Management Considerations for Malignant Tumors of the Skull Base

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KEYWORDS

• Skull-base tumor • Microsurgery • Radiation • Complications

KEY POINTS

- Tumor pathology and behavior should drive the approach to skull-base malignancies and must be considered before undertaking surgical resection.
- A multidisciplinary team with expertise in surgical and oncologic management as well as reconstruction and rehabilitation should assess each case individually to develop an appropriate tailored approach for the patient.
- Induction therapy before resection can be used to minimize the extent and morbidity of surgery and improve tumor control in selected cases.
- Complex craniofacial reconstruction should be used to decrease morbidity associated with surgical complications (cerebrospinal fluid leak, infection) and cosmetic deformity.
- Quality of life after craniofacial resection is as dependent on psychosocial adjustment to disease and deformity as it is on neurologic outcome.

PATIENT POPULATION

Over a 20-year period, 473 patients (32 of whom were children or adolescents) with skull-base malignancies were operated on by the author in the setting of a tertiary-care comprehensive cancer center. A multidisciplinary team experienced in the assessment and treatment of skull-base malignancy evaluated all patients preoperatively. The anterior skull base was most commonly affected in the adult population, whereas the middle skull base was the most commonly affected site in children. **Fig. 1** depicts the skull-base region affected and whether the patient was a child or an adult. In adults the most commonly encountered abnormalities were squamous cell carcinoma, adenoid cystic carcinoma, chondrosarcoma, olfactory neuroblastoma, and adenocarcinoma. Sarcomas constituted 38% of the malignancies in adults but 75% of the malignancies in children. The most common abnormalities by site are listed in **Box 1**. **Fig. 1** shows the breakdown between sarcoma and nonsarcoma pathology at each skull-base site. The middle skull base is relatively the most likely site for a sarcoma.

MANAGEMENT PARADIGMS

The foundation of all management decisions rests on a representative biopsy of the tumor, properly identified and diagnosed by experts in surgical pathology with experience in head and neck malignancy, neural tumors, and sarcoma pathology. Inaccurate diagnoses can lead to both undertreatment and overtreatment, with their attendant toxicity and morbidity. Cohen and colleagues[1] discuss an example of the problems encountered with misdiagnosis with respect to sinonasal olfactory neuroblastoma. In a series of 12 consecutive patients referred with the biopsy-proven diagnosis

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Neurosurg Clin N Am 24 (2013) 1–10
http://dx.doi.org/10.1016/j.nec.2012.08.003
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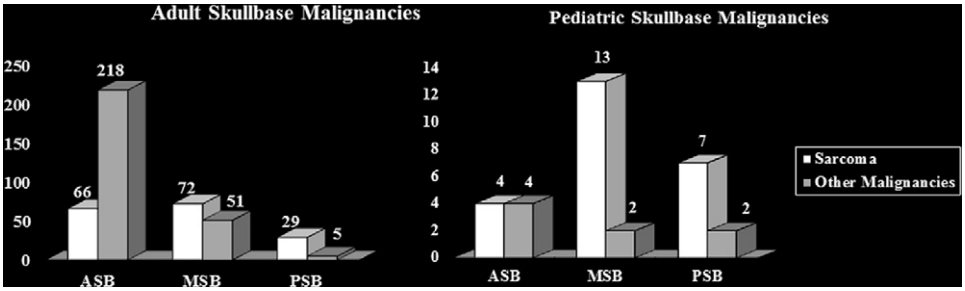

Fig. 1. Skull-base region affected, relative age of patient, and nature of malignancy (sarcoma vs nonsarcoma). ASB, anterior skull base; MSB, middle skull base; PSB, posterior skull base. (*Courtesy of* Department of Neurosurgery, The University of Texas M.D. Anderson Cancer Center; with permission.)

of olfactory neuroblastoma only 2 patients, on review by an expert pathologist, did in fact harbor this tumor. Revised diagnoses included pituitary adenoma (3 patients), neuroendocrine carcinoma (3), sinonasal undifferentiated carcinoma (2), and melanoma (2). These revised diagnoses led to significant alterations in the initially proposed treatment plan in 8 of 10 patients, including the recommendation of observation alone in the 3 patients with pituitary adenomas, 1 of whom had been rendered blind by radiation necrosis of his optic nerves (the tumor had been aggressively treated as an olfactory neuroblastoma).

