

The recent concept in the management of anterior Skull base tumor: A review of the literature.

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ABSTRACT:

Introduction Tumor of the skull base are classified based on their tissue of origin. Tumor originates from epithelium, mesenchyme, and neuroectoderm. Management of tumors depends on location, histologic characteristics, and their behaviors. A sinus endoscopy, Computerized tomography scan, and Magnetic Resonance Imaging should be performed to know the type and extent of the tumor. Treatment includes surgical excision either endoscopic vs open, chemotherapy and immunotherapy. We are highlighting the management option of each tumor according to their type of tissue origin and its location. **Methods:** A PubMed search was conducted for relevant publications using the terms “anterior skull base malignancies” and “anterior skull base malignancies treatment and “open vs endoscopic anterior skull base malignancies.” The publication language should be English. **Results:** Articles published after 2000 that cover the most recent paradigm shift in the treatment of anterior skull base tumors were included. There have been 35 articles found, despite 20 of them are being rejected due to the lack of full text, abstract, and non-english. Three of the fifteen articles have been downloaded twice, thus they have been excluded. **Conclusion:** Skull base tumors are treated based on findings of diagnostic nasal endoscopy and imaging results. CT scans and MRIs are becoming more significant in the diagnosis of diseases. Endoscopic techniques to the skull base were beneficial in treating the malignancy. Chemotherapy can be used as a gold standard first-line treatment with radiation and surgery for significant types of head and neck tumors. Immunotherapy-like checkpoint inhibitors targeting PD1 are the second-line treatments of advanced HNSCC. Prospective research and trials will be required in the future.

Keywords: skull base malignancies, endoscopic vs open approaches, immunotherapy.

Introduction:

Different varieties of tumors are found in the anterior skull base. These tumors derived either paranasal sinus or Neuroectoderm.¹ It can be classified based on their tissue origin, histological characteristics, and anatomical location.² Sinonasal tumor can be of epithelial

(carcinoma) or mesenchymal (sarcoma) origin. Epithelial tumors are the most common and originate from the epithelial lining, accessory salivary glands, neuroendocrine tissue and olfactory epithelium.³ Mesenchymal tumors derive from the supporting tissue. The most common tumor at the anterior skull base includes pituitary adenoma, meningioma and

craniopharyngioma.⁴ Less common ones are schwannomas and osteoma. Malignant tumor includes Esthesioneuroblastoma, adenoid cystic carcinoma, adenocarcinoma, sinonasal undifferentiated carcinoma, squamous cell carcinoma, sinonasal melanoma, clival chordoma and nasopharyngeal carcinoma. Tumors like hemangiopericytoma and metastases also present in these locations.¹

Symptoms arise either through mass effect or through invasion of local structure. Surgical treatment depends on resectability of tumor with reduction of complication. Surgical resection remains the mainstay of treatment of these tumors especially experienced hands with proper patient selection. It can be approached either open or endoscopic. Many endoscopic endonasal approaches were designed which enable resection of tumors comparable to open approaches. Selection of approach depends on type of tumor, its resectability, and reconstruction option. High resolution CT scan in all three planes need to localise bony invasion. MRI T2 weighted scans show intracranial extent and adherent to dura and brain separation from those structures. It is also important to treat tumors with chemoradiation or immunotherapy depending on tumor histology, location, and proper selection of patients.

The selection of surgical approaches to the anterior skull base is based upon balancing risk reduction with maximizing the extent of resection. Here we review a spectrum of neoplastic entities found in the anterior skull base and discuss the clinical and radiographic presentation, treatment options, and outcomes.

Methods:

The search of relevant publications was done on PubMed by keeping the term “anterior skull base malignancies” “anterior skull base malignancies treatment” open vs

endoscopic anterior skull base malignancies.” The language of publication should be in English.

Results:

Only those articles which were published after 2000 AD were included in this review so as to cover the recent change in concept in the treatment of anterior skull base malignancies. Thirty-five articles were found of which 20 articles were rejected due to non-availability of full text, abstract and non-English. Out of fifteen articles, 3 are duplication downloaded, so excluded.

Discussion:

Workup.

Diagnosis of nasal cavity tumors is paramount importance. Routine Diagnostic nasal endoscopy is helpful in locating and evaluating midline nasal cavity tumors. It is important to examine the nasal cavity by endoscopy complementary with CT scan. CT scan provides tumor staging and preoperative mapping of tumor. CT is the best modality to evaluate bony changes such as cortical erosion, destruction, remodeling, sclerosis and thickening. To evaluate bony change, slice thickness should be 1 mm, reformatted into three planes. The radiation dose (>50 mAs) and intravenous contrast medium may be required when using CT for tumor staging and preoperative tumor mapping. In sinonasal imaging, the general rules are that benign tumours cause remodelling and thickening of adjacent bone, while malignant tumours destroy the bone.

