



# Oncologic management of sinonasal undifferentiated carcinoma

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## Purpose of review

This article reviews the latest treatment paradigms in sinonasal undifferentiated carcinoma (SNUC).

## Recent findings

The aggressive biology and associated advanced presentation of SNUC make successful treatment a challenge shared across medical specialties. Still, studies reporting outcomes in SNUC indicate that an aggressive treatment strategy consisting of surgery, radiation and chemotherapy offers the best chance of prolonged survival.

## Summary

Successful treatment of SNUC requires highly specialized care at tertiary cancer treatment facilities. A better understanding of the biology of the disease coupled with increasing outcome reporting will lead to optimized treatment regimens.

## Keywords

sinonasal cancer, sinonasal tumors, sinonasal undifferentiated carcinoma, sinus tumors, skull base cancer, skull base surgery

## INTRODUCTION

Sinonasal undifferentiated carcinoma (SNUC) represents a rare, aggressive subset of sinonasal malignancies. Their rarity, late presentation, and complex associated anatomy, make this cancer arguably one of the most difficult to cure in the head and neck. Still, advances in molecular biology, surgery, chemotherapy, and radiation protocols have allowed incremental improvements in survival outcomes in recent years [1]. This review will examine the state of the art in the management of SNUC, with a focus on the latest clinical outcomes research in this area.

## EPIDEMIOLOGY AND GENERAL CONSIDERATIONS

Occurring at an incidence of 0.5–2.6/100 000 per year, sinonasal malignancies constitute approximately 5% of all head and neck cancers and less than 1% of all cancers [2–4]. Among sinonasal cancers, SNUC represents a relatively recently described clinical entity. Frierson was among the first to publish reports just 30 years ago describing SNUC as a unique clinical and pathologic entity, differentiating it from its less aggressive counterpart, olfactory neuroblastoma/esthesioneuroblastoma [5,6]. SNUC is rare even among sinonasal cancers, making up only 3–5% of all

sinonasal carcinomas [1,3,7]. The etiopathogenesis of SNUC remains largely unknown.

SNUC demonstrates a male predominance (2–3 : 1) and exhibits a wide age range of presentation, from 20 to 90 years (median 60 years) [8<sup>■</sup>,9–11]. Patients with SNUC commonly present with nasal obstruction, epistaxis, proptosis, pain, and cranial neuropathy [12]. The most common location is nasal cavity (38%), followed by ethmoid (23%) and maxillary sinuses (15%) [13<sup>■</sup>]. Physical examination and imaging will reveal the majority of tumors to be fairly advanced upon presentation. Seventy to 90% of patients will present with T4 disease; 50% will possess orbital, skull base, and/or brain involvement [14–17]. Five to 16% of patients will present with regional metastasis and 5.2% will present with distant metastasis [14–20].

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**Curr Opin Otolaryngol Head Neck Surg** 2019, 27:59–66

DOI:10.1097/MOO.0000000000000513

## KEY POINTS

- Sinonasal undifferentiated carcinoma represents a highly aggressive sinonasal cancer with advanced stage at presentation. Most published series do not report 5-year overall survival rates exceeding 50%.
- In appropriately selected patients, endoscopic endonasal surgical approaches offer local control rates comparable with traditional open approaches.
- Incorporation of radiotherapy is standard of care in the treatment of SNUC, with intensity-modulated radiation therapy (IMRT) demonstrating improved survival outcomes with reduced toxicity compared with conventional techniques.
- Chemotherapy has increasingly demonstrated evidence of survival advantages in patients who can tolerate systemic therapy.

resection, whereas PET/CT should be obtained for definitive cancer staging. The most commonly used staging systems for SNUC in published reports are the Kadish and American Joint Committee on Cancer staging systems (Table 1 and Table 2, respectively), both of which have been shown to confer prognostic value [17,21]. Although discussed in greater detail below, the prognosis for this aggressive tumor is categorically poor; most series do not report 5-year overall survival (OS) rates exceeding 50% [1]. The poor prognosis associated with SNUC has mandated a more focused approach towards identifying features that make this tumor more aggressive and a close study of treatment strategies that demonstrate the best survival outcomes in patients afflicted with this disease.

