INTRODUCTION

Management considerations for malignant tumors of the skull base

Franco DeMonte[1]

Introduction

The last two decades have brought refinements in diagnostic imaging, instrumentation, microvascular reconstruction and an improved overall appreciation of the anatomy of the skull base, both open and endoscopic. These refinements have extended the boundaries of tumor resection and have obviated the need for adjuvant therapies in some patients with benign or low-grade tumors. In patients with high-grade malignancies, however, a carefully constructed multimodal treatment plan, incorporating surgery, radiation therapy and chemotherapy, is necessary in order to maximize patient outcome.

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 under and over treatment with its attendant toxicity and morbidity. Cohen et al. 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 of olfactory neuroblastoma only two patients, on review by an expert pathologist, did in fact harbor this tumor [1, 2]. 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 three patients with pituitary adenomas, one of whom had

been rendered blind by radiation necrosis of his optic nerves (had been aggressively treated as an olfactory neuroblastoma). A recent review of 397 patients with sinonasal malignancy at M.D. Anderson Cancer Center identified a 24% discordance of major histopathological diagnosis. The 5 year overall survival was reduced in patients with a major change in diagnosis (55% vs 70.8%) highlighting the importance of a correct diagnosis. (Choi et al. unpublished data) Table 1.

With the correct pathological 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. 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 pathologies/biologies make resection, with its attendant morbidity, worthwhile or those instances when a complete tumor resection may not be necessary (usually in order 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 [3]. 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 skullbase malignancy is that of surgical extirpation followed by external beam radiation therapy. This is generally the recommended treatment for lower-stage squamous cell carcinomas, olfactory neuroblastoma,

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Table 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

adenocarcinoma, adenoid cystic carcinoma and most metastases, and may be utilized in some patients with low-grade sarcomas [4–9]. 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% [10]. 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% [11]. At the author's institution this is an especially common pathway for patients with squamous cell carcinoma and sinonasal undifferentiated carcinoma. Induction chemotherapy with cisplatinum, a taxane, and 5-fluorouracil with or without gemcitabine has been shown to be an effective combination for patients with squamous cell carcinoma [12, 13]. In a recent study from M.D. Anderson patients with advanced sinonasal squamous cell carcinoma were treated with induction chemotherapy with a platinum and taxane based regimen [14]. 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, our 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 upon the response to chemotherapy [15, 16]. The experience with sinonasal undifferentiated carcinoma (SNUC) has recently been documented by Amit et al. In this study 95 treatment-naïve patients with SNUC were treated with a platinum-based doublet chemotherapeutic regimen consisting of cisplatinum and etoposide (carboplatinum

in those patients with renal insufficiency, hearing loss or peripheral neuropathy). For those patients who had a partial or complete chemotherapeutic response to induction the 5 year disease specific survival was 81% when induction chemotherapy was followed by definitive concurrent chemoradiation and 54% when followed by surgery and postoperative radiotherapy or chemoradiotherapy. Patients with progressive or stable disease following induction had a disease specific survival of 0% when treated with chemoradiotherapy post-induction and 39% in patients treated with surgery and postoperative radiotherapy or chemoradiotherapy. The radiotherapeutic dose delivered to the gross disease and a 1–2 cm margin was 66–70 Gy [17].

For certain pathologies 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. This is consolidated with definitive radiotherapy. Long-term survival has been reported with this strategy but a standard chemoradiation schedule has not been defined [12, 13, 12, 13, 12, 13, 12]. Other pathologies, which fall into this treatment paradigm, include lymphoma, Ewing's sarcoma, and most pediatric rhabdomyosarcomas and malignant peripheral nerve sheath tumors.

A relatively recent addition to our 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 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. It is too early to judge the usefulness of this modality in disease control and survival although several of our patients remain without recurrence more than 3 years post-treatment. Our current management paradigms and applicable malignancies are listed in Table 2.