MR imaging is complementary to a CT scan, which evaluates the extent of tumor invasion beyond the bony sinus wall and better differentiate characteristics of the soft tissue of the tumor. Basic protocol for Skull base is unenhanced T1 and T2 which differentiate between different soft tissue structures in the tumor and mucus. In general, benign tumours have well-defined borders with

a narrow transition zone; sclerotic margins are frequently present. On the other hand, malignant tumours have poorly defined margins, a wide transition zone, aggressive periosteal reaction and often have a soft tissue component; these lesions cause dramatic bony destruction with intracranial or extracranial extension.⁵

T1 non-contrast evaluates the signal void cortical bone from high signal fatty bone marrow. Diffusion weighted (DW) MRI is thought to be a cancer imaging marker and compared with histologic indices like cellularity and tissue response.⁶ It not only helps to differentiate between primary tumor and recurrent tumor but also utilise monitoring tumor response from treatment. Usually the apparent diffusion coefficient (ADC) for sinonasal tumor imaging is b value= 500 -1000 mm²/sec. MR imaging is very useful to detect perivascular and perineural spread, enlargement and enhancement of the involved nerve, enlargement and destruction of bony foramina and obliteration of involved skull base.⁷ If tumor invades dura, dural thickening more than 5 mm or focal dural nodule or pial enhancement can be seen.⁸

Specific finding of common tumor.

Osteomas may show both dense cortical bone and ground-glass appearance on CT. It is difficult to differentiate from fibrous dysplasia where the normal medullary bone is replaced by fibrous tissue that displays a ground-glass appearance.

The site of origin of an IP may be detected as focal hyperostosis on the sinus wall at CT.⁹ The study by alexander et al find that osteitis bony changes at the site of tumor attachment in 100% cases in inverted papilloma.¹⁰ Follow-up MR imaging demonstrates the characteristic mucosal infoldings, described as a “convoluted cribriform pattern” on both T2 and contrast-enhanced T1 sequences.

In Juvenile Nasal Angiofibroma, characteristic imaging pattern at CT is large hyperdense destructive soft tissue lesion showing intense contrast enhancement broadening of the pterygopalatine fossa with enlargement of the sphenopalatine foramen medially and the Vidian canal posteriorly. A large tumor may cause bowing of the posterior wall of the maxillary sinus anteriorly, the sphenoid sinus upward and the pterygoid plates posteriorly with erosion and destruction of adjacent bones. The infra-temporal fossa, orbit, and middle cranial fossa on the right side were also encroached by the lesion.¹¹ MRI shows typical flow voids and intense enhancement on T1 after gadolinium injection. A large, well-defined mass found in sphenopalatine foramen and pterygopalatine fossae with a heterogeneous intensity in both T1-weighted and T2-weighted images and encroached into the masticator, buccal, parapharyngeal spaces, floor of the middle cranial fossa, and the right cavernous sinus. Tiny flow void was noted within the lesion consistent with hypervascularity. Residual tumor detected at early postoperative contrast-enhanced CT or MR imaging and which is found at basisphenoid region.^{12,13} The diagnosis is dependent on multiplanar imaging modalities like Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Angiography. These imaging modalities help in assessing the tumor mass, pre-operative embolization of the feeder's vessel, and treatment planning.¹²

Olfactory Neuroblastoma or Esthesioneuroblastoma is a malignant tumor arises from olfactory epithelium accounts for 2-3% of all intranasal tumors.¹⁴ Non-contrast CT exhibits iso to hyperintense image whereas T1 weighted MRI reveals iso to hyperintense and T2 weighted MRI shows hyper to isointense images. Intratumoral cyst formation or necrosis is common.⁸ Intracranial extension has peripheral or marginal cysts.¹⁵

Restricted diffusions was found at Diffusion-weighted MRI imaging.¹⁶

Chondrosarcoma is a multilobulated, heterogeneous lesion with a chondroid matrix, peripheral and scattered central calcifications. The chondroid matrix has high water content which displays lower attenuation compared with muscle at CT scan. The high-water content of the chondroid matrix reveals high signal on T2 and low signal on T1 at MRI imaging. Calcifications of the chondroid matrix shows signal voids at all sequences. Septum shows low signal at both T1 and T2 whereas after injection of contrast.