## HISTOPATHOLOGY

When encountered with poorly differentiated sinonasal tumors, the diagnosis can often be confounded by sampling error and the tumor's dedifferentiated state, which can be challenging for a pathologist and treatment team alike. This tumor can often be confused with small round blue cell tumors and other poorly differentiated carcinomas of the sinonasal tract. Some posit that SNUC arises from Schneiderian epithelium and is of ectodermal origin, which is supported by reports of SNUC transformation from Schneiderian papilloma [11,22–25]. Light microscopic features are highly varied, with these tumors demonstrating trabecular, sheet-like, ribbon, lobular and organoid patterns. SNUCs demonstrate a high nuclear-to-cytoplasmic ratio, increased mitotic activity, atypical

**Table 1.** Modified Kadish staging system

Stage	Description
A	Limited to nasal cavity
B	Involves nasal cavity and paranasal sinuses
C	Extends beyond nasal cavity and paranasal sinuses
D	Regional or distant metastasis

Computed tomography (CT) and MRI are complementary in defining the extent of locoregional disease and in determining feasibility of surgical

**Table 2.** AJCC tumor staging for sinonasal cancers

Maxillary sinus	
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction, including hard palate, middle meatus. Excludes posterior maxillary sinus wall and pterygoid plates
T3	Tumor invades any of the following: bone of posterior wall of maxillary sinus, subcutaneous tissues, floor of medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Moderately advanced. tumor invades any of the following: anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinus
T4b	Very advanced. Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus
Nasal cavity and ethmoid sinus	
T1	Tumor restricted to any one subsite, with or without bony invasion
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
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4b	Moderately advanced. Tumor invades any of the following: anterior orbital contents, skin of nose/cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinus
T4b	Very advanced. Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx or clivus

AJCC, American Joint Committee on Cancer.

mitosis, tumor necrosis, and apoptosis [12]. These tumors, by definition, lack glandular and squamous differentiation. Neuroendocrine features are typically absent. Immunohistochemically, SNUCs demonstrate strong, diffuse staining with epithelial markers AE1/AE3, CK7, OSCAR, CAM5.2, EMA, p16 and CD117 [9]. Typically, these tumors do not stain positive for CK5/6, p40, CEA, EBER, CD34, desmin, S100, and calretinin [9,26–31]. Representative micrographs illustrating tumor histopathology and immunohistochemistry characteristics are shown in Fig. 1.