Low 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 a early study we evaluated management paradigms based on the categorization of primary skullbase sarcomas into high and low biologic aggressiveness (grade). An attempt was made to determine the accuracy of this biologic/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 pathologies encountered. In this study of 64 patients, 31 patients had high-grade sarcomas and 33 patients were categorized as having low-grade sarcomas [22]. Based on our management

Table 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 post-operative chemotherapy, surgical resection and postoperative radiation therapy
  Squamous cell carcinoma
  High-grade sarcomas
  SNUC[a] and other neuroendocrine carcinomas melanoma
Chemotherapy and radiation therapy
  Lymphoma
  Ewing's sarcoma
  Most rhabdomyosarcomas and MPNST[b]
  Some patients with SNUC and other neuroendocrine carcinomas
Chemotherapy, radiation therapy, surgical resection and stereotactic radiosurgery
  Squamous cell carcinoma especially with perineural extension
  Adenoid cystic carcinoma
  Some high-grade sarcomas, SNUC

[a]Sinonasal Undifferentiated Carcinoma = SNUC

[b]Malignant Peripheral Nerve Sheath Tumor = MPNST

algorithm the majority of patients with high-grade sarcomas were radiated (71%) and received chemotherapy (81%). Surgery alone was used in the majority of the 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 to 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 re-evaluate our 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 patient quality of life (QOL). 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 affecting the skull base. Prior to this, overall 5-year survival did not exceed 30% [23]. Several large modern surgical series currently report survival rates of approximately 50–70% at 5 years and 40–50% at 10 years [24–31].

Transdural involvement, however, should not dissuade the consideration of patients for aggressive surgical management. Feiz-Erfan et al. were able to achieve a 5-year overall survival of 58% in a group of 28 patients with transdural invasion of malignancy [32]. Gross total resection with microscopically negative margins was the key positive predictor of overall survival and progression-free survival. In our cohort of patients with sarcomas of the skullbase, 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 to improved progression-free survival. Overall, this group of patients achieved a 5 and 10-year survival of 75 and 56%.

Age, however, as in the case of transdural tumor extension, should not exclude the consideration of aggressive surgical resection in patients with skullbase malignancy. In patients undergoing anterior craniofacial resection we found no significant difference in disease specific survival in a cohort of patients with a mean age of 70 years when compared to a younger cohort (mean age 56 years) [33]. The older age group did, however, have a three-fold greater incidence of systemic complications.

Recent advances in endoscopic instrumentation and surgical technique has created an excitement in the field of skullbase 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 enbloc resection to one of piecemeal resection of sinonasal malignancy. In an effort to address this controversy we reviewed our experience with endoscopic resection of sinonasal malignancies with and without the addition of a craniotomy. In our cohort of patients 93 underwent a purely endoscopic resection of their anterior skullbase malignancy and 27 patients underwent a cranio-endoscopic resection [34]. The main difference between the two groups was the significantly higher T stage

in patients treated with a cranio-endoscopic technique. This difference understood, we found no significant difference in overall survival between the two treatment groups. A follow-up study of 239 patients, 167 (70%) of which had a purely endoscopic resection, revealsed no difference in surgical margin status between the pure endoscopic and endoscopic-assisted groups. There was no significant difference in survival between these groups [35]. These data in our minds are a proof of principle that in appropriately selected patients a purely endoscopic approach to tumoral resection could be safely performed without compromising patient survival.

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 quality of life and patient functional status [36]. Patient-generated responses to the Functional Assessment of Cancer Therapy questionnaire, including its brain and head and neck subscales were used to measure quality of life and the Karnofsky Performance Score (KPS) and Functional Independence Measure (FIM) were used to assess patient function [37, 38]. Anterior craniofacial resection and other indicated adjunctive therapies for paranasal sinus malignancies rarely affected independence. Ninety-four percent of patients (15/16) had KPS of 90 or 100 and 87% of patients had FIM scores over 117: indicative of the ability to perform most or all activities of daily living independently. All patients reported a good QOL from a neurological standpoint and 94% did so from a head and neck standpoint as well. Of importance, however, is that approximately a third of the patients reported a poor quality of life based on their responses to the FACT 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 a patient's perception of their health and QOL is not necessarily related to objectively assessed functionality, also the health-related QOL in patients with brain injury due to tumor and treatment must be analyzed with the potential effect of neurocognitive impairment in mind [39]. In these patients a three-pronged assessment utilizing measures of functionality and performance, cognition, and self-reported quality of life is the most telling approach [40]

Conclusions

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 (IMRT) 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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