after surgical resection of skull base malignancy. For example, it is recognized that neural or neuroendocrine tumors, such as esthesioneuroblastoma or neurodendocrine carcinoma, have significantly optimistic prognosis and outcomes after therapy when compared with the epidermoid tumors such as adenocarcinoma or squamous cell carcinoma.[2,15] Furthermore, mucosal melanoma of the skull base is widely recognized to demonstrate a universally poor prognosis, especially at advanced stage. Therefore, histologically specific survival data for skull base malignancies are required, and this information should be included in any staging system or treatment algorithm that is proposed. It should also be noted that there is currently no universally accepted staging system for malignancies that involve the skull base. Several staging systems have been proposed, including modifications of the American Joint Commission for Cancer (AJCC) staging system, although the majority of investigations that evaluated the validity of these systems have reported that the current staging systems exhibit poor correlation related to outcome measures. In addition, most investigators have reported significantly worsened outcomes related to regions of invasion such as orbital or cranial invasion, dural involvement, cranial nerve involvement (single or multiple), and sphenoid invasion regardless of traditional TNM classification.[2] Therefore, investigations that provide prognostic information related to specific histologic patterns and specific regional involvement would provide the background to develop a more accurate staging system for skull base malignancies. Accurately characterizing and staging these malignancies may lead to improved treatment strategies and outcomes in the future. In an attempt to solidify the data, several recent multi-institutional investigations have been reported, with histologically specific data and outcomes.[2] Current survival data for SCC of the skull base range from 30% to 50% at 5 years for all stages with decreased locoregional control with advanced tumor stages. This is a dramatic improvement compared with the universally poor outcomes reported 20 to 30 years previously. Nevertheless, consistent disease control remains difficult, especially for advanced lesions, and controversy remains with respect to several issues related to the surgical resection of skull base malignancies.

Dural invasion has traditionally been reported as an extremely poor prognostic factor with most investigations on poor long-term survival with dural involvement.[1,14] Several studies have evaluated results with frank parenchymal involvement or extensive cranial nerve extension. These studies and others have pointed out that the magnitude of the extension of the tumor, status of the surgical margin, and region specific involvement (ie, orbit, cranial nerve/ganglia, cavernous sinus, brain parenchyma, etc.) are the most important factors about outcomes related to dural involvement, not the mere presence of dural involvement.[3,13] Recently, the International Study of Craniofacial Surgery,[8] collaborative study of 17 well-known institutions, was published reporting on a total of 334 cases, 101 of which were squamous cell carcinoma (SCCA) involving the skull base. It stated "a resection margin can still be achieved when either bone or dura is involved, but this is less likely when brain parenchyma is involved." The authors found no statistically significant difference with respect to dural involvement in survival or locoregional control, however, dramatic decreased disease-free survival was reported when parenchymal involvement was present.[8] Although MRI scanning in the region of the skull base is highly accurate to assess dural involvement in most cases, we have observed several cases of skull base malignancy in which the preoperative MRI predicted dural or parenchymal involvement, but intraoperatively that did not prove to be the case. This may represent imaging artifact due to edema or other inflammatory reaction to dural involvement without necessarily signifying true dural or parenchymal involvement with the malignant process. Therefore, although somewhat arbitrary, our treatment algorithm includes a 1-cm margin of error for dural or parenchymal involvement when we examine preoperative MRIs in order to determine which patients may be offered surgical resection as part of the treatment plan.

The surgical reconstruction of defects after combined craniofacial resection of skull base malignancy remains an

important and integral part of the surgical management of patients affected with this disease. Fortunately, numerous advances in reconstructive techniques as well as the availability of synthetic reconstructive material have significantly improved the ability of the surgeon to effectively reconstruct these defects. Modern skull base surgery and reconstruction offers safe and reliable management for many advanced malignant lesions once deemed inoperable. The primary goals of skull base reconstruction are to repair dural defects, to prevent the development of cerebrospinal fluid fistulas, to isolate the intracranial contents from the nasopharynx and paranasal sinuses, and to restore the form and function of the facial skeleton. These goals are facilitated by a number of widely used reconstructive techniques that include the vascularized pericranial flap, regional tissue transfer including the temporalis and pectoralis flaps, or microvascular tissue transfer including the radial forearm, anterior-lateral thigh, latisimus, and rectus flaps.[6,7] These reconstructive techniques have been shown to be highly useful and reliable in many investigations and offer superior results when compared with regional tissue transfers such as the pectoralis or latissimus pedicled flaps.[7,14] Interestingly, several of our patients early in our experience had complications related to hydroxyapatite reconstruction, and we do not currently use or recommend this technique in the reconstruction of the skull base itself. In addition, it appears that attempts to reconstruct the osseous framework of the skull base with alloplastic materials or autogenous bone grafts is somewhat problematic and leads to increased complication rates.[16] This may be related to the fact that patients who require such reconstruction have more advanced disease with larger defects rather than the reconstructive technique used.