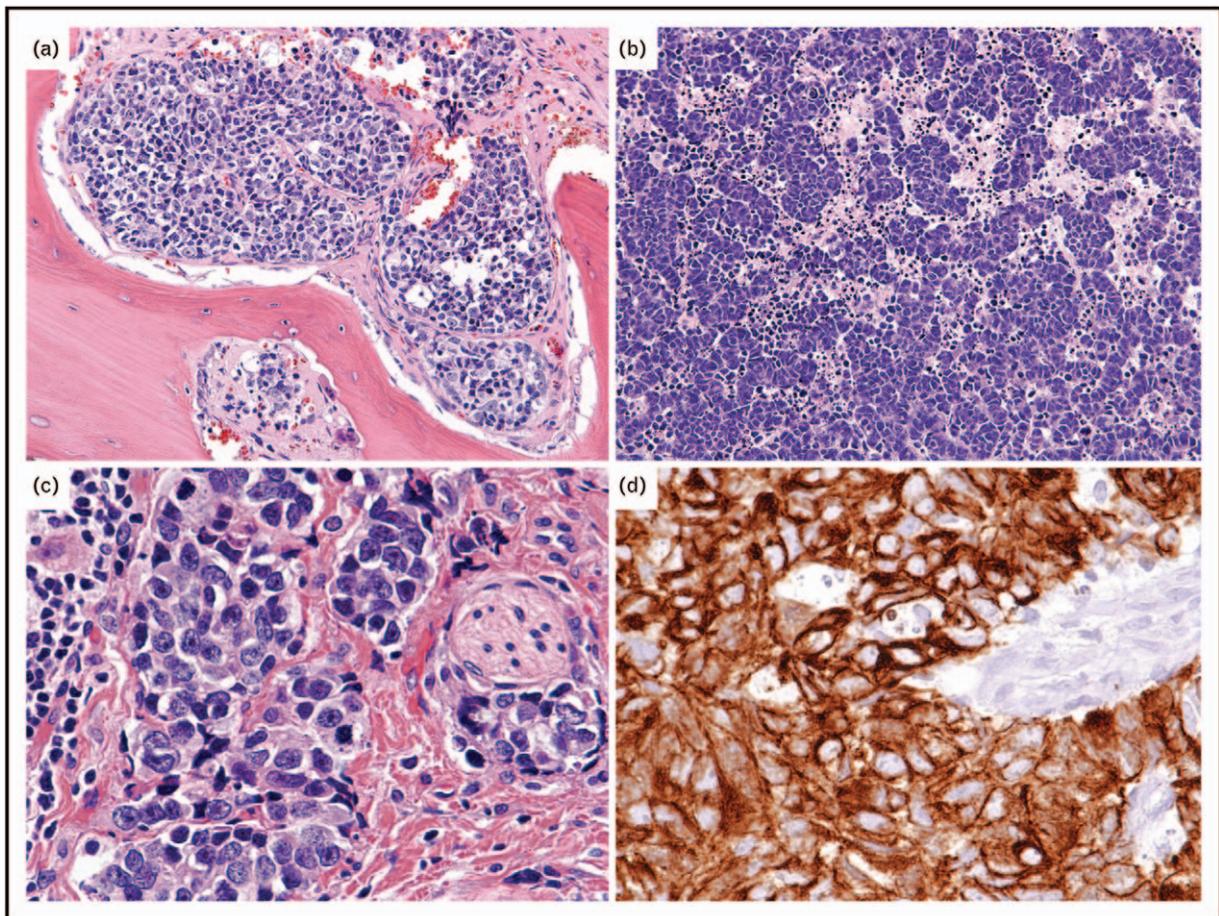
## MANAGEMENT PARADIGMS IN SINONASAL UNDIFFERENTIATED CARCINOMA

### Surgery

Surgical resection remains the primary modality for the management of sinonasal cancers. SNUC is no

exception; however, it is rarely employed as single modality therapy. Indeed, the advanced local stage of disease often poses a significant challenge to the surgical team. Tumors deemed unresectable typically demonstrate significant intracranial extension, optic chiasm invasion, cavernous sinus invasion, and/or carotid artery encasement [17,32]. In these instances, neoadjuvant therapy should be considered for tumor shrinkage, with the goal of achieving a treated tumor that is more favorable for resection. Several case series, systematic reviews, and meta-analyses have demonstrated that when surgery with gross total resection is performed, survival outcomes improve [1,16,20,33–35,36<sup>11</sup>]. Certainly, one must acknowledge the likely selection bias inherent in these series, as surgical resectability implies more favorable tumor characteristics and biology.

The historic gold standard surgical approach for sinonasal tumors was open craniofacial resection,

