Chapter 8
Radiation Therapy for Sinonasal and Skull Base Tumors

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Overview of Radiotherapy for Sinonasal and Skull Base Tumors

Sinonasal and skull base tumors pose a multitude of multidisciplinary challenges. While such cases are relatively rare, there are also numerous distinct pathologies with varied natural histories, and a paucity of high-level evidence to guide treatment decisions. Given the proximity to the visual apparatus, brain, and other cranial nerves, the functional impact of sinonasal and skull base cancers can be devastating and the options for local disease control may be morbid or associated with significant risk of late toxicities.

The challenges in treating patients with sinonasal and skull base tumors with radiation are similar to those associated with surgery. The diseases are uncommon and heterogeneous, the anatomy is complex, the tumors are often in close proximity or compromising critical normal structures, the therapeutic window is narrow, the treatment is often time-consuming, associated with unique and meaningful risks, and may require difficult choices in shared decision-making with the patient. Furthermore, both specialized equipment and capable team members for treatment and periprocedural care are critical.

A report from the National Cancer Database concludes that patients with sinonasal squamous cell carcinoma (SCC) treated at high-volume centers have better overall survival than those managed in lower volume centers [1], similar to findings in other head and neck cancer sites [2]. In the United States, it is somewhat easier to align patient care with regional centers of expertise for complex surgery and expert pathology review, but with radiotherapy typically requiring several weeks of treatment, this poses challenges for patients. In other healthcare systems, patients

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requiring highly complex care are more often consolidated in centers of excellence that have the appropriate resources and can develop the depth of experience required for optimal patient care [3]. A less fragmented approach to patient care has the added benefit of accelerating progress in research and the opportunity for coordinated and iterative optimization of treatment for rare tumors.

In this chapter, we summarize the current evidence that informs the role of radiation in management of various histologies, available recommendations on treatment techniques and volumes, and summarize some of the relevant toxicities and supportive care regimens for this patient population.

Data for Radiation by Histology

Squamous Cell Carcinoma

Nasal Vestibule Squamous Cell Carcinoma

The nasal vestibule is anatomically distinct from the remainder of the nasal cavity where cutaneous squamous epithelium transitions to the respiratory epithelium of the nasal mucosa [4]. The posterior border of the nasal vestibule is approximately 1.5–2 cm from the nostril edge [5, 6]. Nasal vestibule cancers are staged according to the AJCC staging system for cutaneous carcinoma of the head and neck, reflecting their origin in cutaneous epithelium. In addition, the staging system proposed by the late radiation oncologist C.C. Wang is frequently used to guide management [7]. Table 8.1 compares these staging systems.

Table 8.1 Comparison of AJCC and Wang staging system for nasal vestibule

	AJCC 8th edition	Wang staging
T1	Tumor ≤2 cm in greatest dimension	Limited to the nasal vestibule, relative superficial, involving one or more sites within
T2	Tumor >2 cm but ≤4 cm in greatest dimension	Extension from the nasal vestibule to adjacent structures, such as the upper nasal septum, upper lip, philtrum, skin of the nose, and/or nasolabial fold, but not fixed to the underlying bone
T3	Tumor >4 cm in maximum dimension or minor bone erosion or perineural invasion (nerve measuring ≥0.1 mm in caliber or any nerve deeper than the dermis) or deep invasion (beyond the subcutaneous fat or >6 mm as measured from the granular layer of adjacent normal epidermis to the base of the tumor)	Massive with extension to the hard palate, buccogingival sulcus, large portion of the upper lip, upper nasal septum, turbinate, and/or paranasal sinuses, fixed with deep muscle or bone involvement
T4a	Tumor with gross cortical bone/marrow invasion	
T4b	Tumor with skull base invasion and/or skull base foramen involvement	

Surgery in this area poses challenges to preserve function and cosmesis [5]. Limited comparative data found improved patient satisfaction with aesthetic outcomes following primary radiotherapy [8]. Oncologic outcomes with radiation for early stage (T1-T2) tumors of the nasal vestibule with clinically node negative necks are very favorable. A modern experience with image-guided interstitial or intracavitary mold brachytherapy reported 5-year local control rates of 95% in a series of 102 patients with Wang stage T1-T2 disease [9]. Using external beam with or without brachytherapy, 10-year local control of 89% was reported in patients with T1-T2 disease, and 76% in those with more advanced T3-T4 disease, with no significant differences in outcomes between those treated with brachytherapy alone, external beam alone, or combination therapy [6]. Recurrences after upfront radiation therapy can often be salvaged by surgery leading to excellent long-term disease control outcomes for these patients. Given a low incidence of regional nodal failure, elective neck treatment is not recommended for T1-T2 N0 nasal vestibule cancers unless poorly differentiated [5, 6]. For larger tumors (e.g., T3 disease >4 cm) or those with bone involvement (e.g., T4 disease), surgery and postoperative radiotherapy are recommended [6].

With published radiation series typically heterogeneous and accrued over many years using a variety of techniques, no uniform standard radiation fractionation regimen has emerged for nasal vestibule carcinomas. The aforementioned series of interstitial and intracavitary high dose rate brachytherapy used a regimen of 49 Gy in 14 fractions given twice daily over 7 consecutive days with the prescribed dose covering the gross tumor volume and 85% of the prescribed dose covering the clinical target volume, which was the tumor with an anatomically modified 1 cm margin [9]. For external beam radiation, both conventional fractionation and moderately hypofractionated regimens have been used. The Danish Society for Head and Neck Oncology and the Danish Head and Neck Cancer Group published their experience treating 174 patients with nasal vestibule carcinomas [10]. Among those T1 tumors (treated with primary radiation using simple opposed lateral fields), superior outcomes were observed in those treated with 54 Gy in 18 fractions compared to 66 Gy in 33 fractions (5-year local control 87% vs. 56%, $p = 0.007$) suggesting a benefit to a moderately hypofractionated regimen.

The American Society for Radiation Oncology (ASTRO) has published a clinical practice guideline for definitive and postoperative radiation for basal and squamous cell carcinomas of the skin [11]. A selection from one of the recommended conventional or moderately hypofractionated regimens may be appropriate. For irradiation of nasal vestibule or anterior nasal cavity tumors, attention is required to ensure delivery of adequate radiation dose to the tumor and acceptable radiation dose homogeneity, usually with custom bolus.

Nasal Cavity and Paranasal Sinus Squamous Cell Carcinoma

Squamous cell carcinoma is the most common histology arising in the paranasal sinuses, including, from most to least common, the maxillary sinus, nasal cavity, ethmoid sinuses, and frontal and sphenoid sinuses [12, 13]. Some arise from sinonasal papillomas. Primary surgical management is the recommended treatment for

all resectable tumors [13] excepting that T1-T2 tumors of the nasal vestibule or anterior nasal cavity can be treated with primary radiotherapy with good outcomes and cosmesis, reserving surgery for salvage.

Accepted indications for postoperative radiation therapy include T3 or T4 disease, a close or involved surgical margin, perineural invasion, lymphovascular space invasion, pathologic involvement of two or more cervical lymph nodes, or the presence of extranodal disease extension. Although patients with sinonasal SCC were not included in the two large randomized controlled trials evaluating postoperative concurrent chemoradiation therapy for other head and neck SCC [14, 15], by extrapolation of these data, guidelines recommend the addition of concurrent chemotherapy for patients with sinonasal SCC who have an involved surgical margin or extranodal disease extension [13]. A postoperative radiation dose of 60 Gy at 2 Gy per fraction is standard for intermediate risk disease, while a boost to 66 Gy in 30–33 fractions is employed to high-risk areas of an involved surgical margin or extranodal disease extension. For patients with gross residual or unresectable disease, a dose of 70 Gy in 35 fractions is standard with concurrent chemotherapy. In the setting of gross disease, if concurrent chemotherapy cannot be delivered, altered fractionation or other dose intensification may be attempted.

Unfortunately, patients with paranasal sinus squamous cell carcinomas continue to have relatively poor outcomes despite aggressive therapy. In a series of 85 patients with paranasal sinus tumors managed with surgery and postoperative radiation, approximately half of whom had squamous cell carcinomas, the 5-year progression free survival was just 49% [16]. Squamous histology was identified as a significant predictor of local recurrence and worse overall survival on multivariate analysis. The results of non-operative management with chemoradiation with intensity modulated radiation therapy (IMRT) in unresectable disease are poor with a reported 5-year local progression free survival of 21% and overall survival 15% in a series of 39 patients with sinonasal tumors (15 with squamous cell carcinoma) [17]. A more recent series consistently using IMRT included 40 patients with squamous cell carcinoma treated with surgery and postoperative IMRT with or without chemotherapy, reporting a 5-year local control in 79%, versus a 5-year local control of 54% in 16 patients managed with definitive chemoIMRT [18].

Local recurrence remains the most common pattern of failure after both postoperative and definitive radiation [16, 17, 19]. This may be due to the fact that the radiation target volume is typically in very close proximity to several critical structures including the eyes, optic nerves, optic chiasm, brainstem, and normal brain. It is technically challenging to deliver an adequate dose to the entire volume at risk while respecting conventional radiation dose constraints to these critical normal structures. The introduction of IMRT certainly improved coverage and appears to have reduced toxicity in patients with sinonasal cancer [16], but compromises in target coverage are still typical to meet constraints. These challenges are the primary rationale for even more conformal techniques for sinonasal and skull base tumors using particle therapy, discussed later.

The necessity of elective treatment of the clinically node negative neck has been uncertain given limited available evidence to guide treatment decisions. Current

consensus guidelines recommend elective nodal irradiation for T3-T4 N0 maxillary sinus squamous cell carcinomas or T3-4 N0 nasal cavity squamous cell carcinomas that involve the anterior 1/3rd of the nasal cavity [20]. The nodal levels at risk in a clinically node negative neck are levels Ib-III, the bucco-facial and retropharyngeal lymph nodes. Treatment can be limited to the ipsilateral neck provided the primary tumor does not cross midline and there is no contralateral neck gross disease. For squamous cell carcinomas of the ethmoid sinus, frontal sinus, or sphenoid sinus, elective neck radiation does not appear indicated regardless of stage, unless the tumor involves the hard or soft palate, nasopharyngeal mucosa, anterior one-third of the nasal cavity, or the skin of the face (Fig. 8.1).

For advanced tumors, definitive surgery may require orbital exenteration or skull base resection that is associated with meaningful risk of mortality and morbidity [21, 22], and has tremendous cosmetic, psychological, and functional impact for patients. Some institutions have adopted an approach of neoadjuvant chemotherapy [23, 24] in an attempt to offer organ-preserving surgery to responders or to shrink tumor away from the optic apparatus in patients destined for non-operative therapy. An ongoing phase II randomized trial by ECOG-ACRIN, EA3163 [25] is directly comparing the strategy of neoadjuvant chemotherapy followed by surgery and postoperative radiation versus surgery and postoperative radiation. In both arms, concurrent chemotherapy is added in the postoperative setting for high-risk pathologic features. The primary endpoints are the structure preservation rate of the orbit and skull base, and overall survival.

Key Points for Squamous Cell Carcinomas

- T1-T2 N0 nasal vestibule/nasal fossa SCC can be treated with definitive radiation alone with good long-term outcomes and cosmesis.
- Sinonasal SCC in more proximal nasal cavity and paranasal sinuses should receive upfront surgery followed by evaluation for postoperative radiation with or without concurrent chemotherapy based on pathologic risk factors.
- Patients with advanced sinonasal SCC patients may be evaluated for induction chemotherapy for response-based decisions on local therapy, or concurrent chemoradiation, or palliative interventions.
- Elective nodal irradiation is recommended for T3-T4 N0 maxillary sinus squamous cell carcinomas or T3-4 N0 nasal cavity squamous cell carcinomas that involve the anterior one-third of the nasal cavity.