There is little doubt that advances in reconstruction techniques have been the primary reason for decreasing the once dramatic complication rate when performing surgery of the skull base. Major complications such as blindness, cerebrospinal fluid leak, meningitis, cerebral abscess, sepsis, and subdural hemorrhage, which were a significant source of morbidity and mortality in the past, are far less common with current techniques. In our small series of patients, we observed no major complications when we used the stated technique, however, it should be noted that major complications do occur with a frequency of approximately 10% to 35% in most series.[2,17] It is likely that the current series does not offer sufficient numbers to reflect the expected rate of major complications. The overall complication rate associated with skull base resection ranges from approximately 32.9% to 51.0% in most investigations.[2,3,7,17] Minor complications, such as wound infection, dehiscence, and flap necrosis, are the most commonly reported; and we observed 3 cases of delayed skin atrophy and temporal bone exposure in our series. In agreement with the literature, these complications occurred in patients who underwent postoperative radiation therapy that is known to increase postoperative wound complication rates. Perioperative mortality rates associated with skull base resections range from 4.5% to 7.6%, and we observed no perioperative deaths in this group of patients.[2,17]

The role of adjuvant radiotherapy in the treatment of skull base malignancy warrants discussion as it is as critical as the surgical management of this disease. A review of the literature on survival and locoregional control after therapy for skull base malignancy indicates that the benefit of radiotherapy in the treatment of patients who are affected by these disease processes is clear. Radiotherapy is especially important in cases where negative surgical margins cannot be obtained.[2,9] Although there is some debate as to the effect of microscopically positive surgical margins on outcomes after radiotherapy, most investigators report decreased locoregional control and survival with grossly positive margins; therefore, adjuvant radiotherapy of the appropriate dosage and delivery is paramount.[2,9] A variety of preoperative, postoperative, or intraoperative regimens have been evaluated with encouraging results including external beam or newer techniques such as intensity modulated radiotherapy.[9,13] Currently there are no compelling data that offer a clearly superior adjuvant radiotherapy regimen, although most investigators recommend surgery followed by postoperative radiotherapy with dosages ranging in the 5500 to 7000cGy range.[2,9,13] Recent advances in the precision of radiotherapy offer increased regional dosage with remarkable improvements related to current organ-sparing techniques.[13] This is the approach preferred at our institution although several of the patients in this series received radiation preoperatively for various reasons.

Although adjuvant chemotherapy for malignant skull base tumors has been reported in the literature, the current role and appropriate regimens remain unknown. Various investigators have reported improved outcomes in terms of survival and locoregional control when combining adjuvant chemotherapy with surgery and radiation for malignant tumors of the skull base such as nasopharyngeal carcinoma or the relatively radioresistant esthesioneuroblastoma.[18,19] Of interest, however, is the fact that in most of the large, multi-institutional trials to date, the use of adjuvant chemotherapy for patients with skull base malignancy ranges from 0 to 16%.[2,15] Currently at our institution, at the recommendation of the tumor board, we are treating approximately 40% of advanced stage SCC patients with adjuvant 5-fluorouracil and cisplatin although our current numbers prohibit any meaningful analysis. Clearly, further work is required to elucidate the role of adjuvant chemotherapy in malignant tumors of the skull base. In addition, not included in this article is the role of chemoradiation in initially more intracranially advanced but still locally isolated lesions. We have some favorable experience with patients for whom surgical salvage was offered when they had a significant diminution in the size of their intracranial disease to meet our algorithm criteria after initial chemoradiation. Unfortunately, as we do not have long enough follow-up in this

subset of patients yet, we cannot endorse it wholeheartedly at this time. Future studies are planned in this regard.

Currently, reported 5 year recurrence-free survival for SCC of the skull base after surgical resection followed by radiotherapy (and in some instances adjuvant chemotherapy) ranges from approximately 43.6% to 53.0%.[2,13,20] In our series, we have found that 67.7% of patients were alive and disease-free at an average of 4.1 years, however, this data should be viewed with caution for a number of reasons. First, we have attempted to present a series of patients with similar stage and histologic diagnosis, namely advanced stage (T4) SCC in order to evaluate the treatment algorithm in use at our institution. This has resulted in a small number (15) of subjects for analysis leading to inadequate power to perform meaningful statistical calculations. Second, because the study design is a preliminary report, our length of follow-up time (average, 4.1 years) is inadequate as we have included patients with a range of follow-up intervals. Finally, the patients presented in this series are somewhat heterogeneous; some patients received preoperative versus postoperative radiotherapy, and 8 of 15 received adjuvant chemotherapy. For these reasons, a follow-up report with our 5-year recurrence-free survival data is planned.

CONCLUSION

In light of the previous discussion, we have attempted to develop a treatment algorithm that reflects the current knowledge on skull base malignancy in order to offer optimal treatment for our patients without inflicting undue morbidity when surgical resection is futile. As outlined, we have presented a specific algorithm for the surgical resection of advanced stage skull base malignancy with intracranial extension. The application of this algorithm in the treatment of advanced stage squamous cell carcinoma of the skull base appears promising. It does appear that full thickness dural involvement should be considered to have a high potential for distant metastasis. Careful analysis of preoperative imaging studies as well as appropriate decision-making during surgical resection avoids unnecessary surgical morbidity. Improved imaging techniques such as PET scanning and dedicated head and neck MRI protocols will likely provide increased accuracy when determining candidacy for surgical resection when intracranial involvement is present.

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AUTHOR CONTRIBUTIONS

Yadranko Ducic, concept, patients, discussion; **Brett Miles**, introduction, literature review; **Peter Sabatini**, results, introduction, data retrieval.

FINANCIAL DISCLOSURES

None.

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