With the correct pathologic diagnosis in hand, each patient should be evaluated by members of a multidisciplinary group including medical and radiation oncology, dental oncology, head and neck surgery, neurosurgery, and plastic surgery.

Box 1
Skull-base site and most common malignancies encountered

Anterior skull base
- Squamous cell carcinoma
- Sarcoma
- Olfactory neuroblastoma
- Adenocarcinoma
- Adenoid cystic carcinoma
- Sinonasal undifferentiated carcinoma

Middle skull base
- Sarcoma
- Squamous cell carcinoma
- Adenoid cystic carcinoma

Posterior skull base
- Chordoma
- Basal cell carcinoma

Additional consultations with speech pathology, audiology, otology, and ophthalmology may be necessary. In this setting the combined expertise of each individual is brought to bear on the patient's problem and leads to the construction of the optimal management plan for each patient. The skull-base neurosurgeon's main contribution is the determination, along with the rest of the surgical team, as to whether the tumor can be completely encompassed by a surgical resection that carries acceptable morbidity. With experience the neurosurgeon can also identify which tumor pathologic/biological factors make resection (with its attendant morbidity) worthwhile, or those instances whereby a complete tumor resection may not be necessary (usually to maintain function). Along with the determination of tumor resectability, the availability and nature of adjuvant therapies and the medical and psychic candidacy of the patient for surgery/treatment is taken into consideration.

The simplest management paradigm, surgical excision alone, may be applicable to certain low-grade malignancies such as low-grade chondrosarcomas, low-grade papillary adenocarcinomas, and desmoid tumors.[2] Complete resection can result in cure or long-term remission, although late recurrence can be an issue.

The management paradigm most applicable to the majority of patients with skull-base malignancy is that of surgical extirpation followed by external beam radiation therapy. This approach is generally the recommended treatment for lower-stage squamous cell carcinomas, olfactory neuroblastoma, adenocarcinoma, adenoid cystic carcinoma, and most metastases, and may be used in some patients with low-grade sarcomas.[3–8] Induction chemotherapy may also be used in the context of an organ-sparing (usually orbital-sparing) approach. Data supporting this approach are limited although early studies show promise, with one group of investigators reporting a response rate in

excess of 90%.[9] Similarly, investigators from the University of Chicago reported complete histologic response in 5 of 16 patients and a 10-year locoregional and distant control rate exceeding 90%.[10] At the author's institution this is an especially common pathway for patients with squamous cell carcinoma and sinonasal undifferentiated carcinoma. Induction chemotherapy with cisplatin, a taxane, and 5-fluorouracil with or without gemcitabine has been shown to be an effective combination for patients with squamous cell carcinoma.[11,12] In a recent study from M.D. Anderson, patients with advanced sinonasal squamous cell carcinoma were treated with induction chemotherapy with a platinum-based and taxane based regimen.[13] Just over two-thirds of the patients achieved at least a partial response, while 24% had progressive disease and 9% had stable disease. The 2-year survival for patients with at least a partial response or stable disease after induction chemotherapy was 77%, in contrast to only 36% for patients with progressive disease. Similarly, the author's practice, and that of others, has increasingly been to use induction chemotherapy with cisplatin-based programs (usually in combination with etoposide) for sinonasal undifferentiated carcinoma with or without surgical resection, dependent on the response to chemotherapy (**Fig. 2**).[14,15] For certain abnormalities surgical resection may not be a necessary part of the management paradigm. For patients with moderate to poorly differentiated neuroendocrine carcinoma, induction chemotherapy with cisplatin or carboplatin with etoposide frequently results in a complete or substantial response, which may be consolidated with definitive radiotherapy. Long-term survival has been reported with this strategy, but a standard chemoradiation schedule has not been defined.[1,3,16–19] Other abnormalities that fall into this treatment paradigm include lymphoma, Ewing sarcoma, and most pediatric rhabdomyosarcomas and malignant peripheral nerve sheath tumors.

A relatively recent addition to management paradigms has been the planned use of postoperative single-fraction stereotactic radiation boost to areas of either proven or potential microscopic tumor residual. This approach has been most commonly applied in patients with squamous cell carcinoma and adenoid cystic carcinoma in the presence of, or potential presence of, perineural tumor extension (**Fig. 3**). It is too early to judge the usefulness of this modality in disease control and survival, although several patients remain without recurrence more than 3 years after treatment. The author's current management paradigms and applicable malignancies are listed in **Box 2**.