Adenoid Cystic Carcinoma

Nearly all studies show superior outcomes for adenoid cystic carcinoma (ACC) managed primarily with surgery. Given the high propensity for local recurrence, postoperative radiotherapy is recommended in most instances. Current NCCN clinical guidelines

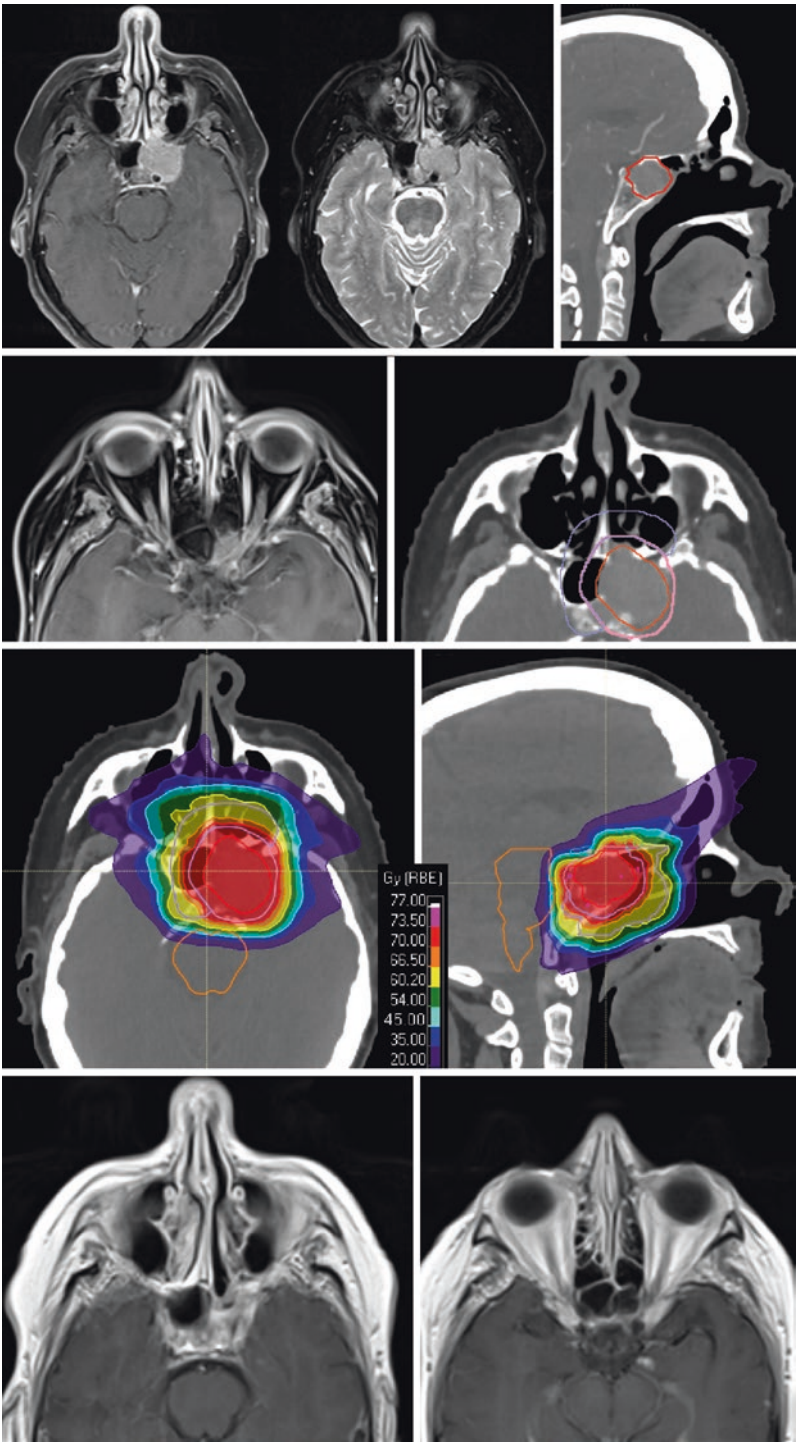
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Fig. 8.1 This patient presented with a 2-year history of intermittent epistaxis and CT imaging showed an expansile sphenoid sinus mass. An endoscopic tumor biopsy and debulking showed poorly differentiated squamous cell carcinoma. PET, CT, and MRI showed tumor involvement of the left cavernous sinus, the medial margin of the superior orbital fissure, floor of the anterior clinoid, and widening of the foramen rotundum and sphenopalatine foramen. The MRI on the second row shows the disease on either side of the left optic nerve. The tumor was deemed not reasonably resectable and concurrent chemoradiation was offered. The second row CT image shows the gross tumor volume (red), the clinical target volume to receive 70 Gy (pink) and an intermediate volume to receive 60 Gy (purple). The proton colorwash is shown on the third row. Because of the disease extent, it was not possible to spare the left optic nerve and the patient was informed of and consented to an expectation of eventual vision loss in the left eye. While the mean dose to the left optic nerve was 54 Gy, 29% of the nerve received a dose of 70 Gy. The optic chiasm and right optic nerve constraints were met to avoid risk of bilateral vision loss. Because the tumor did not involve the nasopharyngeal mucosa, only the primary site was treated, without elective nodal irradiation. A complete response was noted on PET/CT at 3 months post-treatment. At 14 months post-treatment a small focus of enhancement was noted in the left medial temporal lobe/uncus consistent with asymptomatic (grade 1) radiation necrosis. In an effort to prevent progression to potentially symptomatic necrosis, pentoxifylline with vitamin E was recommended, but the patient preferred not to take it. The bottom row shows an MRI 18 months after completion of treatment with stable post-treatment changes and no change in the area of necrosis. The patient retained normal vision at 2 years after treatment

recommend postoperative radiation therapy for all head and neck ACC, considering observation for T1-T2 N0 disease with clear surgical margins and no perineural invasion [26]. A number of large retrospective studies have found improved local control in patients with ACC receiving postoperative radiotherapy [27, 28] although in this indolent disease, it is unclear whether such improvements may translate into improved overall survival as seen in an NCDB analysis [29] but not in a Danish database or SEER analysis [28, 30]. A recursive partitioning analysis performed in 319 patients with head and neck ACC managed with surgery with or without postoperative radiation stratified patients into low, intermediate and high risks groups [31]. Postoperative radiation therapy was associated with a significant improvement in local recurrence-free survival except for those in the low-risk group (those with T1 or T2 tumors arising in a major or minor salivary gland with surgical margins uninvolved).

Sinonasal ACC appears to have inferior outcomes compared to other head and neck sites, likely related to more often having advanced stage disease, the greater likelihood of an R1/R2 resection, and the challenges of delivering adequate postoperative radiotherapy next to many critical structures. For example, there was a 30% local recurrence rate in the MDACC series of 105 patients with sinonasal ACC, mostly treated with surgery and postoperative radiation [32], and nearly 2/3rds of the local recurrences seen in the MSKCC series were in those with skull base involvement [33].

Skull base involvement, either by direct extension or perineural invasion, is often unresectable or results in an R2 resection. Outcomes with IMRT for patients with residual disease are poor. For example, in a series of 21 patients with head and neck ACC, mostly with R2 resections, the 3-year local control was 38% after IMRT to a median dose of 66 Gy [34]. Conversely, good local control outcomes have been observed in patients with gross disease when treated with dose-escalated radiation, often delivered with charged particle therapy. In a small series of 23 patients with

skull base ACC, 87% of whom had gross disease at the time of treatment, a dose of ~76 Gy using combined photon and proton therapy achieved a 5-year local control rate of 93% [35]. In a series of 26 patients with head and neck ACC treated with proton therapy to a median dose of 72 Gy, the 2-year local control was 95% when treating initial disease, and 86% when treating previously irradiated patients with recurrent disease [36]. A series of 41 sinonasal ACC patients treated with particle therapy (carbon ion ± proton therapy), 32 of whom had gross disease at the time of radiotherapy, and 10 of whom had recurrent disease after prior photon-based radiation, achieved a 3-year local control of 90% using a variety of moderately hypofractionated dose-escalated regimens [37]. A series of 29 patients with skull base ACC treated with photon therapy with a carbon ion boost achieved a 4-year local control rate of 78% [38]. A series of 34 patients with skull base salivary gland tumors (mostly ACC) treated for gross residual disease with neutron therapy and a Gamma Knife radiosurgery boost reported a 40-month local control of 81% [39].

With adequate follow-up, at least half of patients with ACC will eventually develop distant metastatic disease, most commonly to the lung [40–42]. However, the clinical course of patients with non-solid ACC with distant metastatic disease can be very indolent, with a median survival after distant metastases of 3 to 6 years [40, 42] and 10% reaching 10 years [43]. For this reason, even in the setting of known distant metastatic disease, it may be appropriate to consider aggressive local therapy of the primary site, including surgery and postoperative radiation, to reduce the risk of toxicities from uncontrolled head and neck disease. Patients with solid-type ACC, as well as those with high-grade transformation or dedifferentiated ACC have a higher risk of lymph node involvement and distant metastatic disease with poor survival [27, 44, 45].

The risk of occult cervical lymph node involvement in ACC varies considerably in different series, making the role of elective lymph node dissection controversial. Similarly, there is some controversy about the role of elective nodal irradiation in head and neck ACC. However, the risk of occult lymph node disease in sinonasal non-solid ACC appears quite low. A literature review including 774 patients with ACC of the sinonasal tract, nasopharynx, lacrimal glands, and external auditory canal found regional lymph node metastases in 5.3% [46]. Elective nodal irradiation does not appear indicated in patients with sinonasal ACC, but should be strongly considered in patients with solid-type ACC, high-grade, or dedifferentiated ACC.

Key Points for Adenoid Cystic Carcinoma

- Postoperative radiation therapy should be strongly considered in all patients, with the potential exception of those with T1-T2 N0 tumors with negative margins and no PNI.
- Patients with unresectable disease or gross residual disease should be considered for radiation dose escalation >70 Gy, for which most experiences have used proton or carbon ion therapy.

- Patients with solid-type ACC or high-grade/dedifferentiated ACC often have an aggressive disease course and are more likely to have regional and distant metastatic disease.
- For conventional cribriform or tubular ACC, even those with distant metastatic disease can have an indolent course and aggressive local therapy to a skull base primary may be indicated.
- Except solid-type ACC or high-grade/dedifferentiated ACC, elective nodal irradiation does not appear indicated for sinonasal ACC.

Esthesioneuroblastoma

Esthesioneuroblastoma, also known as olfactory neuroblastoma, is a small round blue cell tumor, which may be confused with other pathologies [47]. Esthesioneuroblastomas often have a protracted and relatively indolent disease course but occasionally can be very aggressive. Prognosis and treatment are informed by both tumor extent (stage) and histologic grade. Hyams grading system uses a score from 1 to 4 based mitotic activity, nuclear pleomorphism, rosette formations, necrosis, disorganized architecture, and sparse fibrillary matrix [48]. Hyams score 1–2 are typically considered low grade, and 3–4 high grade [49].

In addition to AJCC staging system, patients with esthesioneuroblastoma are also often staged according to the system proposed by Kadish [50], and subsequently modified [51]. The AJCC system provides significantly more discrimination among the otherwise heterogeneous presentations of Kadish C disease. Table 8.2 compares these staging systems.

Table 8.2 Comparison of AJCC and Kadish staging systems for nasal cavity and ethmoid sinuses

AJCC 8th edition Nasal Cavity and Ethmoid Sinuses		Kadish staging	
T1	Tumor restricted to any 1 subsite[a], with or without bony invasion	A	Tumor confined to nasal cavity
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion	B	Limited to nasal cavity and one or more paranasal sinuses
T3	Tumor extends to involve the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate	C	Extends beyond the nasal cavity and paranasal sinuses including involvement of the orbit, base of the skull, or intracranial cavity
T4a	Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid, or frontal sinuses		
T4b	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus		
	[a]Subsites of the nasal cavity: septum, floor, lateral wall, edge of naris to mucocutaneous junction. Subsites of ethmoid sinuses: left, right	D	Presence of metastatic cervical lymph nodes or distant metastatic disease

Combined modality therapy has consistently demonstrated favorable outcomes for patients diagnosed with esthesioneuroblastoma. In one relatively large series (n = 138), patients treated with surgery or radiation alone had significantly worse overall survival compared with those who received surgery, radiation, and/or chemotherapy in some combination [52]. Local control with postoperative radiation was superior to surgery alone despite more adverse features (higher stage and grade) in patients receiving radiation [53]. Institutional preference drives preoperative versus postoperative radiation for esthesioneuroblastoma, with both approaches demonstrating 5-year disease free survival rates exceeding 85% [54, 55].