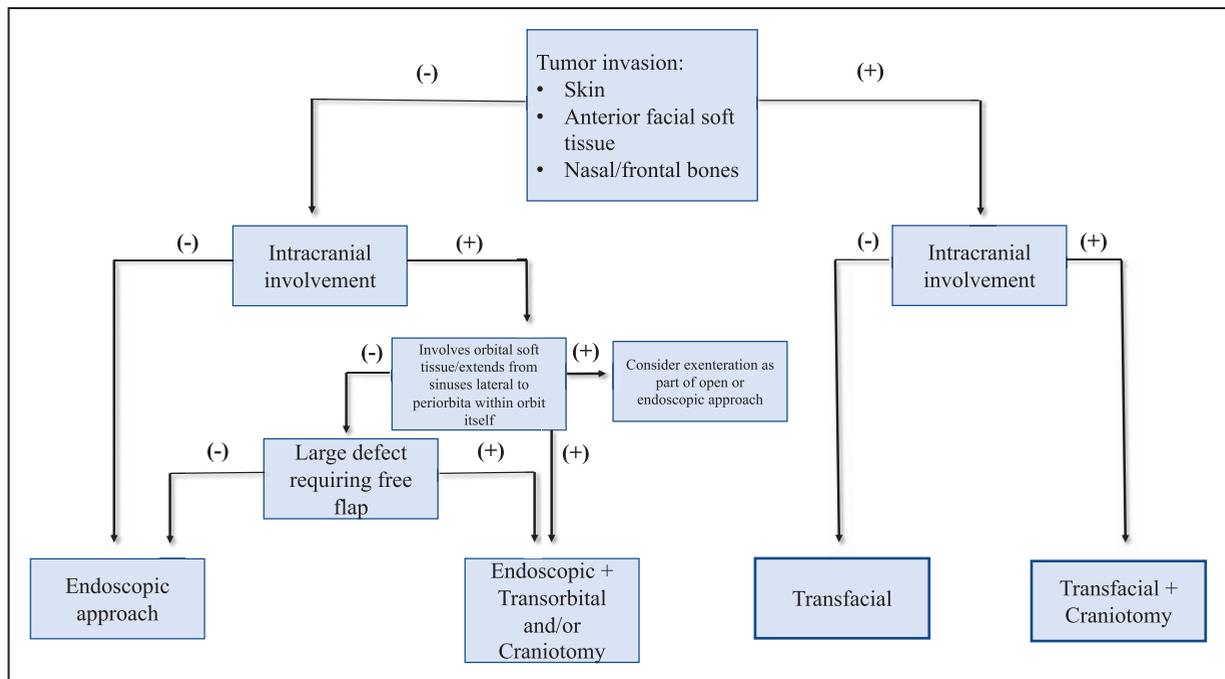


**FIGURE 1.** Histopathologic findings of sinonasal undifferentiated carcinoma. (a) SNUC forms lobulated nests of neoplastic cells that invade surrounding structures, such as bone. (b) In addition to a lobulated pattern, trabecular or diffuse sheet-like growth may also be seen. Frequent mitotic figures and apoptotic debris are present. (c) At higher magnification, the neoplastic cells (center) are large in comparison with normal lymphocytes (top left) with scant cytoplasm, irregular nuclei, coarse chromatin, and variably prominent nucleoli. A small peripheral nerve branch is entrapped by tumor (right). (d) By immunohistochemistry, the tumor cells demonstrate cytoplasmic expression of cytokeratins, supporting epithelial origin, but are typically negative for other specific markers of differentiation. Endothelial cells serve as a negative internal control (right).

which includes coronal or transfacial incisions (Weber–Ferguson, lateral rhinotomy, sublabial, midfacial degloving) combined with craniotomy when significant intracranial extension exists. The advent of endoscopic, endonasal surgical technology has resulted in somewhat of a paradigm shift in the surgical management of these tumors. Endoscopic endonasal approaches offer improved visualization of vital skull base and intracranial structures, while also reducing external scars and postoperative complications encountered with open approaches [4,37–39]. In the appropriately selected patients, endoscopic endonasal approaches to sinonasal cancer can be performed as the sole approach [endoscopic endonasal approach (EEA)] or combined with open approaches [combined endoscopic endonasal approach (CEEAA)] without compromising oncologic results [39–42]. Naunheim *et al.* [39] recently published their experience with both open and endoscopic surgical approaches in 48 patients with sinonasal malignancies (19.4% patients with SNUC). They found no difference in disease free survival (DFS, 5 years – 82.1% overall) or intracranial (CSF leak, meningitis, stroke) and orbital (diplopia, vision worsening, epiphora) complications when comparing endoscopic and open approaches. The criteria for incorporating an EEA in surgery is multifactorial and institution-dependent; however, general principles apply. The following tumor characteristics warrant consideration of incorporating

an open approach: tumor involving skin, nasal bone, frontal bone, facial soft tissues, or soft tissue surrounding/involving the orbit (summarized in Fig. 2) [39].

Several studies have evaluated outcomes with regard to surgical approach in patients with SNUC. Revenaugh *et al.* [43] described their experience with endoscopic approaches in 13 patients with SNUC. In their study, seven patients underwent endoscopic resection (one combined with bifrontal craniotomy). Six out of seven patients had T4 tumors. Two-year OS and DFS estimates for patients undergoing endoscopic resection were 85 and 71.4%, respectively. All patients undergoing surgery also received both chemotherapy and radiation therapy. Gamez *et al.* [8<sup>\*\*\*</sup>] recently performed a single-institution, retrospective study involving 40 patients with SNUC. In their series, 75% patients underwent surgery, 45% underwent endoscopic resection (11 patients, 61% had T4 disease). Negative margins were obtained in 78% of patients. All patients undergoing surgery received radiotherapy (radiotherapy) with or without chemotherapy. The study found no difference in 5-year outcomes when comparing patients undergoing endoscopic vs. craniofacial resection (OS: 55 vs. 53%; RFS: 61 vs. 60%; LRC: 83 vs. 80%, respectively). Together, these studies support the use of both endoscopic and open techniques in appropriately selected patients with SNUC.



**FIGURE 2.** Flowchart depicting updated criteria for endoscopic vs. open resection of sinonasal malignancies. Modified from Naunheim *et al.* [39].