LOW-GRADE AND HIGH-GRADE MALIGNANCIES

As indicated by the preceding discussion, management paradigms clearly differ based on the biological nature of the malignancy being treated. In an early study the author's group evaluated management paradigms based on the categorization of primary skull-base sarcomas into high and low biological aggressiveness (grade). An attempt was made to determine the accuracy of this biological/managerial grading scheme and to identify prognostic indicators for survival and progression-free survival. Such a scheme helps to logically manage the numerous and highly diverse malignant abnormalities encountered. In this study of 64 patients, 31 patients had high-grade sarcomas and 33 patients were categorized as having low-grade sarcomas.[20] Based on the management algorithm, the majority of patients with high-grade sarcomas were radiated (71%) and received chemotherapy (81%). Surgery alone was used in the majority of patients with low-grade sarcomas, although 46% were also radiated and 21% given chemotherapy. Also of note is that based on a philosophy of preservation of function, 40% of patients with low-grade sarcomas had gross residual disease following resection compared with only 16% of patients with high-grade sarcomas. This management resulted in an overall survival at 1, 5, and 10 years of 83%, 66%, and 52% for the patients with high-grade sarcomas and 100%, 85%, and 57% for the patients with low-grade sarcomas, respectively. Progression-free survival at 1, 5, and 10 years was 86%, 56% and 46% for the patients with high-grade sarcomas and 90%, 65% and 0% for the patients with low-grade sarcomas, respectively. These results, especially the 100% recurrence rate at 10 years for patients with low-grade malignancies, indicate the need to reevaluate the management of this patient population. Improved surgical resection, possibly at the expense of function, needs to be considered, although this must be weighed against the expected diminution of quality of life (QOL) of patients. Increasing the use of postoperative radiation and/or chemotherapy also needs to be considered. These questions are as yet unanswered.

OUTCOMES

Oncologic

It was not until the introduction of craniofacial resection that a substantial improvement in long-term disease control was appreciated in patients with malignancies of the paranasal sinuses