Current NCCN clinical guidelines recommend postoperative radiation therapy for all esthesioneuroblastomas, although observation can be considered for those with T1 N0 disease not involving the cribriform plate or medial orbital wall, resected with clear surgical margins (R0) without perineural invasion and without high-grade features [26]. ACR Appropriateness Criteria recommend standard radiation dose and fractionation in the postoperative setting (e.g., 60–66 Gy in 30–33 fractions depending on surgical margin status) [13].

The role of elective nodal irradiation has been unclear for esthesioneuroblastoma, given the limitations of small and heterogeneous studies and the long natural history of the disease. Cervical lymph node failures can be delayed, with reports of median time to failure of 58–74 months [56, 57]. In a series of 71 patients with clinically node negative neck, approximately one-third of whom received elective nodal irradiation, long-term locoregional control rates were 100% for patients receiving neck radiation and 82% when the neck was not irradiated, with the majority of neck failures occurring in patients with Kadish stage C disease [58]. A meta-analysis found that the risk of cervical lymph node metastases was markedly higher in high-grade esthesioneuroblastoma (Hyams 3–4) compared to low-grade (18% vs. 8%) [49]. Consensus guidelines suggest elective lymph node irradiation for patients with Kadish stage C disease and those with high-grade (Hyams 3–4) tumors [20].

The role of chemotherapy is unclear, but meta-analysis noted a significantly high rate of distant metastatic disease (21% vs. 9%) in high-grade versus low-grade esthesioneuroblastomas [49], and current NCCN clinical guidelines recommend including systemic therapy as part of treatment for patients with high-grade esthesioneuroblastoma [26].

Progression is most commonly local and loco-regional and can occur 5–10 years after treatment [59], underlining the importance of long-term follow-up.

Key Points for Esthesioneuroblastoma

- Postoperative radiation therapy should be strongly considered in all patients, potentially excepting those with T1 N0 disease not involving the cribriform plate or medial orbital wall, resected with clear surgical margins and no perineural invasion, without high-grade features.
- Elective lymph node irradiation is recommended for patients with Kadish stage C disease and those with high-grade (Hyams 3–4) tumors.

- Systemic therapy should be incorporated in treatment for patients with high-grade esthesioneuroblastoma.

Sinonasal Undifferentiated Carcinoma

Sinonasal undifferentiated carcinomas (SNUC) are locally aggressive, poorly differentiated neuroendocrine tumors that lack glandular or squamous features. They are rare tumors with a very poor prognosis, and are a diagnosis of exclusion, after ruling out other epithelial and non-epithelial high-grade malignancies [12]. A subset of these tumors, designated as SMARCB1-deficient carcinomas, have rhabdoid histologic features and loss of SMARCB1(INI1), but remain within the spectrum of SNUC in WHO classification [12]. Current treatment paradigms are largely informed by limited and small retrospective experiences, with considerable variation in institutional practice.

Multi-modality therapy appears to be extremely important in the management of these tumors as they have a high tendency for both local and distant recurrence. A meta-analysis including 167 patients found a worse prognosis in those managed with a single modality [60]. An NDCD analysis found that for those with Stage III or IV non-metastatic disease, the addition of surgery did not improve survival compared to definitive chemoradiation, except a small subset of patients who were able to undergo surgical resection with uninvolved surgical margins [61]. Current NCCN clinical guidelines recommend that systemic therapy be incorporated in treatment for patients with SNUC with neuroendocrine features [26]. Given that distant metastases are the predominant pattern of failure in SNUC [62], early integration of systemic therapy seems appropriate.

MD Anderson Cancer Center reported on 95 patients with SNUC, the largest institutional series to date [63]. All patients received induction chemotherapy with a median of three cycles of a platinum-based doublet regimen, most commonly cisplatin with etoposide or docetaxel. The response to upfront chemotherapy was found to be useful to optimize the choice of local control modalities. For those who had a partial or complete response to induction chemotherapy, survival outcomes were improved with definitive chemoRT using additional concurrent cycles of platinum and etoposide (5-year DSS 81%) compared to surgery and postoperative therapy (5-year DSS 54%). For those who did not respond to induction chemotherapy, survival outcomes were better in those who could undergo surgery and postoperative therapy (5-year DSS 39%) compared to definitive chemoRT (5-year DSS 0%). Therefore, their preferred treatment approach is to use induction chemotherapy in all patients. Those with a partial or complete response receive concurrent chemoradiation, while those without a response undergo surgery and postoperative therapy if resectable or definitive chemoradiation if not reasonably resectable [64].

Bilateral elective nodal irradiation is recommended in all cases of clinically node negative SNUC [20]. Radiation dose and fractionation follows those employed in head and neck squamous cell carcinomas. If definitive chemoradiation is employed for tumors abutting critical neural structures, a hyperfractionated (twice daily) radiation therapy schedule may be considered in an effort to decrease the risk of late toxicities, such as optic neuropathy.

Key Points for Sinonasal Undifferentiated Carcinoma

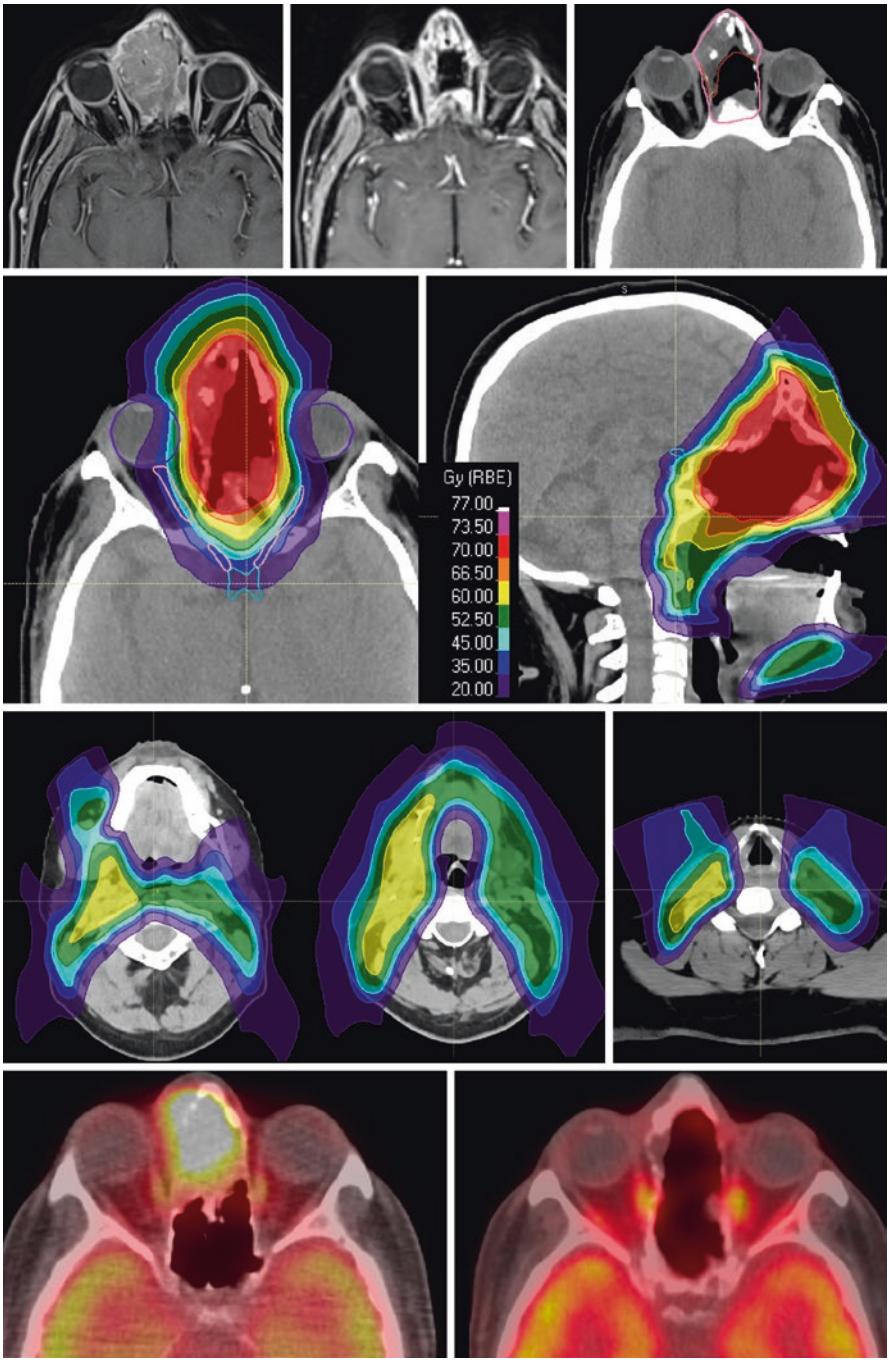
- Given the high risk of distant metastases, upfront chemotherapy may be considered. The response to induction chemotherapy can guide the most appropriate local control modality.
- Elective lymph node irradiation is recommended for all patients.

Sinonasal Neuroendocrine Carcinomas

Sinonasal neuroendocrine carcinoma (SNEC) is an epithelial neoplasm with both morphologic and immunohistochemical features of neuroendocrine differentiation [65]. This very rare entity is also heterogeneous with well differentiated (carcinoid), moderately differentiated (atypical carcinoid) and poorly differentiated (small cell) variants described. Neuroendocrine tumors tend to present at advanced stage [66]. Current NCCN clinical guidelines recommend that systemic therapy be incorporated in treatment for patients with SNEC [26]. Cisplatin and etoposide are commonly employed for systemic therapy given their proven effectiveness for treatment of neuroendocrine tumors in other anatomic sites (Fig. 8.2).

A NCDB analysis with 415 patients found improved survival with definitive chemoradiation and with surgery followed by chemoradiation compared to single modality therapy [67]. In the absence of robust evidence, one proposed treatment strategy for poorly-differentiated SNEC is induction chemotherapy followed by response-based local therapy (surgery with postoperative therapy vs. definitive

Fig. 8.2 This patient presented with nasal obstructive symptoms and epistaxis and found to have a large right nasal cavity mass, biopsied and debulked with pathology showing a poorly differentiated neuroendocrine carcinoma. MRI (top left) showed the tumor with bony erosion of the right lamina papyracea, broad contact with the anterior medial rectus and the right superior oblique muscle and mass effect on the globe, and intracranial invasion along the cribriform plate. The patient was stage cT4a N1 M0, with no evidence of distant disease on PET/CT. The patient received three cycles of cisplatin and etoposide with a near complete response on MRI followed by endoscopic anterior skull base resection and right neck dissection. Pathology showed minute foci of carcinoma in the primary site and minute foci of carcinoma present in 4/38 lymph nodes. Unfortunately, the patient experienced rapid tumor regrowth by the time of postoperative radiotherapy with enlarging soft tissue fullness at the bridge of the nose and MRI (top middle) showing recurrent enhancing tumor. The top right image from the radiation planning CT shows the gross disease at the time of radiation (red) and the target planned for 70 Gy (pink). The proton colorwash shows the coverage of the pre-chemotherapy tumor extent and the recurrent gross disease to 70 Gy, inclusive of intracranial extension, with steep dose gradients around the optic apparatus. The dissected right neck received 60 Gy while the elective right buccofacial lymph nodes and left neck received 54 Gy. With proton therapy, it was possible to achieve excellent sparing of the oral cavity, larynx, and posterior pharyngeal wall below the purposefully treated retropharyngeal lymph nodes. The bottom row images show the initial PET/CT scan on the left and the 3-month post-treatment PET/CT on the right showing resolution of the primary site disease. Unfortunately, that imaging showed evidence of distant metastatic disease. The patient succumbed to distant disease 10 months after completion of radiation while maintaining locoregional disease control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chemoradiation), while the rare resectable well-differentiated tumor may be managed with surgery alone and moderately differentiated tumors with surgery and postoperative radiation [64, 66]. Elective nodal irradiation is recommended for patients with moderate and poorly differentiated neuroendocrine carcinomas [68, 69].