## Radiotherapy

The use of radiotherapy in the management of SNUC remains a standard of care. In a meta-analysis conducted by Van der Laan *et al.* [20] including 459 patients with SNUC, 84.2% of patients received radiation therapy in some form. In the same study, the authors found that incorporating radiotherapy with surgery conferred improved 5-year disease-specific survival vs. single modality therapy (DSS, 54.7 vs. 15.7%). Kuan *et al.* [21] performed multivariate analysis using outcome data obtained from the SEER registry in 328 patients with SNUC and found that radiation therapy independently predicted improved OS and DSS. Surgery followed by adjuvant radiotherapy with or without chemotherapy is the most common sequence of radiotherapy in SNUC, similar to cancers at other subsites of the head and neck. Tanzler *et al.* [18] published a case series of results, which highlighted the benefits of aggressive adjuvant radiotherapy after aggressive surgery. In their series of 13 patients, 9 patients undergoing craniofacial resection (5 underwent orbital exenteration) received preoperative (2 patients) or postoperative (7 patients) hyperfractionated radiotherapy totaling 59.4–74.4 Gy. These patients had 3-year local control rates of 100%.

Intensity-modulated radiotherapy (IMRT) has become the most common method for delivering radiation in the head in neck; its use in SNUC has yielded favorable results with regard to toxicity and overall survival. In a study by Al-Mamgani *et al.* when IMRT was compared with 2D and 3D conventional radiotherapy (CRT), IMRT was associated with significantly less late toxicity, including serious complications (14 vs. 57%, respectively) and treatment-related blindness (0 vs. 29%, respectively). In the case series reviewed by Gamez *et al.* [8<sup>\*\*\*</sup>], 60% of patients received IMRT, which was associated with improved 5-year OS (59 vs. 16%,  $P=0.01$ ) and reduced late toxicity and serious complications. Patients receiving total doses at least 60 Gy to the tumor bed also had improved 5-year OS (73 vs. 23%,  $P=0.01$ ). In a retrospective review conducted in 54 patients with SNUC by de Bonnecaze *et al.* [44], IMRT delivery was associated with improved 3-year recurrence free survival (RFS) on univariate analysis, but not on multivariate analysis.

Neoadjuvant radiotherapy delivered with or without chemotherapy has shown some feasibility in selected series. In the treatment cohort reviewed by Musy *et al.* [15], patients undergoing neoadjuvant chemoradiotherapy followed by craniofacial resection had 2-year survival rate of 64% and mean survival of 44 months. Fried *et al.* [45] reported results

from their case series in 15 patients with SNUC. In their study, neoadjuvant CRT was delivered prior to surgery. Patients demonstrating complete responses to neoadjuvant therapy predicted favorable survival outcomes; the 3-year OS in their treatment cohort was 64%. The authors of this case series advocate for neoadjuvant CRT to increase odds of successful tumor resection.

With its enhanced tumor dose-distribution characteristics, proton therapy can provide higher doses of radiation while sparing surrounding healthy tissue. Although this radiation delivery technique holds promise for SNUC, few centers possess this newer technology. As such, series publishing results with the use of proton therapy in SNUC are rare, and they do not necessarily examine for any benefit with its use [27]. Further study is needed with regard to the management of SNUC as its use becomes more common.

## Chemotherapy

The use of systemic therapy in SNUC is common. It is never used as single modality with curative intent, but instead as part of a multimodality treatment strategy including radiotherapy with or without surgery. In a systematic review of data from the National Cancer Database (NCDB) involving 435 patients, Kuo *et al.* found that 72.6% of patients received chemotherapy. The most common agents used in published studies include platinum-based regimens, with cisplatin being the most common agent. Other commonly used systemic therapies include etoposide, 5-FU, docetaxel, and paclitaxel.

The reports indicating benefit of chemotherapy are hard to tease out, because as alluded to above, most studies are limited to single-institution case series. Still, several reports indicate a benefit on outcomes when chemotherapy is incorporated into the treatment regimen. Mourad *et al.* in a series of 18 patients with SNUC, found that trimodality therapy, including either concurrent chemo with cisplatin, or neoadjuvant chemotherapy with cisplatin, 5-FU, docetaxel (TPF), conferred improved local control (83 vs. 50%) and diabetes mellitus-free survival (92 vs. 33%) compared with other modalities [7]. One of the largest single institution series including 40 patients showed that patients receiving trimodality therapy had significantly improved 5-year OS (51 vs. 38%,  $P=0.002$ ), suggesting a benefit to the addition of chemotherapy to the overall treatment strategy [8<sup>\*\*\*</sup>]. The series published by Al-Mamgani *et al.* [17] boasts some of the highest disease control rates in the literature. In this study, 76% ( $n=16$ ) of the patients received chemotherapy: 9 received concurrent chemotherapy with cisplatin