Pituitary adenomas typically show iso- to mild hyper density on non-contrast CT, iso- to hypo intensity on T1-weighted MR images and mild hyper to iso intensity on T2-weighted MR images. They sometimes contain intratumoral cysts or hemorrhage. Contrast enhancement of the tumor is moderate and mostly homogeneous. Large adenomas expand the Sella. Invasive pituitary adenomas may erode or destroy adjacent bones.

Sinonasal undifferentiated carcinoma are aggressive tumor which have bone erosion especially lamina papyraceae and cribriform plate similar to that of squamous cell carcinoma. but no imaging shows the exact extent of the disease. Fig 1. showing squamous cell carcinoma of nose which erode cribriform plate and entred into brain. The correct diagnosis can be done by immunohistological examination. In some patients, carcinoma is looks like nasal polyp but lamina papyraceae eroded.¹⁷

Malignant mucosal melanoma (MMM) can be seen as a polypoid lesion in the nasal cavity that remodels the surrounding bone, but bony erosion may also be seen at CT scan. Strong enhancement seen after contrast medium injection due to the rich vascular network. At MR imaging, the lesion is homogeneous, but sometime

T1 shows high signal due to bleeding or melanin in the tumor.¹⁸

Most guidelines recommend against the use of [18F] fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT imaging for routine diagnosis and staging of head and neck cancer¹⁹, but it has been shown to be useful for imaging residual and recurrent tumor treatment response monitoring tumor volume measurement.²⁰ With its great sensitivity but moderate specificity, FDG-PET/CT imaging beats CT and MR imaging.²¹ Because the inflammatory side effects of radiation and chemotherapy might cause false-positive FDG uptake, the ideal time for [18F] FDG-PET/CT has been shown to be more than 3 months after therapy completion.

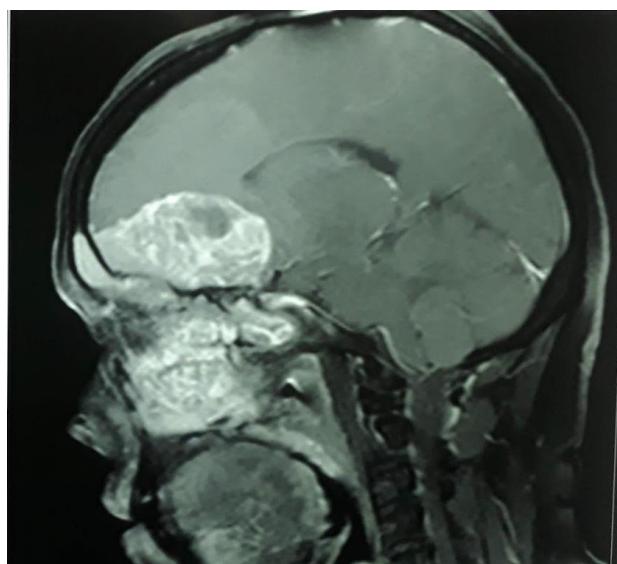


Fig 1. MRI T2 image showing Squamous cell carcinoma of nose invading dura and brain.

Treatment

Inverted papilloma can be treated by Medial Maxillectomy either open or endoscopic approaches. Nowadays, it can be performed by endoscopic method. It has potential for both recurrence and malignant transformation. Kim et al found in their study that 16 out

of 228(7%) patients with IP had been associated with Sino nasal carcinoma. IP originating in the frontal sinus or frontal recess was more likely to be associated with malignancy. Moreover, they reported that nearly one-third of the patients developed distant metastases after primary treatment.²² Krouse et al reviewed data of 33 studies involving 1,426 patients and found that inverted papilloma can be treated successfully through endoscope with low recurrence rates and less morbidity comparable to open approaches.²³ some cases which involves superior and lateral part of frontal sinus that needed open approach.²⁴

Treatment of JNA would be always challenging due to excessive the intraoperative bleeding, spreading via different routes of skull base. Surgical approach should provide adequate visualization in a bloody surgical field and easy control of blood supply. Pre embolization can reduce the intraoperative bleeding. Different open skull base approaches like Weber Fergusson, Le Fort 1 osteotomy, lateral rhinotomy, midfacial degloving, facial translocation, anterior craniofacial resection is used depends on the extent of the tumor. During last decades, Endoscopic approach had gained popularity among surgeon due to avoidance of facial scar, more complete inspection due to magnified angle view behind the corner and shorter hospitalization rate. Four handed binostril technique allows exposure of the nasopharyngeal portion of the lesion after resection of the posterior third of nasal septum. Some experienced endoscopic surgeons use expanded endonasal endoscopic approach to more advanced lesions involving infratemporal fossae, basisphenoid and parasellar area.²⁵ Nicolai et al presented a series of 46 JNAs cases treated only by an endoscopic approach after preoperative vascular embolization.²⁶

Olfactory neuroblastoma has high local recurrence rate. Treatment includes surgery and radiation therapy even

for a small tumor confined to the nasal cavity.²⁷ Open approach via craniofacial resection needed if tumor extend to intracranium but at recent days, advance endoscopic skull base technique gives same control of tumor.