Key Points for Sinonasal Neuroendocrine Carcinoma

- Systemic therapy should be incorporated in treatment for patients with sinonasal neuroendocrine carcinomas.
- Elective lymph node irradiation is recommended for all moderate and poorly differentiated SNEC patients.

Skull Base Chordomas and Chondrosarcomas

Although two distinct pathologies with substantially different prognoses, skull base chordomas and chondrosarcomas are often discussed together given their similar presentation and treatment approaches. Both are malignant tumors of bone. Chordomas have a notably higher propensity for local recurrence and metastasis [70, 71]. Staining for cytokeratin and brachyury, a marker of notochord differentiation, is used to diagnose a chordoma from a chondrosarcoma [72]. Chordomas, which are believed to arise from remnants of the embryonic notochord, are typically midline, T2 hyperintense on MRI, and have a lytic or cystic appearance on CT. Skull base chondrosarcomas, likely derived from chondrocyte rests of the basilar skull bones, are more often paramedian (e.g., petrous apex) and may show areas of calcification on CT [73]. The proximity of numerous critical neurovascular structures, which are often affected by tumor, pose challenges for both surgery and radiotherapy.

Chordomas

Guidelines recommend MRI assessment of the spinal axis at presentation to screen for metastatic or multifocal disease [74, 75], and a CT chest, abdomen, pelvis for systemic staging. Imaging of the spinal axis can identify other T2 hyperintense well circumscribed and presumed benign notochord remnant tumors, which should be observed for growth. The lack of bone destruction, absence of soft tissue extension, and radiographic stability over time distinguish such notochord remnants from chordoma [76].

Gross total or near total resection is desired for improved local control [77], and a smaller volume of tumor at the time of radiotherapy also appears associated with improved local control [78]. Patients should be evaluated by an experienced skull base surgical team to increase the likelihood of maximal safe surgical resection [79].

Some have advocated that after a gross total resection, radiotherapy should be reserved for future recurrence. However, since en bloc resection and margin assessment is generally not feasible for skull base tumors, the recurrence rate following aggressive surgical resection is still significant (e.g., ~60% recur in 5 years) and future surgeries are associated with both inferior extent of resection and greater complications [80]. Outcomes after radiotherapy are better in those treated with radiation for initial rather than recurrent disease [78, 81, 82]. International chordoma consensus guidelines, developed by experts and patients, recommend radiotherapy after macroscopic complete resection and support the use of proton therapy or carbon ion therapy as the preferred radiation approach [74]. The guidelines recommend a clinical target volume (CTV) encompassing the preoperative tumor extent and all areas at risk for microscopic residual disease receiving at least 50–54 Gy, with a second CTV boost encompassing any residual tumor or areas of known microscopic residual disease, receiving a cumulative dose of at least 74 Gy in 2 Gy fractions, with daily image guidance. The initial volume includes the sphenoid sinus after endoscopic surgery but does not include the entire operative approach [83]. The radiation oncologist should take care to correlate preoperative and postoperative MRIs to distinguish residual T2 hyperintense tumor from postoperative fluid and debris, to encompass all lytic areas of bone, and to identify and adequately cover tumor involvement of the prevertebral muscles or nasopharynx (Fig. 8.3).

Adequate target/tumor coverage is correlated with improved local control after radiotherapy [78]. Adequate coverage is dictated by adequate surgical decompression of critical structures, experienced treatment planning, ideally with particle therapy, and acceptance of more aggressive dose constraints to critical organs at risk. Based on published experience from multiple centers treating skull base chordomas with proton therapy, the international consensus guidelines summarize the recommendations, which, for conventional fractionation, include constraining the dose to 2% of the optic nerves and chiasm to <60 Gy, the surface dose to the brainstem to <63 Gy, and the central brainstem dose to <50 Gy [74]. These constraints are higher than used in other clinical scenarios, but when one considers that these doses levels are within the penumbra of the prescription dose cloud at a lower fractional dose, the biologically effective dose is lower (e.g., 63 Gy in 37 fractions is approximately equal to 58 Gy in 2 Gy fractions for $\alpha/\beta = 2$ tissues like brain). As a result, the risk of vision loss when following these constraints is extremely low [84]. The majority of published clinical outcomes data for skull base chordomas are with particle therapy, where local control results are among the highest in the literature. The group at PSI reported on their experience treating skull base chordomas with pencil beam proton therapy, reporting a 5-year local control of 81% in 64 patients [85] and later, a 7-year local control of 71% in 151 patients [81]. A series of 155 patients treated with carbon ion therapy to a median dose of 60 Gy in 20 fractions (moderately hypofractionated) reported a 5-year local control of 72% [82]. A series of 24 skull base chordoma patients treated with image-guided IMRT to a median dose of 76 Gy reported a 5-year local control of 65% [86]. A series of 12 patients treated with IMRT to a median dose of 66.6 Gy reported a 5-year recurrence-free survival of 38% [87]. A report from a multi-institutional dataset of 71 patients

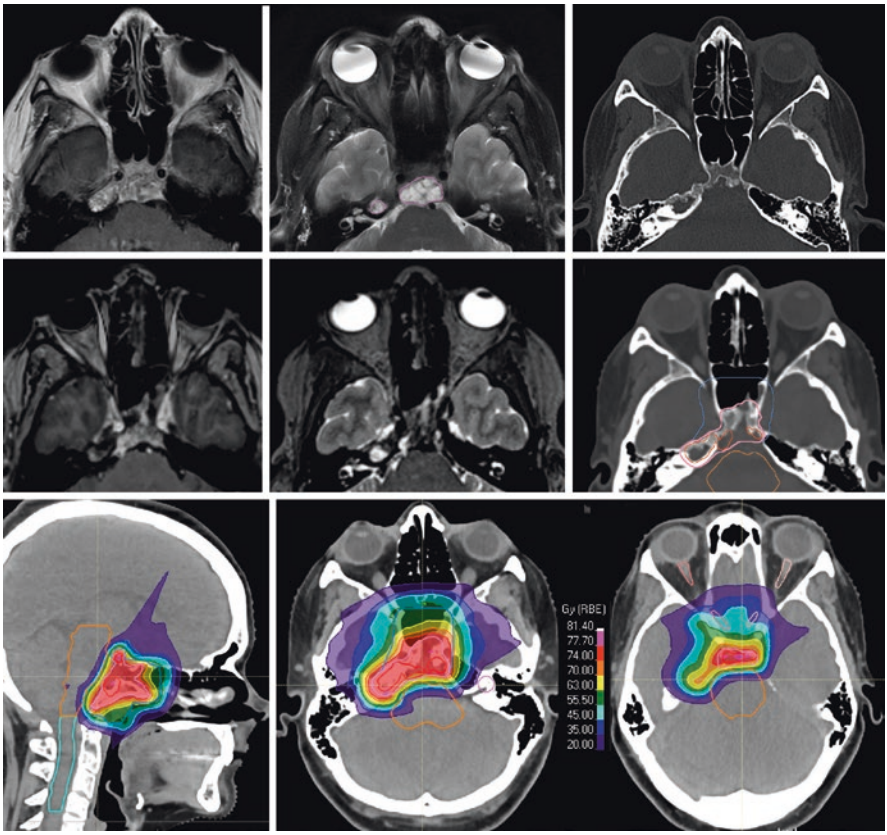

Fig. 8.3 This patient presented with diplopia and a left cranial nerve VI palsy. The top row shows the preoperative imaging, with a T1 heterogeneously enhancing, T2 hyperintense tumor (note the second focus of tumor in the right petrous apex immediately adjacent to the right cochlea) and CT showing lytic process involving the majority of the clivus and a portion of the petrous apex of the right temporal bone. A transnasal transsphenoidal resection was performed with tumor debulking, pathology showing chordoma. The second row shows the postoperative imaging, with expected postoperative enhancement in the central skull base, and T2 MRI showing the residual focus of tumor in the right petrous apex and small blebs on the lateral margin of the central tumor bed resection. The radiation planning CT on the second row far right shows the T2 tumor in red, the target to receive 55.5 Gy in blue and the target to receive 74 Gy in pink, which includes all of the abnormal clivus. The proton dose colorwash shows the entire clivus is included in the 74 Gy volume, including good coverage of the posterior clinoids, in close proximity to the optic chiasm. The sphenoid sinus is covered in the 55.5 Gy volume. Due to the disease in the right petrous apex, it was not possible to spare the right cochlea, but the left cochlea received a mean dose of 6 Gy

treated for skull base chordoma with Gamma Knife radiosurgery to a median dose of 15 Gy in 1 fraction reported a 5-year treated tumor rate 66%, with an additional 15% of patients experiencing recurrences within the volume recommended to be covered with fractionated therapy (i.e., 5-year skull base local control of 51%) [88].

Chondrosarcomas

For chondrosarcomas, the management approach is similar: maximal safe surgical resection followed by high dose radiotherapy, although the radiation dose is typically less: 70–72 Gy in conventional fractionation [83]. Unlike chordoma, residual tumor volume for chondrosarcoma has not consistently been found to be prognostic [89], and the prospects for long-term local control with smaller volume (<25 mL) gross residual tumor are excellent following radiotherapy [90]. Therefore, a more conservative surgical approach may be appropriate with a lower tolerance for morbidity in pursuit of gross total resection (Fig. 8.4). Surgically decompressing the optic apparatus and brainstem to allow for adequate target coverage by radiotherapy is highly correlated with disease control [90]. If a gross total resection has been obtained, observation is reasonable if a higher likelihood of future recurrence and salvage therapy is acceptable. The Mayo institutional experience in 32 patients with skull base chondrosarcomas retrospectively compared outcomes in those treated with surgery and adjuvant radiotherapy (nearly all with residual disease) versus surgery and a watch and wait approach (many after a complete resection) [91]. At 5-years after therapy, all patients treated with radiation maintained local control while about 67% of those observed after surgery had experienced progression. However, salvage therapies were effective in nearly all patients with recurrence so there was no observed difference in disease-specific survival in patients observed after surgery.

The majority of published clinical outcomes data for skull base chondrosarcomas are with particle therapy; however, local control results also appear favorable with other radiotherapy strategies. A combined analysis from two institutions of 251 patients treated with proton therapy (with or without a component of photon therapy) for skull base chondrosarcoma to a median dose of 70 Gy reported a 7-year failure-free survival of 93% [90]. A series of 79 patients treated with carbon ion therapy to a median dose of 60 Gy in 20 fractions (moderately hypofractionated) reported a 5-year local control of 88% [92]. A series of 18 skull base chondrosarcoma patients treated with image-guided IMRT to a median dose of 70 Gy reported a 5-year local control of 88% [86]. A report from a multi-institutional dataset of 46 patients treated for skull base chondrosarcoma with Gamma Knife radiosurgery to a median dose of 15 Gy in 1 fraction reported a 5-year progression free survival of 86% [93].

Key Points for Skull Base Chordomas and Chondrosarcomas

- Although management is similar, patients with skull base chondrosarcomas have a markedly better prognosis than those with chordomas.
- Efforts should be made to maximize surgical resection with an experienced skull base team, especially to decompress tumor away from the optic apparatus and brainstem.
- Patients with chordoma are preferentially treated with particle therapy (proton or carbon ion therapy).