and 7 received induction with cisplatin and etoposide. The 5-year OS rate was 74%. On multivariate analysis, the authors found that dual modality therapy was associated with significantly poorer local control when compared with trimodality therapy. A recent multicenter, retrospective study including 54 patients conducted by de Bonnecaze *et al.* found on multivariate analysis that the use of induction chemotherapy with TPF was associated with improved 3-year RFS [44]. In the same study, concurrent CRT was associated with improved RFS when compared with surgery with radiotherapy. Finally, in a retrospective review of 435 cases of SNUC from the NCDB, Kuo *et al.* demonstrated that both definitive CRT and surgery with CRT was associated with improved OS when compared with surgery and adjuvant radiotherapy; however, there was no difference between the two groups. Additionally, there was no difference in survival when comparing adjuvant CRT vs. neoadjuvant CRT [13<sup>11</sup>]. Taken together, the above-mentioned studies highlight the important role of chemotherapy in the overall management of SNUC.

### ELECTIVE MANAGEMENT OF THE NECK

According to a SEER database study conducted in 141 patients with SNUC and sinonasal small cell carcinoma, 22% of the patients will exhibit nodal involvement [46]. The same study found that nonnasal, nonethmoid site with SNUC histology demonstrated the highest rates of nodal involvement. Levels 1–3 remain at greatest risk for regional spread (levels 2–3 for nasal or ethmoid SNUC and bilateral levels 1–3 for nonnasal, nonethmoid SNUC). Nodal metastasis has also been correlated with poorer outcomes and studies have also shown high regional failure rates for SNUC [16]. A single-institution study consisting of 21 patients performed elective nodal irradiation in high-risk patients (tumor involved skin of cheek, infratemporal fossa, pterygoid, or cribriform plate) and found no regional failure in their series [17]. Similarly, in a series of 16 patients with SNUC published by Yoshida *et al.* [47] all but one patient received elective nodal irradiation to the neck totaling 50–60 Gy and the authors report a 2-year locoregional control rate of 78% in patients receiving trimodality therapy. Given these findings, elective treatment of the neck to high-risk nodal basins should be strongly considered in SNUC.

### TREATMENT PRINCIPLES: SUMMARIZING THE AVAILABLE EVIDENCE

The aggressive biology of SNUC necessitates an equally aggressive treatment strategy. Tumors of

this rarity should be treated at tertiary cancer centers with head and neck oncologists, surgeons and radiation oncologists. With the available evidence, it remains difficult to deduce the ideal treatment regimen for SNUC; however, we advocate for aggressive trimodality therapy consisting of surgery, radiotherapy, and chemotherapy in patients with good performance status. Treatment should be tailored to the tumor characteristics and the patient's ability to tolerate aggressive therapy. Surgery should be performed when tumor characteristics are favorable. Neoadjuvant chemotherapy with or without radiotherapy should be strongly considered in patients with good performance status in order to reduce tumor volume and achieve favorable dimensions for resection, or in select instances, to convert an open resection to one that can be performed endoscopically. In patients in whom surgery is unlikely or poorly tolerated, concurrent chemoradiotherapy should be planned, with a strong consideration for induction chemotherapy, especially in advanced tumors. Treatment regimens including only chemoradiotherapy regimens without surgery have shown acceptable results comparable with trimodality therapy that include aggressive surgery [13<sup>11</sup>,19,36<sup>11</sup>,44].

### CONCLUSION

Many of the above series reporting outcomes in SNUC paint a somewhat dismal picture for this disease. However, epidemiological studies have demonstrated there is a trend towards increasing survival in this patient population [21]. Prospective multiinstitutional data collection, which is already underway, will allow us to examine this cancer in a more directed and specific way. Incremental improvements in survival outcomes for these rare tumors will result from a better understanding regarding the molecular derangements involved in the pathogenesis of SNUC and increasingly enhanced outcomes reporting across multiple tertiary care institutions [27,48–55]. The authors advocate that whenever feasible, trimodality therapy consisting of surgery, radiation, and chemotherapy should be endeavored.

### Acknowledgements

*None.*

### Financial support and sponsorship

*None.*

### Conflicts of interest

*There are no conflicts of interest.*

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