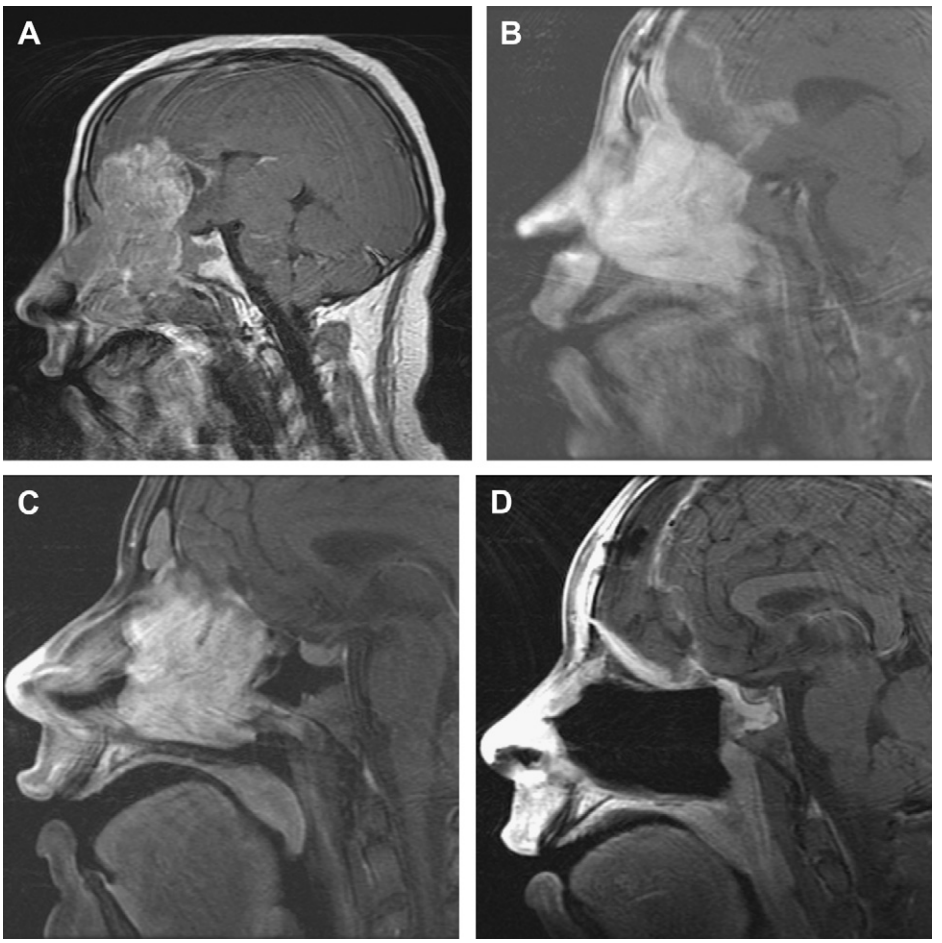

Fig. 2. This 23-year-old man presented with acute obtundation and headache. Computed tomography imaging revealed a large frontal tumor with intracerebral hematoma. Initial sagittal postcontrast T1-weighted magnetic resonance imaging (MRI) (*A*) revealed a large sinonasal tumor with intracerebral extension. The patient was taken to the operating room emergently, and underwent resection of all intracranial tumor and evacuation of hematoma. (*B*) Postoperative sagittal postcontrast T1-weighted MRI. Pathology was consistent with sinonasal undifferentiated carcinoma. He was subsequently treated with 4 cycles of cisplatin and etoposide with partial response evident on the post-chemotherapy sagittal postcontrast T1-weighted MRI (*C*). He then underwent formal anterior craniofacial resection. The postoperative sagittal postcontrast T1-wieghted MRI (*D*) confirmed complete tumor removal. Extensive pathologic analysis could not identify any viable tumor. He was treated postoperatively with intensity-modulated radiation therapy to a dose of 60 Gy in 30 fractions. He is free of disease 3 years later. (*Courtesy of* Department of Neurosurgery, The University of Texas M.D. Anderson Cancer Center; with permission.)

affecting the skull base. Before this, overall 5-year survival did not exceed 30%.[21] Several large modern surgical series currently report survival rates of approximately 50% to 70% at 5 years and 40% to 50% at 10 years.[22–29] McCutcheon and colleagues[30] reported median survivals of 20 months for patients with squamous cell carcinoma, 26 months for adenocarcinoma, and 40 months for olfactory neuroblastoma in the 26 of 76 patients who died during the course of their review. This group reported an overall 63% 2-year nonactuarial survival. Lund and colleagues[26] identified malignant histology, brain involvement, and orbital involvement as negative predictors of patient outcome. As well as confirming the negative effect of brain invasion on survival, Clayman and colleagues[31] also identified positive histologic margins as predictors of local recurrence and shorter survival. Transdural involvement, however, should not dissuade the consideration of patients for aggressive surgical management. Feiz-Erfan and colleagues[32] were able to achieve a 5-year overall survival of 58% in a group of 28 patients with transdural invasion of malignancy. Gross total

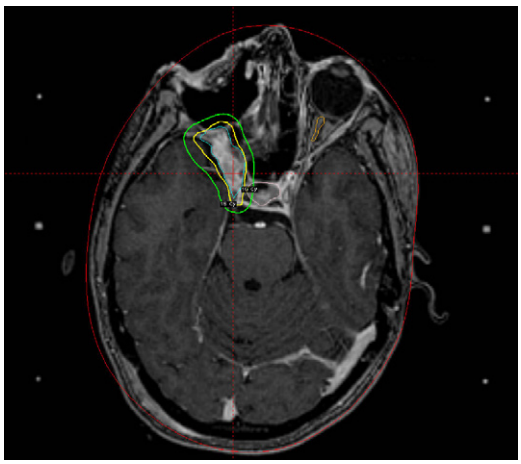

Fig. 3. Axial postcontrast T1-weighted MRI with superimposed radiosurgical treatment plan. This female patient with invasive squamous cell carcinoma of the skin of the right eyebrow had been extensively treated with multiple surgeries and external beam radiation. At recurrence she underwent wide local excision of the tumor with orbitectomy. Residual disease in the cavernous sinus was treated with radiosurgery to a dose of 15 Gy at the 50% isodose line. (*Courtesy of* Department of Neurosurgery, The University of Texas M.D. Anderson Cancer Center; with permission.)

resection with microscopically negative margins was the key positive predictor of overall survival and progression-free survival. In the author's cohort of patients with sarcomas of the skull base, only brain parenchymal involvement was significantly associated with a shorter survival and progression-free survival, although achieving microscopically negative margins, rather than leaving grossly positive margins, had a strong trend toward improved progression-free survival. Overall, this group of patients achieved a 5- and 10-year survival of 75% and 56%.