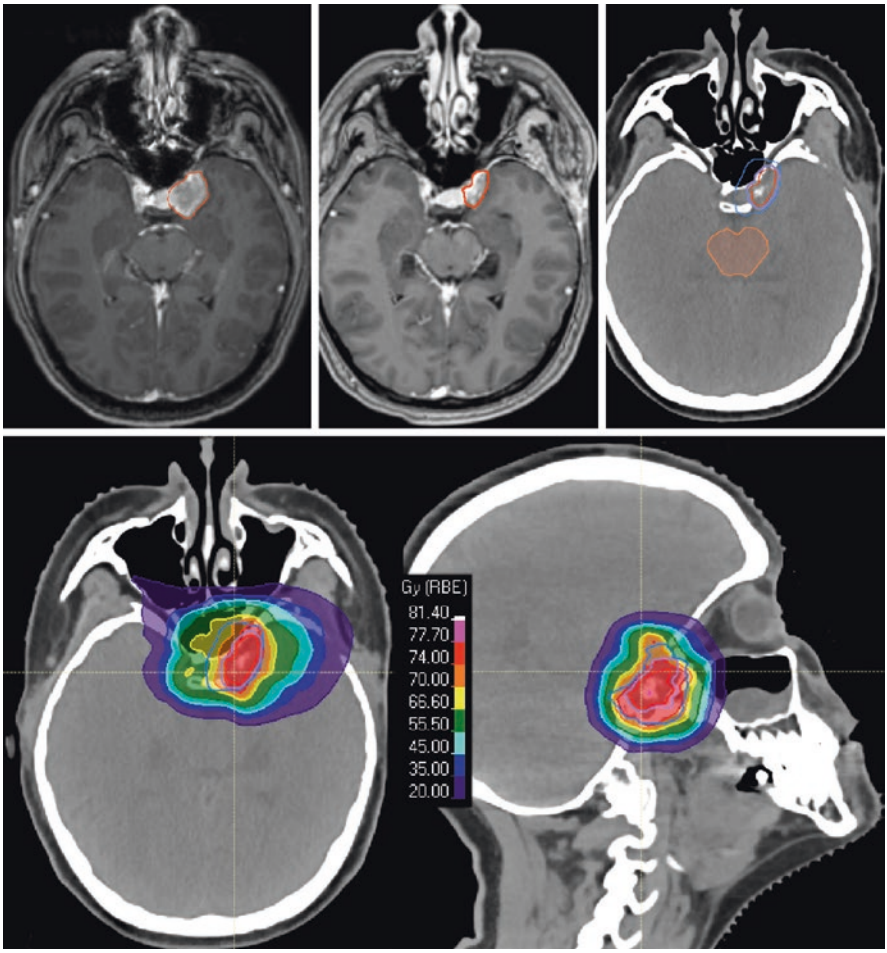

Fig. 8.4 This patient presented with diplopia and a left cranial nerve VI palsy. On the top row, left image, a T1 heterogeneously enhancing mass is seen in the left cavernous sinus. A left frontotemporal craniotomy was performed for tumor resection, with pathology showing a WHO grade 2 chondrosarcoma. The middle image shows residual disease. The top right image shows the residual tumor (red) with the high dose radiation target in purple and an intermediate dose target covering the preoperative tumor bed. Targets are cropped out of the temporal lobe. A dose of 74 Gy was delivered in 37 fractions

Sinonasal Mucosal Melanoma

Sinonasal mucosal melanoma is an extremely rare tumor with a poor prognosis. In the AJCC staging system, all tumors are either T3 or T4. T4a tumors involve deep soft tissue, cartilage, bone, or overlying skin and T4b tumors involve the brain, dura,

skull base, lower cranial nerves (i.e., IX, X, XI, XII), the masticator space, carotid artery, prevertebral space, or mediastinal structures. All other disease presentations limited to the mucosa and immediately underlying soft tissue are T3 regardless of dimension or thickness. Surgical resection is the preferred treatment approach. Surgical margin status has been shown to be a significant predictor of survival [94, 95]. Postoperative radiation appears to improve local control [94, 96]. NCCN guidelines recommend postoperative radiation therapy to the primary site for T4 tumors and to strongly consider postoperative radiation for T3 tumors [26]. Clinical guidelines on head and neck mucosal melanoma from the United Kingdom recommend consideration of postoperative radiation only for those patients deemed at high risk for locoregional recurrence (T4, close or positive margins, and multifocal primary lesions) [97].

Attempted definitive radiation has been associated with high local recurrence rates and inferior survival compared to surgery [98, 99]. However, nonoperative therapy with hypofractionated proton therapy has shown encouraging local control in patients who decline surgery or are not reasonably resectable (Fig. 8.5). A retrospective series delivering 70 Gy (RBE) in 20 fractions reported a 3-year local control of 70% [100]. A small (n = 32) phase II trial using 60 Gy (RBE) in 15 fractions reported a 1-year local control of 76% [101]. A comparison between outcomes using proton therapy and carbon ion therapy using the same fractionation regimen at Hyogo Ion Beam Medical Center in Japan found no significant differences between these two particle therapies, with a 2-year local control of 78% [102].

Elective neck radiation is not indicated, as elective neck dissection is not indicated [26, 97]. Distant metastases remain the most common site of recurrence with half of patients developing distant disease within the first year [103]. Immunotherapy, which has been shown to provide a survival benefit among patients with metastatic melanoma [104–106], has the potential to improve treatment outcomes. Initial clinical experience with immunotherapy as first-line therapy for head and neck mucosal melanoma suggests improved outcomes when radiotherapy is used concurrent with immunotherapy [107].

Key Points for Sinonasal Mucosal Melanoma

- US guidelines recommend postoperative radiation for T4 disease and to strongly consider postoperative radiotherapy for T3 tumors.
- For patients who decline surgery or are not reasonably resectable, hypofractionated particle radiation (proton or carbon-ion therapy) shows promising local control.
- The predominant pattern of failure is distant metastatic disease and patients should be evaluated for immunotherapy or other systemic therapy.

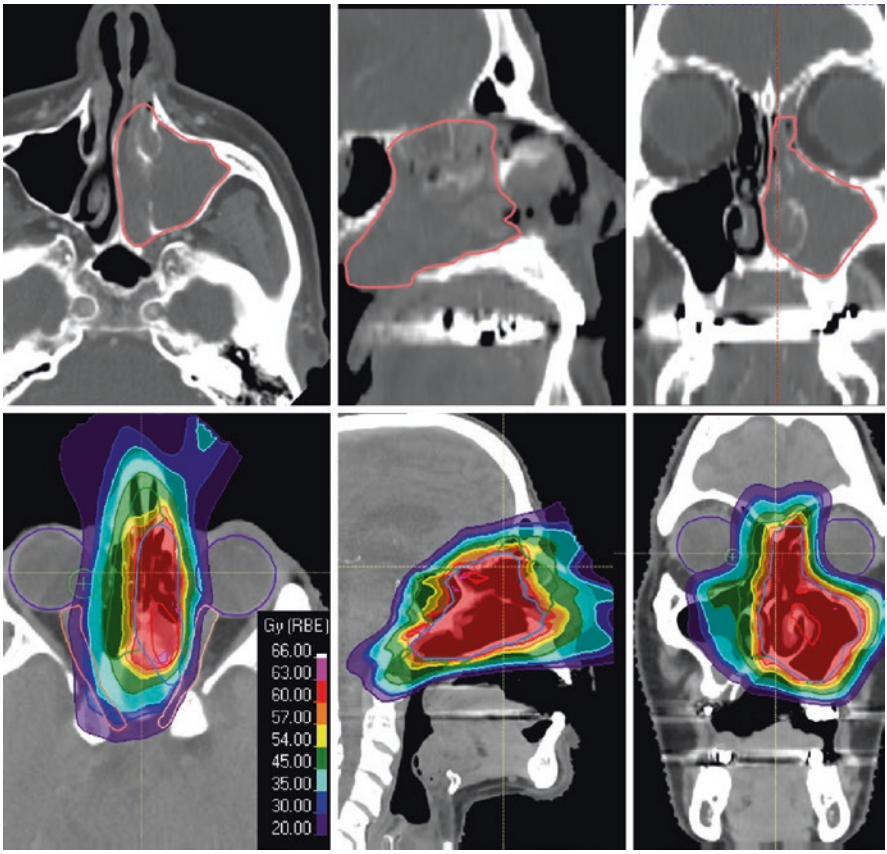

Fig. 8.5 This patient presented with nasal obstructive symptoms and a 6-month history of epistaxis. A non-contrast CT showed a left nasal polypoid mass with opacification of the left ethmoids and maxillary sinus. An endoscopic excisional biopsy and debulking was performed that noted tumor in the maxillary sinus. Pathology showed a mucosal melanoma. Subsequent PET/CT and MRI showed no regional or distant metastatic disease and the patient was staged cT3 N0 M0. Surgery was recommended including maxillectomy with obturation, which the patient declined. Definitive radiation was then offered with hypofractionated proton therapy. A dose of 60 Gy in 15 fractions covered the preoperative tumor volume with margin including the left nasal cavity, ethmoids, and maxillary sinus with an elective dose of 45 Gy in 15 fractions covering the contralateral right nasal cavity, ethmoids, and remainder of the sphenoid sinus. The patient had no evidence of disease 2-1/2 years after treatment

Paragangliomas

Head and neck paraganglioma are neuroendocrine tumors arising in the autonomic ganglia, derived from neural crest tissues [108]. They are rare tumors, estimated to occur in 2–5 patients per million per year [109]. Paragangliomas were previously denoted as chemodectoma and glomus tumors, but these terms are no longer used.

In the head and neck, paragangliomas arise in parasympathetic ganglia along the glossopharyngeal or vagal nerves or branches thereof in the temporal bone (tympanicum), jugular foramen, vagal, or carotid body locations. Other head and neck locations, including sinonasal paragangliomas [110], have been reported but are exceedingly rare.

Paragangliomas do not require pathologic confirmation. Paragangliomas are highly vascular with avid enhancement on contrast-enhanced CT and MRI and the "salt and pepper" appearance on MRI from serpiginous flow signal voids in the tumor is essentially pathognomonic. A biopsy should not be performed, given the risk for life-threatening complications [111].

The natural history of these tumors is of slow progression, at an estimated rate of 1 mm enlargement per year with a median tumor-doubling time of 4.2 years [112]. Asymptomatic tumors that are not threatening neurological compromise may be considered for active surveillance, to reduce the iatrogenic risks associated with therapy.

While most paragangliomas arising at the skull base are non-secretory, approximately 5–10% are hormone-producing, primarily of norepinephrine, and can cause labile hypertension. British Skull Base Society consensus guidelines recommend that patients with head and neck paragangliomas have plasma metanephrine levels measured at presentation (including adrenaline, normetadrenaline, and 3-methoxytyramine) [113]. Elevated metanephrines may also indicate the presence of a synchronous pheochromocytomas or thoracoabdominal paraganglioma. Other recommended workup at presentation includes contrast-enhanced MRI of the head and neck, a skull base CT for jugular and tympanic paragangliomas, whole body (skull base to kidneys) MRI or DOTATATE PET/CT to screen for synchronous primaries or metastatic disease, and genetic counseling [113].

Approximately 40% of paragangliomas are associated with a germline mutation, most commonly of the *SDHx* genes [114]. Consensus guidelines recommend genetic counseling be offered to all patients with paraganglioma [113, 115]. Younger patients (<30 years old), those with multiple tumors, and those with a family history of paragangliomas are most likely to have a familial genetic syndrome. It is estimated that 15% of cases can develop metastases [116].

The mainstays of treatment include active surveillance, surgery, and radiation, with an expanding role for radionuclide treatments for refractory and metastatic disease [117]. Early intervention is recommended for patients with secretory tumors, metastatic disease, evidence of rapid early growth, brainstem compression, tympanic paragangliomas (early intervention to preserve hearing), or jugular paragangliomas causing bothersome pulsatile tinnitus or conductive hearing loss, or threatening or causing facial nerve weakness [113].

Tumor control outcomes with radiotherapy are at least as good as those with surgery for paragangliomas [118], so the choice of treatment modality must consider the anticipated risks of each therapy. Surgery for jugular and vagal paragangliomas is associated with a significant risk of morbidity and lower cranial neuropathies, so radiation is typically preferred for patients who retain lower cranial nerve function [113, 119]. Radiotherapy is often employed in patients with bilateral disease to avoid the risk of bilateral neurological impairment [113]. Radiotherapy

may be preferred in older patients with carotid body tumors, or those with larger carotid body tumors where the risks of surgery are higher. There is no benefit to planned combined modality therapy over radiation therapy alone, so tumor debulking is not a recommended strategy unless surgical decompression is clinically indicated.