Most of pituitary adenoma were treated by total endoscopic methods. Jean A et al did two consecutive series of 60 consecutive patients presenting with active pituitary adenoma via endoscopic transsphenoid surgery and microsurgical approach and concluded that fully endoscopic transsphenoidal surgery for functioning pituitary adenomas leads to a better endocrinologic outcome for noninvasive macroadenomas compared to the traditional microsurgical technique. However, morbidity with the endoscopic technique was higher in terms of the rate of postoperative CSF leaks.²⁸

Clival chordomas had an invasive nature which made its treatment difficult. An aggressive surgical approach needed to attempt radical resection via various skull base approaches either open or endoscopic, followed by postoperative radiotherapy. Takamatsu et al treated 24 patients with skull base chordoma using an aggressive approach. All patients should be followed up with MRI and treated with gamma-knife radiosurgery or surgical resection with the mean postoperative follow-up duration was 10.2 years. The 5-, 10-, and 15-year overall survival rates were 86%, 72%, and 72%, respectively. Tumor extension to the brainstem and partial tumor removal were the poor survival factors.²⁹

Skull-base chondrosarcoma is a rare malignant bone tumor that arises from chondrocyte. Damien et al in their series reported that these tumors were treated with 70 GY pencil beam scanning proton therapy and photon therapy.³⁰ After a mean follow-up of 69.2 months, 6 local (7.8%) failures were observed, 2 of which were late failures. Five (6.5%) patients died. The actuarial 8-year

OS was 93.5%. A higher rate of high-grade toxicity was observed for older patients ($P = .073$), with larger tumor volume ($P = .069$), and treated with 5 weekly fractions ($P = .069$).

The management of craniopharyngioma is very challenging due to its position in the skull base near by many critical structures, its recurrence and adverse effect on the quality of life. It is impossible to get total clearance of tumor. Patel et al performed an endoscopic endonasal transsphenoidal approach to such a tumor and gross total resection of the tumor was done in only 66.3% of patients. He compared with 62 patients who underwent endoscopic pituitary macroadenoma resection, patient with craniopharyngioma had worse postoperative quality of life (QOL).³¹

In endoscopic resection of paranasal sinus, benign tumors are more favored compared to malignant lesions. It is more aesthetic and less invasive than conventional approaches like caldwel luc's operation and lateral rhinotomy. Even in malignant lesions, selection of patient is important to do endoscopic approach in low grade malignant tumor. The final decision is made on an individual basis. Miko Suzuki et al performed endoscopic method of excision over 27 patients, of them 23 patients were benign and 4 malignant tumors, which included olfactory neuroblastoma, acinic cell carcinoma, squamous cell carcinoma, and chondroid chordoma. Preoperative arterial embolization, laser coagulation, and ligation of the sphenopalatine artery were very useful in reducing blood loss during surgery and maintaining a clear endoscopic view.³²

Squamous cell carcinoma is the most common malignant sinonal tumor (80%), followed by adenocarcinoma. There are two types of adenocarcinomas, intestinal and non-intestinal. Carcinomas most often originate from the maxillary sinuses followed by the ethmoid sinuses, nasal

vestibule and cavity; carcinomas originating from the sphenoid and frontal sinuses are very rare. Ongren line (a line from the medial canthus of the eye to the angle of mandible) is important for treatment of sinonal cancer in the past. Tumor posterior to this line was considered to be inoperable. But with the development of advanced surgical technique, it is possible to treat tumors which grow into the orbital apex, dura, middle cranial fossae, nasopharynx and clivus. Bhattacharyya reported a three-fold decrease in survival from T1 to T4 cancers and concluded that early tumor detection was the single most important modifiable treatment factor.³³ Another important factor is tumor site; carcinomas originating in the nasal cavity have a better prognosis than carcinomas in the ethmoid and maxillary sinuses.³⁴

Mucinous adenocarcinoma can be managed via either endoscopic or transcervical and trans axillary approach. Control of carotid artery is important during intraoperative period, for that balloon occlusion test should be performed before surgery. Open transfacial approach via weber fergusson or lower transfacial and transmaxillary approach is suitable for advanced diseases. Reconstruction can be performed with a radial forearm flap that should cover the internal carotid artery. In some cases, it would be needed both endoscopic and maxillary swing approach. There is no evidence that Neck dissection will increase survival but it can be done if free flap is needed. No induction chemotherapy is helpful in this type of tumor. Mucinous type adenocarcinoma is a low-risk tumor but other high-risk tumor features like perineural invasion and perivascular invasion should be treated with concurrent and post-op radiotherapy.³⁵