Malignancy involving the anterolateral skull base is clinically and pathologically distinct from malignancy involving the anterior skull base or the parotid/temporal bone.[30,33,34] These tumors commonly invade the infratemporal fossa and the walls of the maxillary sinus, and frequently present with facial pain and an externally evident mass. There is usually involvement of the maxillary and mandibular divisions of the trigeminal nerve. The most common tumors of this region were sarcomas, followed by squamous cell carcinoma and adenoid cystic carcinoma (**Fig. 4**). With aggressive multimodal therapy the author's group found an overall median survival of 5 years, a 2-year survival of 81%, and a 5-year survival of 53%.[35] Cavernous sinus and internal carotid artery involvement was present in about 20% of the patients. The overall median survival for patients not requiring cavernous sinus dissection or internal carotid artery resection was twice that of patients undergoing these maneuvers. Statistically significant predictors of decreased overall survival included dural and central nervous system invasion by tumor, presence of high-grade sarcoma, complications of therapy, and age 65 years or older.

Age, however, as in the case of transdural tumor extension, should not exclude the consideration of aggressive surgical resection in patients with skull-base malignancy. In patients undergoing anterior craniofacial resection the author found no significant difference in disease-specific survival in a cohort of patients with a mean age of 70 years, when compared with a younger cohort (mean age 56 years).[36] The older age group did, however, have a 3-fold greater incidence of systemic complications.

Patients with malignant tumors of the sphenoidal sinus, although accounting for only 1% to 2% of patients with paranasal sinus malignancy, are an especially difficult subgroup to manage effectively. Even in this patient population, aggressive multimodality therapy can result in a 2-year survival rate of 44% for patients with squamous cell carcinoma.[37]

Tumor pathology is an important predictor of outcome in these patients. Five-year overall survival ranges from 89% for olfactory neuroblastoma to 39% for mucosal melanoma.[6,8,38–40] Mucosal melanoma is associated with a particularly poor patient outcome. In the author's series the disease-free survival was only 18.4%.[39] In contradistinction, olfactory neuroblastoma has the best patient outcome, with a 10-year survival rate of 81%. It should be noted, however, that the mean time to recurrence in these patients was around 4.5 years, which mandates careful long-term patient follow-up.[6]

Adenoid cystic carcinoma is a rare tumor with a high recurrence rate. In the author's patient population recurrence was noted in 56.2%. This result is in the context of a 5-year disease-specific survival rate of 70.9%. Many patients remain alive with disease for years, and survival from this disease exceeds that of most other sinonasal malignancies.[7,8,41]

Recent advances in endoscopic instrumentation and surgical technique has created excitement in skull-base surgery. Initially applied to the repair of cerebrospinal fluids leaks, endoscopic approaches to benign and malignant tumors have been increasingly reported. One major concern has been the paradigm shift from en bloc resection to one of piecemeal resection of sinonasal

Box 2
Management paradigms and applicable malignancies

Surgical resection
- Low-grade chondrosarcoma
- Basal cell carcinoma
- Desmoid fibromatosis
- Some other low-grade sarcomas and low-grade adenocarcinomas

Surgical resection and postoperative radiation therapy
- Olfactory neuroblastoma
- Adenocarcinoma
- Adenoid cystic carcinoma
- Squamous cell carcinoma
- Most metastases
- Some low-grade sarcomas

Pre- and postoperative chemotherapy, surgical resection, and postoperative radiation therapy
- Squamous cell carcinoma
- High-grade sarcomas
- SNUC and other neuroendocrine carcinomas
- Melanoma

Chemotherapy and radiation therapy
- Lymphoma
- Ewing sarcoma
- Most rhabdomyosarcomas and MPNST
- Some patients with SNUC and other neuroendocrine carcinomas

Chemotherapy, radiation therapy, surgical resection, and stereotactic radiosurgery
- Squamous cell carcinoma, Adenoid cystic carcinoma } especially with perineural extension
- Some high-grade sarcomas, SNUC