Radiotherapy achieves a high rate of durable local tumor control using a modest dose of radiation. Larger tumors are typically treated with fractionated therapy. The standard in the United States is 45 Gy in 25 fractions with a 10-year local control of 94% and no high-grade toxicities in a series of 104 patients with 121 lesions treated at the University of Florida [120]. This same regimen is also suggested by the U.K. Royal College of Radiologists [121]. A moderately hypofractionated regimen of 35 Gy in 15 fractions achieved a similar ~93% local control at a median follow-up of 10 years in a series of 45 patients with temporal bone paragangliomas treated at Princess Margaret Hospital [122]. Using these dose regimens, the risk of severe radiation-induced toxicity is quite low.

Proton therapy is an attractive treatment option to reduce or avoid radiation to normal tissues in patients with benign disease (Fig. 8.6), and may be preferred in younger patients and those with genetic mutations that may make them more susceptible to secondary malignancy. Tumor control outcomes appear equivalent to photon techniques. A series from Indiana University including 7 patients treated with proton therapy (35 Gy (RBE) in 15 fractions) reported sustained local control in all patients at a median follow-up time of 52 months [123], and a series of 37 patients from Massachusetts General Hospital reported a 5-year recurrence-free survival of 97% after a median dose of 50.4 Gy (RBE) [124].

Smaller tumors, particularly tympanic and jugular paragangliomas, may be treated with stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiotherapy. Dose regimens reported for SRS are more varied, from 12 to 18 Gy in a single fraction, 18–24 Gy in 3 fractions, or 25–30 Gy in 5 fractions. A systematic review suggests that for single fraction SRS, a dose of 15 Gy is required to achieve a local control expectation ≥ 90% [125]. Tumor control after SRS is high, with 7-year PFS of 97% reported in a series of 40 patients treated for jugulotympanic paragangliomas [126].

Symptomatic improvement after radiotherapy is seen in the majority of patients after radiation, particularly for symptoms such as pulsatile tinnitus, tinnitus, pain or pressure [122, 124, 127] but the improvement of pre-existing cranial neuropathies is more variable and is presumably influenced by the degree and duration of impairment prior to therapy [119]. Over time, a radiographic response is commonly seen with a steady reduction in size over years. In a series of 22 patients with volumetric imaging assessment, there was an average of 14% volume reduction at 2 years after radiation [128]. Another series of 13 patients with volumetric imaging noted a median 33% volume reduction after a median follow-up of 68 months [123].

The gross tumor volume (GTV) is readily defined by avid enhancement using both contrast-enhanced MRI and CT. CT is helpful to identity areas of osseous erosion and bone involvement. An excellent overview of the imaging characteristics of head and neck paraganglioma has been published [129]. Clinical practice guidelines from the U.K. Royal College of Radiologists recommend a minimum expansion of

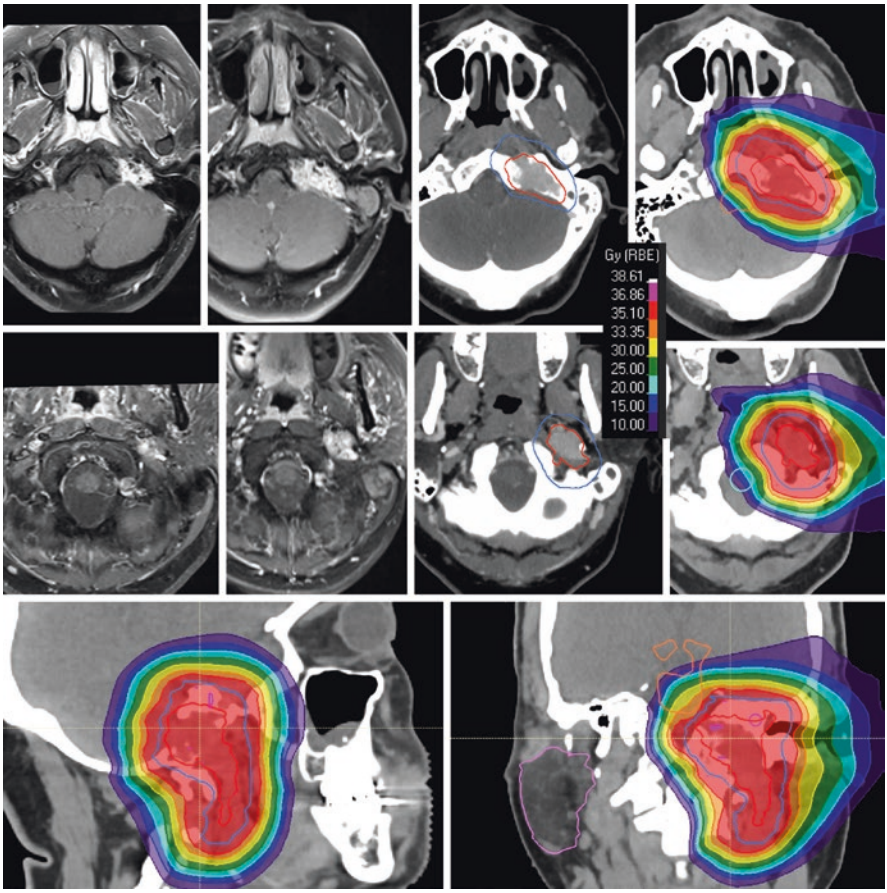

Fig. 8.6 This patient presented with left-sided hearing loss around the age of 40 and an MRI showed an enhancing tumor in the temporal bone with minimal extension to the jugular fossa consistent with paraganglioma (far left MRI). Given the patient's young age and absence of additional symptoms, observation was planned, but the patient did not return for follow-up until 7 years later with new symptoms of left-sided middle ear pressure and intermittent hoarseness and dysphagia. The second from left MRI shows significant interval tumor enlargement. Lower cranial nerves were intact on physical exam. Primary radiotherapy was recommended given the risk for lower cranial nerve injury with surgery. The third column of images show the contrast-enhanced CT obtained at simulation with the gross tumor volume (red) and clinical target volume (blue) outlined. A dose of 35 Gy (RBE) in 15 fractions was delivered using proton therapy

0.5 cm to create a clinical target volume, plus additional expansion for set-up uncertainties to create the planning target volume (PTV) [121]. This is consistent with the total GTV to PTV expansion of 1 cm used in several series [120, 123, 130]. Anecdotally, some tumors experience transient swelling upon initiation of radiotherapy. Reducing the risk of a marginal miss likely outweighs any potential increase in toxicity from using a slightly larger target volume at the moderate dose levels employed for paragangliomas.

Key Points for Paragangliomas

- Pathologic confirmation is not required and a biopsy should not be undertaken.
- Initial workup should include screening plasma metanephrine levels, whole body MRI or DOTATATE PET/CT, and genetic counseling.
- Primary radiotherapy is the preferred treatment for many patients including most with jugular and vagal tumors, those with bilateral disease, and others for whom surgery is expected to have a meaningful risk of morbidity.
- A radiation dose of 45 Gy in 25 fractions is associated with excellent local control and no anticipated risk of high-grade toxicity.

Radiotherapy Modalities

Radiation treatment planning for paranasal sinus tumors is frequently challenging given the complex anatomy and close proximity of the eyes, optic apparatus, and brain parenchyma, all organs whose tolerance to radiotherapy is lower than the desired dose to the target.

Intensity-Modulated Radiation Therapy

Intensity modulated radiation therapy with photons (X-rays) was a significant advancement in the field of radiation oncology and became widely adopted in the United States in the early 2000s. In contrast to 3D conformal radiotherapy (3DCRT) that employs multiple treatment fields with a homogenous dose-intensity of radiation, IMRT delivers "beamlets" of varied dose-intensity from each treatment field dispersed over multiple different treatment angles. The ability to modulate the dose intensity at different points within each beam allows for improved target dose conformality and decreased dose to non-target normal tissues. This is achieved through the process of an inverse planning algorithm in which dose-volume objectives are assigned to the target volume and organs at risk, and prioritized according to the clinically desired outcome.

A primary objective with IMRT is to reduce the risk of acute and late toxicity of treatment. For sinonasal tumors, it can be extremely challenging to adequately cover the target volume while respecting dose tolerances of nearby structures, particularly the optic apparatus (i.e., retina, optic nerves, and chiasm). With older 3DCRT techniques, a study from the University of Florida reported an incidence of radiation-induced optic neuropathy or retinopathy in up to 27% among patients treated for sinonasal tumors [131]. During the transition from 3DCRT to IMRT, multiple single-institution studies reported a reduction in toxicity associated with IMRT without a compromise in tumor control compared to historical 3DCRT controls [16, 132–137].

A randomized phase 3 clinical trial in patients with oropharynx and hypopharynx cancer receiving definitive or postoperative radiation therapy compared patient-reported outcomes among patients treated with IMRT (n = 47) versus 3DRCT (n = 47) to test whether a reduction in radiation dose to the parotid glands would decrease the incidence of symptomatic xerostomia [138]. At 1-year post-treatment, the incidence of grade 2 or worse patient-reported xerostomia was significantly reduced with IMRT (38%) compared to 3DCRT (74%). These differences remained significant at 2 years (29% vs. 83%). These data are extrapolated to the treatment of other head and neck sites making IMRT a standard technique for photon-based external beam radiation in the treatment of head and neck cancer.

Further technological evolution including image-guided treatment delivery and volumetric modulated arc therapy, with or without non-coplanar beam arrangements, confer additional improvements in radiation dosimetry and delivery [139]. IMRT is widely available and is the standard technique for photon-based external beam radiation in the head and neck.

Stereotactic Radiosurgery/Stereotactic Body Radiation Therapy

Stereotacic radiosurgery (SRS) is a radiation technique, typically with ablative-intent, used for intracranial and spine targets. SRS is classically delivered in a single fraction, but multifraction SRS in up to 5 fractions has become increasingly common. In the body, the analogous technique is called stereotacic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR), also delivered in 1–5 fractions. These techniques may be used with photons, gamma rays, or particle therapy such as proton therapy. Both SRS and SBRT/SABR techniques are used to treated well-defined and generally small targets. In SRS, the treatment volume generally equals the visible tumor with 0 or 1 mm margin. In body sites, the SBRT treatment volume generally equals the visible tumor, defined during all phases of respiratory motion, with a 5 mm margin. Because the treatment is ablative-intent with little or no margin for error in 1–5 treatments, precise target localization, immobilization, and image guidance is required. These techniques require a sharp dose gradient to deliver the intended high dose to target volumes while simultaneously minimizing dose to nearby organs at risk.

SRS may be used in management of a variety of skull base tumors including pituitary adenomas, tympanic and jugular paragangliomas, chordomas, chondrosarcomas, in conjunction with fractionated therapy to boost disease extension in the cavernous sinus, and may be used in salvage therapy for intracranial recurrences or distant metastases. SBRT is an emerging technique in the setting of head and neck cancer re-irradiation. A phase 2 trial of SBRT and cetuximab for the treatment of 50 patients with previously irradiated recurrent head and neck squamous cell carcinoma noted a 1-year local progression free survival of 60% [140].

Charged Particle Therapy

Rather than using photons (X-rays or gamma rays), charged particle therapy uses atomic particles, such as protons or carbon ions. Proton therapy has become more widely available in the United States in the last decade, while carbon ion therapy, which is available in centers in Asia and Europe, is not yet available in the Americas. Both proton therapy and carbon ion therapy take advantage of a physical difference in radiation dose deposition in tissue called the Bragg peak. The particles enter the body with an energy-dependent finite range, and the maximal radiation dose deposition occurs as the particles come to rest, creating a "peak" in dose deposition followed by an abrupt fall-off as the particles come to rest. Proton therapy causes DNA damage similar to photon therapy with similar radiobiological effects. Carbon ions are much heavier and cause more intense DNA damage with far more complex radiation biology that must be modeled in the treatment planning system. Compared to X-ray based IMRT, charged particles like proton therapy and carbon ion therapy can offer further improvements in radiation dose distribution [141].