Sinonal undifferentiated carcinoma (SNUC) has a high rate of distant metastases which favors chemotherapy. Early-stage tumors should be differentiated between operable vs inoperable. Induction chemotherapy after

discussion with a multidisciplinary team should be instituted.³⁶ Two cycle of carboplatin and etoposide will be sufficient. TPF regimen is best for squamous cell carcinoma, only PF is a good choice for SNUC. Tax323 and Tax 324 regimens both show a better control rates.³⁷ It is important to observe the tolerability of chemotherapy.

Mucosal melanoma had a high submucosal spread and 10% neck metastases. Complete removal/respectable should be performed with selective neck dissection. 30% of cases had local uncontrolled disease. Single-agent Immunotherapy ie Durvalumab should be given in a post-operative setting.³⁸ Endoscopic endonasal resection and stage neck dissection is good approach. Adjuvant radiation can be given post-op case at unilateral cases. Phase II study shows Nimolumab had better control rate

Recurrent disease.

For patients with recurrent disease, chemotherapy trials and immunotherapy should be considered. Chemotherapy for recurrent squamous cell cancer of the skull base has been shown to be efficacious as palliation and may improve a patient's quality of life and length of survival. Various drug combinations, including cisplatin, fluorouracil, and methotrexate, are effective.

Immunotherapy

Immunotherapy is now primarily utilized to treat recurrent and metastatic head and neck squamous cell carcinoma. Two novel medicines (Nivolumab and Pembrolizumab), which are immune-checkpoint inhibitors targeting PD1 for the treatment of recurrent locally progressed and/or metastatic HNSCC have been approved.³⁹ These are the most active medications in second-line therapy. The chemotherapy treatment (cisplatin, 5-fluorouracil) coupled with cetuximab remains the first-line treatment. Many phase III studies

are underway to assess the efficacy of anti-CTLA4 combined with anti-PD1 or anti-PDL1 therapy. Early phase research has shown very encouraging results.

Management of Neck

Sinonasal carcinoma metastasis to level I, II and III lymph nodes and retropharyngeal lymph node and distant metastases in 20% to 40 % of patient's which did not respond to treatments. Cantu et al found that lymph node metastases were rare, and when present, the prognostic factors were low with 5-year survival of 17% for maxillary sinus and 0% for ethmoid sinus carcinomas.⁴⁰ The highest rate of lymph node metastases was found in T2 squamous cell carcinoma that involved the floor of the maxillary sinus. Most of the patient die due to locoregional recurrence and direct extension to vital areas of the skull bases. National Comprehensive Cancer Network (NCCN) guidelines recommend for maxillary carcinoma that adjuvant radiation therapy to the N0 neck in the setting of T3 and T4a disease.⁴¹ However, for smaller primary lesions, (T1 and T2) no elective treatment of the neck is recommended.

Reconstruction

Skull base reconstruction is important to separate the nose from the brain after surgery. The mind should be makeup to reconstruct the skull base even prior to surgery. Occult dural invasion occurs in 54% of the patient which needs to need partial resection of the dura. Resection of dura provides margin control without oncological benefit.⁴² Total endoscopic procedures can be reconstructed with a vascularized Nasoseptal flap. The Nasoseptal flap can able to cover from cristia galli to clivus defect. If surgery is performed by both endoscopic and open approach, a Nasoseptal flap with a pericranial flap may be needed.⁴³ Cerebrospinal fluid leak, headache, meningitis or intracranial abscess are

developed if proper reconstruction was not done. Some cancer may involve the eye which needed exenteration that needed vascularized free flap too. Such reconstruction is determined by surgical factor, donor site morbidity, thin mucosal surface coverage performed by radial forearm flap. In orbital exenteration, total maxillectomy and orbital exenteration, anterolateral thigh flap and rectus abdominus flap would be appropriate.^{44,45}

Conclusions: Nasal endoscopy and imaging findings are used for the treatment of skull base tumors. CT scans and MRIs are becoming increasingly important in an illness diagnosis. The threat of a tumor is determined by its location and behavior. Endoscopic skull base approaches were even effective in curing the tumor. The importance of chemotherapy cannot be overstated. Immunotherapy-like checkpoint inhibitors targeting PD1 are the most effective drugs in the second-line treatment of advanced HNSCC (nivolumab and pembrolizumab). Prospective research and trials are required in the future.

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