Abbreviations: MPNST, malignant peripheral nerve sheath tumor; SNUC, sinonasal undifferentiated carcinoma.

malignancy. In an effort to address this controversy the author's group reviewed its experience with endoscopic resection of sinonasal malignancies with and without the addition of a craniotomy. In this cohort of patients, 93 underwent a purely endoscopic resection of their anterior skull-base malignancy and 27 patients underwent a cranioendoscopic resection.[34] The main difference between the two groups was the significantly higher T stage in patients treated with a cranioendoscopic technique. This difference understood, no significant difference was found in overall survival between the two treatment groups. In the author's opinion, this was a proof of principle that in appropriately selected patients a purely endoscopic approach to tumoral resection can be safely performed without compromising patient survival.

Complications of Treatment

A considerable complication rate accompanies the craniofacial resection of skull-base malignancies. Most surgical series report complication rates of 25% to 60%.[25,29,42–45] The most commonly identified complications in the literature are infectious, with wound infection (especially osteomyelitis) and meningitis predominating.[46] Other commonly reported complications include cerebral spinal fluid leakage, delayed return of neurologic function, and tension pneumocephalus. In a review of 209 patients undergoing anterior craniofacial resection at M.D. Anderson Cancer Center between 1992 and 2008, a 20% complication rate was seen.[47] In contrast to reports in the literature, the cerebrospinal fluid (CSF) leak rate