A meta-analysis of 41 studies compared clinical outcomes of patients with paranasal sinus and nasal cavity malignancies treated with particle therapy such as proton therapy with outcomes in those receiving photon therapy such as IMRT. In this analysis, proton therapy was associated with a significantly better overall survival at 5 years and at last follow-up, disease free survival at 5 years and local control at last folow-up [142]. The University of Florida reported results using proton therapy in sinonasal tumors of varied histologies treated with or without surgery, with or without concurrent chemotherapy [143]. The 3-year local control was 83%. The team at Massachusetts General Hospital have reported on 54 patients with stage III/IV squamous cell carcinoma of the paranasal sinuses managed with proton therapy to a median dose of 72.8 Gy (RBE), with or without surgical resection [144]. The 5-year local control was 80%, 5-year overall survival 47%. According to ASTRO's model policy on proton beam therapy, cancers of the paranasal sinuses and other accessory sinuses are considered a "Group 1" disease site indication where clinical evidence and medical necessity requirements frequently support the use of proton therapy [145].

Carbon ion therapy for definitive management of locally advanced sinonasal cancers has been reported by the Japanese Carbon-Ion Radiation Oncology Study Group (J-CROS). In their analysis, 2-year overall survival and local control were reported at 79.6% and 84.1%, respectively. Grade 3 or higher late toxicity was noted in 17% of patients [146]. The group from Shanghai Proton and Heavy Ion Center have also published their experience with particle therapy for sinonasal cancers [147]. In their report, the majority of patients received treatment with carbon ion therapy for the entire treatment course or as the boost treatment. They reported 2-year local progression free survival and overall survival of 83% and 82%, respectively. Only 3.6% of patients experienced late grade 3 or higher toxicity.

Radiation Target Volumes

Treatment Volumes for Postoperative Radiation

Delivery of radiation in the postoperative setting is the most common radiotherapy application for sinonasal malignancies. Treatment volumes should be based on evaluation of preoperative imaging, consideration of both the preoperative and postoperative clinical exam findings, operative report, pathology report and communication between the surgeon and radiation oncologist.

Preoperative anatomic imaging should be coregistered to the simulation CT to aid in defining the preoperative gross tumor volume (GTV). The clinical target volumes (CTV) may be defined as follows:

- High risk primary tumor CTV (e.g., 66 Gy) is defined as any area of involved surgical margin(s) with a 5 mm margin, modified to respect anatomical boundaries.
- Intermediate risk primary tumor CTV (e.g., 60 Gy) is defined as preoperative GTV with a 10 mm margin, modified to respect anatomical boundaries. Surgically manipulated tissues and sinuses should be included in this volume. Expansion in the region of high priority organs at risk such as the optic nerves, chiasm and brainstem can be limited to 0–1 mm.
- High risk nodal CTV (e.g., 66 Gy) is defined as nodal levels in which radiographic or pathologic evidence of extranodal extension is noted.
- Intermediate risk nodal CTV (e.g., 60 Gy) is defined as the remainder of the dissected neck lymph node levels. If there is/was nodal involvement of the sternocleidomastoid or other neck musculature, the CTV includes the muscle at least 2 cm above and below the level of the node.
- Elective nodal CTV (e.g., 50 Gy equivalent) is defined as clinically uninvolved cervical nodal levels that harbor risk of subclinical disease. As described above, not every histology merits elective lymph node irradiation. Generally, ipsilateral levels Ib-IV are included in this volume. Parotid lymph nodes should be included for tumors involving the skin of the forehead and temple. The contralateral neck should be included for tumors involving the soft palate, nasopharynx, sinonasal tumors that extend past midline, or in the setting of bulky ipsilateral adenopathy or multiple ipsilateral nodes. Nasopharyngeal involvement also necessitates coverage of level V and retropharyngeal spaces.

Treatment Volumes for Intact Disease

Gross residual disease or unresectable disease necessitates delivery of a higher dose of radiation and usually concurrent chemotherapy to provide best probability of tumor control. The GTV is defined by coregistered diagnostic imaging and CT/MRI

simulation imaging to delineate all radiographically visible gross disease. In the setting of residual disease after surgery, communication between the surgeon and radiation oncologist is important to identify areas of gross disease that may not be apparent on imaging but were noted intraoperatively.

- Primary tumor CTV (e.g., 70 Gy) is defined as the GTV with a 5 mm margin, modified to respect anatomical boundaries.
- Intermediate risk primary CTV (e.g., 60–63 Gy) should include the entire involved sinus and may include adjacent sinuses felt to be at high risk for subclinical disease.
- Elective primary CTV (e.g., 50 Gy equivalent) may be appropriate in certain cases, for example, elective coverage of the cavernous sinus.
- Nodal CTVs are defined as in the postoperative setting.

Treatment Volumes After Induction Chemotherapy

A multi-institutional practice guideline recommends that the pre-induction gross tumor volume be used for radiation treatment planning [148]. The original tumor volume should be modified to account for changes in patient anatomy following induction chemotherapy. In situations where the pre-chemotherapy tumor volume, when transferred onto the post-chemotherapy anatomy, overlaps with tissues originally uninvolved by disease, the volume should be edited to confine it to the originally involved anatomy [149], and similarly to remove extension into air or extracorporeal extension [148]. In two phase II trials, a reduction in radiation dose has been explored following induction chemotherapy in HPV-associated oropharyngeal squamous cell carcinomas [150, 151], but similar data are scant in sinonasal squamous cell carcinomas. One single-institution phase I/II trial has evaluated modest radiation dose reduction and reduced radiation volumes based on response to induction chemotherapy, omitting intentional elective nodal irradiation in patients with a good response to induction chemotherapy [152].

Specific Considerations

Skin Involvement

In the setting of intact disease, clinically appreciable skin involvement should be wired at the time of simulation to aid in delineation. In the postoperative or post-chemotherapy setting, pretreatment imaging should be augmented by description or images from the initial clinical examination to aid in an understanding of the original extent of skin involvement. Involvement of the skin of the face increases the risk of regional lymph node metastases and should prompt elective lymph node irradiation if a neck dissection has not been performed. Involvement of the skin of the forehead or temple increases the risk of preauricular or parotid lymph node metastases and elective radiation of the parotid should be considered. Unfortunately, midline forehead skin involvement puts both parotid glands in jeopardy.

Perineural Invasion

The presence of perineural disease invasion influences the radiation volume. It is critical to note whether patients had any preoperative clinical symptoms or imaging findings consistent with malignant cranial nerve involvement, or pathologic involvement of a named nerve, in which case the radiation volume should include the course of the nerve to the base of the skull. For patients with sinonasal tumors, cranial nerve involvement is often at the level of the skull base foramina, and elective intracranial coverage to the ganglion or to the insertion at the brainstem should be considered. Patients with gross cranial nerve involvement are at risk for both antegrade and retrograde tumor spread, and attention should be paid to interconnections between cranial nerves, for example, between V3 and VII via the auriculotemporal nerve or between V2 and VII via the greater superficial petrosal nerve. A detailed multi-institutional guideline for radiation treatment design in cases of perineural invasion and malignant perineural tumor spread is an excellent resource [153].

Supportive Care Measures and Toxicities

Radiation therapy for sinonasal tumors can be associated with significant acute and late toxicity due to the close proximity to critical structures in the head and neck region. The primary structures that may be affected include the mucous membranes of the oral cavity and sinuses, salivary glands, optic structures, hearing apparatus and muscles of swallowing and mastication. The toxicity profile and intensity of anticipated side effects varies depending on the tumor location but in general can include skin irritation, mucositis, xerostomia, dysgeusia, dysphagia, odynophagia, anorexia, dry eye and hearing or vision changes. Practitioners should be aware of common acute and late toxicities observed during radiation treatment for sinonasal tumors and of supportive care measures to ameliorate or prevent these side effects.

Sinonasal Mucositis

Radiation to the mucosa of the paranasal sinuses results in inflammation and edema with thick mucosal secretions and dry mucous membranes. In the latter part of a radiation treatment course, patients often develop progressive sinus congestion or obstructive symptoms. Minor epistaxis may be reported. Nasal saline rinses multiple times per day can soothe the mucosa and help to loosen and flush out secretions. A high-volume low-pressure compressible nasal douching device (aka squeeze bottle) is used, with distilled water and pre-measured packets of sodium chloride and sodium bicarbonate. A number of trials support the benefit of routine saline irrigation to improve patient symptoms following endoscopic sinus surgery [154]. Chronic inflammation can sometimes result in narrowing or fibrosis of the nasal passages leading to stenosis or formation of nasal synechiae.

Maintaining adequate nasal moisturization and frequent irrigation may reduce the risk of stenosis or synechiae, which may require lysis or dilation in severe cases [155, 156]. Using a cotton swab, patients may apply an emollient to the inside nasal passages to keep them moist and patent. Some add an emollient oil or corticosteroid to nasal irrigation. Over-the-counter isotonic sodium chloride nasal sprays and nasal gels with sodium hyaluronate and aloe vera can provide extra moisturization. Some patients appreciate a benefit with air humidification.

Patients may also benefit from in-office nasal debridement in both the postoperative period and during radiotherapy. While the evidence for a lasting benefit from nasal debridement is mixed, it can provide significant relief for patients with significant crusting and nasal obstruction. A position statement from the American Academy of Otolaryngology—Head and Neck Surgery notes that postoperative debridement after endoscopic sinus surgery aids healing and optimizes the ability to achieve open, functional sinus cavities [157].

Oral Mucositis

Oral mucositis may be caused by both radiation and chemotherapy. The radiation dose and volume of the oral mucosa exposed to radiation are correlated with the risk and severity of oral mucositis [158, 159]. Patients who require cervical nodal irradiation, especially if level Ib must be treated, experience higher radiation dose to the oral cavity and are much more likely to experience oral mucositis. Patients who require irradiation only of the paranasal sinus complex often still develop oral mucositis on the palate due to the close proximity of the floor of the nasal cavity and floor of the maxillary sinus to the oral cavity. A bite block device can be used at the time of radiation simulation to open the mouth and displace the oral tongue and floor of mouth away from the roof of mouth, markedly limiting the volume of oral mucosa exposed to radiation to restrict the volume of potential mucositis.

Radiation-induced oral mucositis presents as painful ulcers and burning sensation that progressively worsens throughout treatment. This often impairs nutritional intake and can lead to significant weight loss and failure to thrive. Mucositis can be exacerbated by concurrent chemotherapy, smoking and alcohol intake, consumption of hot/spicy foods, and poor dental hygiene. Oral mucositis is associated with more severe pain and greater risk of clinically significant weight loss, as well as significant incremental costs for management [160].

The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) have published clinical practice guidelines for the management of mucositis secondary to cancer therapy [161]. The guidelines recommend dental evaluation and treatment as indicated before cancer therapy to reduce the risk for local and systemic infections from odontogenic sources. Benzydamine mouthwash is suggested to reduce the risk of oral mucositis. While available in Canada, it is not currently available in the United States. Topical morphine 0.2% mouthwash is also suggested by the guidelines for management of pain from oral mucositis; this would require a pharmacy compound mixture in the

United States. A small trial found the morphine mouthwash was more effective and more satisfactory to patients than the widely used compound mouthwash 1:1:1 mixture of lidocaine, diphenhydramine and antacid [162]. Oral glutamine is also a suggested intervention for prevention of oral mucositis. The most common dosing regimen in prior studies was 30 g per day in 3 divided doses [163].

Congruent with the MASCC/ISOO guidelines, patients are encouraged to use frequent sodium bicarbonate rinses with or without salt. Despite a lack of evidence, these oral rinses are helpful for maintaining oral hygiene and improving patient comfort. Subsequent to the most recent update of the MASCC/ISOO guidelines, an Alliance randomized controlled trial provides evidence for a benefit from the widely used compound mouthwash 1:1:1 mixture of lidocaine, diphenhydramine and antacid [164].

Early use of gabapentin may reduce the likelihood and/or duration of opioids for mucositis-related pain in patients undergoing radiation for head and neck cancer [165]. Beginning at the onset of radiation, patients can be titrated up to 900 mg three times daily with associated decrease in pain, and both general and neurosensory symptoms [166]. Both short and long-acting opioid pain medications may also be required to manage severe mucositis-related pain.