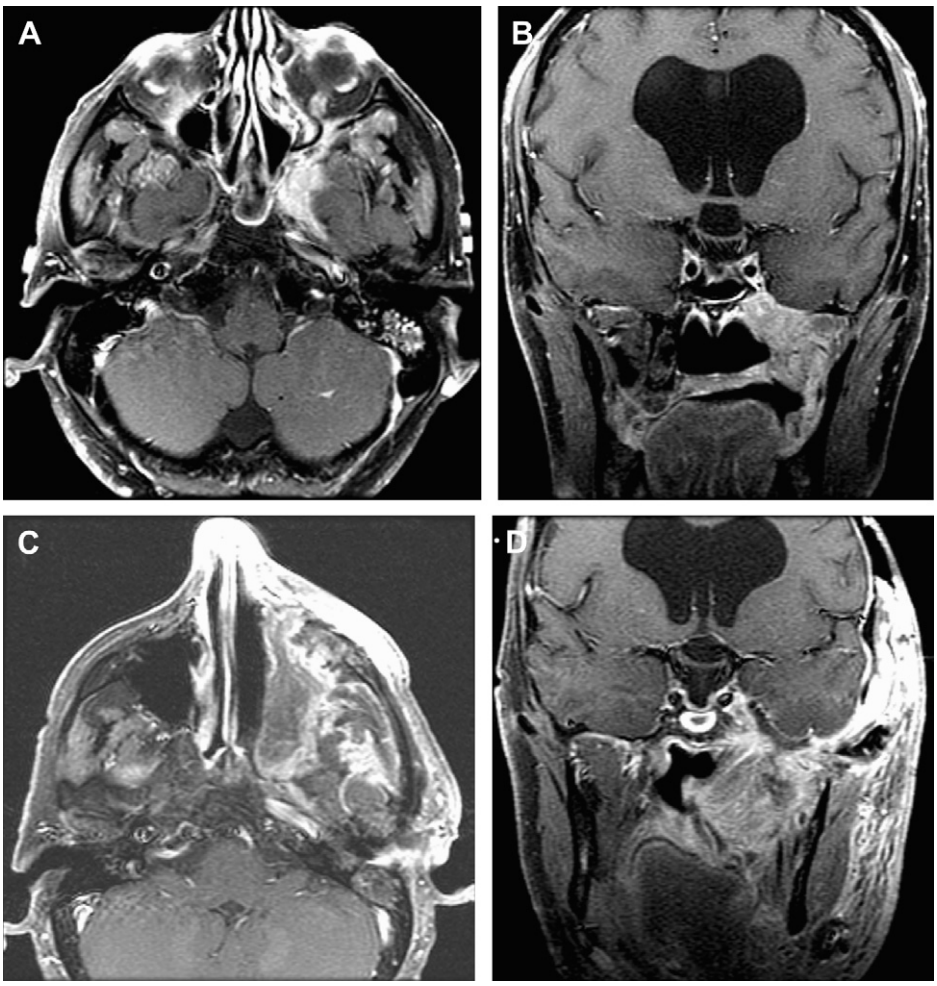

Fig. 4. Axial (*A*) and coronal (*B*) postcontrast T1-weighted MRI of a male patient with a recurrent malignant fibrous histiocytoma of the left infratemporal fossa and anterolateral skull base. He underwent a transfacial and anterolateral skull-base approach with complete tumor removal. Reconstruction with a free anterolateral thigh flap was performed following watertight dural closure. Final pathology was read as pleomorphic sarcoma. Postoperative axial (*C*) and coronal (*D*) postcontrast T1-weighted MRI confirmed complete tumor removal. Chemoradiation is planned. (*Courtesy of* Department of Neurosurgery, The University of Texas M.D. Anderson Cancer Center; with permission.)

and rate of infection were both less than 1%. When appropriate reconstructive choices are made, which in most cases means using a well-vascularized pedicled pericranial flap or a free tissue transfer over a watertight dural closure, the CSF leak rate and the incidence of orbital morbidity are reduced.[48–50] The author's routine use of broad-spectrum antibiotics has resulted in a low rate of wound infection, and there has been no bone flap loss. Delayed return of neurologic function needs to be differentiated from postoperative delirium. The former complication is almost certainly due to excessive frontal lobe retraction, and has been eradicated from this series because of careful patient positioning and operative technique that emphasizes the use and importance of the operating microscope. The later complication, that of postoperative delirium, occurs in almost 20% of patients older than 70 years and is likely multifactorial in nature, with drug interactions and preexisting pre-clinical dementia being the most likely culprits.[36] Tension pneumocephalus is due to overdrainage of CSF either late in surgery or in the postoperative period. This complication can be seen even if the lumbar drain has been removed. Treatment consists of needle aspiration of the intracranial air, the delivery of 100% oxygen, and intubation or tracheostomy if severe. An epidural blood patch may be necessary. A less acute intracranial hypotension-like

syndrome can be associated with persistent headache, usually with a significant postural component, and imaging evidence of poor cerebral expansion. Perturbed CSF dynamics, leading to intracranial hypotension, were the single most common cause of complications in this series. Just over a third of all complications identified were considered to be related to this underlying process. These complications have been eliminated with the cessation of the use of lumbar spinal fluid drainage.

Quality of Life

In a previously reported cohort of 16 patients undergoing anterior craniofacial resection for paranasal sinus malignancy affecting the skull base, the author assessed health-related QOL and functional status of patients.[51] Patient-generated responses to the Functional Assessment of Cancer Therapy questionnaire, including its brain and head and neck subscales, were used to measure QOL, and the Karnofsky Performance Score (KPS) and Functional Independence Measure (FIM) were used to assess patient function.[52,53] Anterior craniofacial resection and other indicated adjunctive therapies for paranasal sinus malignancies rarely affected independence. Ninety-four percent of patients (15 of 16) had KPS of 90 or 100 and 87% of patients had FIM scores higher than 117, which indicates the ability to perform most or all activities of daily living independently. All patients reported a good QOL from a neurologic standpoint, and 94% did so from a head and neck standpoint as well. Of importance, however, is that approximately one-third of the patients reported a poor QOL based on their responses to the FACT (Functional Assessment of Cancer Therapy) general questionnaire. It appears that this diminished QOL is less related to the specifics of the treatment than to the psychosocial changes and adjustments that accompany an illness and its treatment. Several other disclaimers need to be made, notably that a patient's perception of their health and QOL is not necessarily related to objectively assessed functionality; moreover, the health-related QOL in patients with brain injury arising from tumor and treatment must be analyzed with the potential effect of neurocognitive impairment in mind.[54] In these patients a 3-pronged assessment using measures of functionality and performance, cognition, and self-reported QOL is the most telling approach.[55]

SUMMARY

Although great strides have been made in the management of skull-base malignancies, much room for improvement exists. Ideally, improvements in the chemotherapeutic management of these tumors, almost certainly with novel agents, would lessen the need for extensive extirpative surgeries. Improved treatment targeting and radiotherapeutic technologies such as intensity-modulated radiation therapy are reducing the morbidities associated with radiation and will likely become even more refined. Surgery will remain an integral part of the treatment of these malignancies, be it in the current role of ablative surgery, either open or endoscopic, or in future roles of drug/virus/gene delivery.

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