Xerostomia

Xerostomia, or mouth dryness, is a very common side effect of head and neck radiotherapy. Xerostomia has been directly correlated with radiation dose to both the major salivary glands (i.e., parotid and submandibular glands) and the oral cavity (minor salivary glands) [167, 168]. A primary goal of modern radiation techniques, including IMRT and proton therapy, is to reduce radiation dose to the major salivary glands, which has been shown to reduce symptomatic xerostomia [138]. Nevertheless, the desired dose constraints are sometimes not achievable and even when they are met, patients are still at risk for clinically relevant xerostomia. While lower radiation doses to the salivary tissue improves the chance of salivary recovery, many patients still experience acute alterations in salivary function during radiation. Post-treatment recovery of salivary function is dependent on the volume of the gland irradiated and the mean dose to the gland, which predicts the ability of stem cell regeneration of serous acinar cells.

Patients may experience symptoms as early as 2 weeks into radiotherapy, with complaints of sticky saliva and dry mouth. Thick secretions can cause nausea, dysgeusia, and a gagging sensation contributing to dysphagia. In addition to impairing quality of life, reduced saliva output and changes in salivary composition increase the risk of dental caries. During radiotherapy, the mean pH of saliva has been reported to fall from 7.0 to 5.0, which greatly increases the risk of dental demineralization [169]. The altered saliva changes the oral microbiome, increasing growth of acidogenic and cariogenic microorganisms [170]. Depending on the radiation dose to the mandible and to the teeth themselves, radiotherapy may contribute to dental decay through reduced vascularity and fibrosis affecting the dental pulp and enamel [171].

During radiation and recovery, patients are strongly encouraged to perform frequent mouth rinses with a sodium bicarbonate (baking soda) solution, with or without salt, increased their hydration and may use lozenges such as sugar-free lemon drops or vitamin C tablets to stimulate salivary flow or over-the-counter saliva substitute sprays or gels to increase oral lubrication. Pharmacologic interventions to stimulate muscarinic cholinergic receptors, such as pilocarpine and cevimeline, have been investigated with mixed results [172, 173]. Acupuncture for chronic xerostomia has been associated with a subjective improvement in symptoms [174, 175].

Ototoxicity

Otologic complications are common for nasopharyngeal and skull base tumors both before and after radiation treatment [176]. Potential mechanisms of injury include fibrosis and atrophy of the muscles or cartilage, or radiation neuropathy in the middle and inner ear, and mucosal inflammation leading to fluid accumulation or effusion, fibrosis and ossification of the inner ear. This damage can manifest as frequent inner ear infections, sensorineural and/or conductive hearing loss, otorrhea, otalgia, tinnitus, vertigo, or perforation of the tympanic membrane. Post-treatment mastoid air cell opacification is commonly seen on response assessment or surveillance imaging and has been correlated with a mean radiation of >30 Gy dose to the mastoid air cells and posterior nasopharynx [177]. Myringotomy can be performed to treat otitis-media effusions and preserve hearing [176].

An increasing mean radiation dose to the cochlea is the predominant risk factor for radiation-induced sensorineural hearing loss (SNHL) [178]. Concurrent cisplatin chemotherapy has independent and synergistic risks of ototoxicity [179]. Because no threshold dose has been established, the dose to the cochlea should be kept as low as possible. A typical conservative constraint of a mean cochlear dose $\leq$35 Gy is employed in patients receiving concurrent platinum chemotherapy. In more challenging cases with tumor proximity to the cochlea, a mean dose constraint $\leq$45 Gy is associated with about a 19 dB decrement in high frequency hearing loss, where $\geq$10 dB is considered clinically significant [180]. Unfortunately for tumors involving the petrous apex in close proximity to the cochlea, it is not always possible to spare both cochlea, and patients must be counseled on a significant risk of progressive hearing loss after treatment (e.g., Fig. 8.3). Patients with radiation-induced severe and permanent SNHL may benefit from a cochlear implant [181], although the presence of a cochlear implant poses a significant challenge to MRI for disease surveillance and creates imaging artifact.

Visual Toxicity

Radiation to the paranasal sinuses is often in close proximity to the eyes, lacrimal glands, optic nerves, or optic chiasm. Dose to the anterior portion of the globe and eyelids can cause irritation, excessive tearing, and/or vision changes. In the setting

of low-to-moderate radiation dose, these symptoms are generally mild. Patients may be advised to avoid wearing contact lenses during treatment, and to clean their eyes daily with over-the-counter pre-moistened lid wipes (e.g., OcuSOFT), and to use over-the-counter lubricating eye drops, such as those containing polyethylene glycol and/or propylene glycol.

Providers should be cognizant that patients with malignant involvement of the trigeminal nerve root or the ophthalmic division of the trigeminal nerve are at risk for neurotrophic keratopathy, since the cornea receives sensory innervation from V1. Diminished or absent corneal sensation can rapidly results in corneal epithelial damage or ulceration from environmental insults, loss of blink reflex, and tear film abnormalities [182].

Radiation induced-optic neuropathy (RION) occurs due to vascular injury to the optic nerve and subsequent demyelination. RION often presents with abrupt and painless loss of vision, with MRI typically showing discrete enhancement of the affected prechiasmatic optic nerve, often with expansion and high T2 signal in the enhancing segment [183]. Pathology of optic nerves with RION shows ischemic demyelination, reactive astrocytosis, endothelial hyperplasia, obliterative endarteritis, and fibrinoid necrosis [184]. There is often a significant latency between radiation and vision loss. In one study, the mean latency period to developing RION was 31 months [185].

Using conventional fractionation (1.8–2 Gy per fraction), the risk of RION is very rare when the optic apparatus maximum dose is <55 Gy, estimated at 3–7% for a maximum dose of 55–60 Gy, and more substantial (>7–20%) for doses >60 Gy [186]. In some skull base scenarios, it is not possible to adequately treat the tumor and meet these dose constraints. A hyperfractionated (twice daily) radiation therapy schedule may be considered in an effort to decrease the risk of RION [187]. Alternately, in shared decision making patients can be carefully counseled and consented to an expectation of vision loss in the affected eye in an effort to cure a life-threatening disease (e.g., Fig. 8.1).

Cataracts are a common late side effect following paranasal sinus radiation given the exquisite radiosensitivity of the lens. Radiation-induced cataracts are often posterior subcapsular in location. Given the success of cataract surgery in radiation-induced cataracts [188] and the mortality threat posed by most sinonasal malignancies, an increased risk of cataractogenesis is rarely a dominant clinical concern.

Brain Radiation Necrosis

Parenchymal brain radiation necrosis is a potential toxicity after high-dose radiation to the paranasal sinuses. Symptomatic necrosis can be devastating and life-threatening. Unfortunately, adequate treatment of aggressive skull base tumors requiring high-dose radiotherapy often entails a risk of future radiation necrosis.

The Quantitative Analysis of Normal Tissue Effects in the clinic review suggests that partial brain irradiation to 72 Gy in standard fractionation is associated with a

5% risk of symptomatic radiation necrosis, but provides no specific guidance on volume constraints [189]. One study found that the risk of radiation necrosis increased sharply when the absolute volume of temporal lobe receiving 60 Gy exceeded 5.5 cm^3 or the volume receiving 70 Gy exceeded 1.7 cm^3 [190]. International guidelines for radiation planning in nasopharyngeal cancer suggest a planning goal that the temporal lobe dose to 0.03 cm^3 be restricted to ≤70 Gy with a maximum acceptable constraint of 72 Gy [191]. In radioresistant tumors such as chordomas that involve the cavernous sinus or otherwise abut parenchymal brain, these constraints cannot be met while adequately covering tumor.

Asymptomatic MRI changes can cause diagnostic confusion and concern for tumor recurrence, brain metastases, or glioma. Correlating the MRI findings with the prior radiation treatment plan can improve the assessment of probable radiation necrosis. MRI with perfusion or spectroscopy (depending on the size and location of the abnormality) can help distinguish radiation necrosis from tumor. Asymptomatic radiation edema or necrosis may be treated with pentoxifylline and vitamin E in an effort to improve or stabilize the process, hoping to avoid progression to symptomatic necrosis. The combination (typically pentoxifylline 400 mg twice daily taken with Vitamin E 400 IU twice daily) is thought to improve oxygenation to tissues by reducing blood viscosity and increasing deformability of erythrocytes, to reduce cytokine-mediated inflammation, and to reduce oxidative damage by scavenging free radicals, among other effects [192]. The combination has shown some promise in the brain [193]. For patients with symptomatic radiation necrosis, dexamethasone is first-line therapy, but provides only symptomatic relief without addressing the underlying pathophysiology. Bevacizumab has been shown to improve symptoms and imaging in a small randomized controlled trial [194]. For those with contraindications to bevacizumab, hyperbaric oxygen can provide clinical and radiologic improvement or stability [195].

Endocrine Dysfunction

Patients receiving radiation to the neck may develop hypothyroidism from radiation dose to the thyroid gland. The incidence of hypothyroidism varies widely in reports, perhaps because not all cases are recognized given the nonspecific symptoms of early hypothyroidism. In one small prospective study of head and neck cancer patients with planned thyroid function monitoring after radiation, 31% of patients developed clinical hypothyroidism and an additional 11% subclinical hypothyroidism [196]. Using an endpoint of abnormally elevated TSH (i.e., including both subclinical and clinical hypothyroidism), the risk appears to rise sharply from about 10% with a mean thyroid dose of 30 Gy to 50% with a mean thyroid dose of 44 Gy [197]. The American Cancer Society head and neck cancer survivorship guideline recommends testing of TSH every 6–12 months after therapy to monitor thyroid function [198].

Patients treated for paranasal sinus tumors and anterior skull base tumors may also develop dysfunction of the hypothalamic–pituitary axis, as the pituitary gland often receives a fairly high dose of incidental radiation when treating the ethmoids, sphenoid sinus, or cavernous sinuses. Posterior pituitary function does not appear to

be affected by radiation [199]. A systematic review and meta-analysis of the published literature on adult patients receiving cranial radiation for non-pituitary tumors who had data on endocrine evaluation identified 813 patients, 75% of whom were treated for nasopharyngeal cancer [200]. Hypopituitarism developed in about two-thirds of patients. If one endocrinopathy is suspected or present, the patient should be screened for other deficiencies as they may have panhypopituitarism.

The growth hormone axis is the most susceptible to radiation [201]. Growth hormone deficiency in adults is associated with unfavorable changes in body composition and metabolic profile [202]. However, there is no consensus on growth hormone replacement in adults.

After growth hormone, gonadatropin and ACTH deficiency are the second and third most common deficiencies [203]. Gonadatropin deficiency is silent in postmenopausal woman, but can lead to irregular menses or amenorrhea with premature menopause in women and testosterone deficiency in men. For women with early menopause, the American Association of Clinical Endocrinologists/American College of Endocrinology position statement supports the use of hormone replacement therapy until at least the age of natural menopause [204]. Hormone replacement in young women with early menopause appears to reduce the risk of coronary vascular disease, atherosclerosis, mood disorders, and cognitive dysfunction [205]. For men, a study of young (25–45 years old) male cancer survivors found impaired quality of life, fatigue, and sexual function were common concerns, and those symptoms were worse in patients with hypogonadism [206]. The American Urological Association has published clinical practice guidelines on the evaluation and management of testosterone deficiency [207].

ACTH deficiency can cause secondary adrenal insufficiency. Secondary adrenal insufficiency can be a cause of depression, fatigue, weight loss, nausea, diarrhea, hypoglycemia, and potential hyponatremia [208]. Hydrocortisone replacement is required. Unlike primary adrenal insufficiency, patients with ACTH deficiency do not require fludrocortisone.

TSH deficiency was the least common pituitary abnormality after radiation, which can cause a central hypothyroidism: low free T_4 with low to normal TSH concentrations. Clinical symptoms from central hypothyroidism may be milder than those observed in primary hypothyroidism [209]. Thyroid hormone replacement is the same as primary hypothyroidism, but TSH levels cannot be used to monitor adequacy of replacement therapy. If central hypothyroidism is suspected, it is important to screen for ACTH deficiency and treat adrenal insufficiency before initiating thyroid replacement therapy to avoid inducing an adrenal crisis.

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