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Head and Neck Cancer (CP Rodriguez, Section Editor)

Multimodal Therapy for Sinonasal Malignancies: Updates and Review of Current Treatment

Mayur D. Mody, MD[1,2]
Nabil F. Saba, MD, FACP[1,2,*]

Address
[1]Department of Hematology and Medical Oncology, Emory University, Atlanta, GA, USA
[*,2]Winship Cancer Institute of Emory University, Atlanta, GA, USA
Email: nfsaba@emory.edu

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Opinion statement

Sinonasal malignancies pose a significant challenge in management due to their low incidence, biologic diversity, and significant symptom burden. Even though surgery remains the primary therapeutic modality, a multi-modality approach has been shown to benefit a significant proportion of patients and its success depends largely on stage and histologic type. Non-surgical approaches such as novel radiation approaches as well as intensification with systemic therapy hold promise in altering the organ preservation rate as well as overall survival for patients. Practice changing randomized trials to test these novel modalities are overdue and desperately needed.

Introduction

Sinonasal malignancies are uncommon, representing about 3% of head and neck cancers and less than 0.5% of all cancers; it is estimated that approximately 2000 Americans per year are diagnosed with sinonasal cancers (SNC) [1]. A higher frequency of these tumors is seen in some parts of the world, including Asia, specifically Japan and South Africa [2]. The male to female ratio is 1.8:1, and it is most often diagnosed in patients between 50 and 70 years of age [3, 4]. Certain environmental and occupational factors have been correlated with increased

incidences of SNC: heavy or long-term smokers have a twofold greater risk of SNC, with a notable reduction in risk after long-term cessation. Furthermore, after adjusting for smoking, a meaningful dose-response correlation was also noted between alcohol use and SNC. Increased risk was noted with a high consumption of smoked/salted foods, and decreased risk with increasing intake of vegetables [5]. Moreover, non-keratinizing SCC has been recently linked to high-risk HPV, and other possible risk factors include nasal polyposis, chronic sinusitis, and allergies [6, 7]. Increased occurrences of squamous cell carcinomas (SCC) of the sinonasal cavities have been observed in bakers, pastry cooks, grain millers, construction workers, carpenters, farm workers, female textile workers, and nickel workers [8, 9]. Wood dust, synthetic wood, binding agents, and glues have all been implicated as possible carcinogens [10]. SNC are also seen more frequently in those with occupational exposures in the production of chromium, mustard gas, isopropyl alcohol, and radium [1].

SNC often present with nonspecific symptoms such as nasal obstruction and blood-tinged nasal discharge, and this often leads to delayed diagnosis [11]. These cancers involving the nasal cavity and paranasal sinuses remain challenging to treat not only because of their rarity but also as a result of the variety of histologies observed and the anatomic complexity of the surrounding vital organ structures [12]. A historical analysis of population-based data from SEER of all sinonasal malignancies reported between 1973 and 2006, ($n = 6379$) by Turner and Reh indicated that the most common histologies for SNC were SCC (51.6%) and adenocarcinoma (12.6%). Other histologies observed included esthesioneuroblastoma (6.3%), adenoid cystic carcinoma (ACC) (6.2%), melanoma (6.6%), sinonasal undifferentiated carcinoma (SNUC) (3.1%), and various pathologies representing the remaining tumors (13.7%) [4]. By comparison, more than 90% of traditional head and neck cancers are SCCs [13]. The anatomic distribution of SNC includes approximately 40–50% occurring within the nasal cavity, 30–40% within the maxillary sinus, 10% in the ethmoid sinuses, and less than 5% in the frontal and sphenoid sinuses [4].

The natural history of SNC is dependent on the histologic type, anatomic location, and tumor stage. When taking the variability of these factors into consideration, SNC remains one of the most challenging malignancies to treat. Despite a decrease in the proportion of patients presenting with advanced disease based on SEER data analyzed by Ansa et al. (from 14.7% during the period 1983–1992 to 12.4% during 1993–2002 and 9.5% during 2003–2009), overall survival has remained stable [14]. Radiation or surgery is frequently recommended for primary therapy depending on the anatomic location, and a combination of surgery and postoperative radiotherapy is indicated for the management of more advanced resectable cancers. Locally advanced disease often requires a multidisciplinary approach with surgery, radiation, and systemic therapy serving as key components of treatment. In this review article, we aim to highlight and review the current treatment options of SNC, including emerging therapies and future directions.

Treatment

Surgery

SNC are located in close proximity to the orbit, brain, cranial nerves, and carotid arteries, making surgical resection technically challenging with a high risk of morbidity. Historically, the gold standard surgical procedure for SNC has been open craniofacial resection. Within the last decade, endoscopic endonasal approaches have emerged as a viable alternative for a certain subset of patients. These approaches do not compromise survival and have lower complication rates. The rarity and heterogeneity of these cancers, however, precludes comparison of surgical techniques via randomized controlled trials (RCT) [15].

A population-based study of the National Cancer Database by Husain et al. identified 2292 patients with SNC between 2010 and 2015 that underwent definitive surgical treatment. Of these patients, 71.9% underwent an open approach and 28.1% had a purely endoscopic approach. Tumor histology, treatment facility type, margin status, and length of stay were all variables

associated with significant differences between the two surgical approaches. Ultimately, 5-year survival rates for the open (59.6%) and endoscopic (60.8%) cohorts were similar [16•]. In general, the endoscopic approach is associated with shorter hospital stays and less morbidity [17]. Based on evidence from case series and multi-analyses, the endoscopic approach is at least equivalent to the open approach in obtaining negative margins, which is the most significant variable predictive of survival that surgery can influence [15, 18]. Although en bloc resection is traditionally performed, data indicates that obtaining negative margins optimizes survival independent of the surgery being performed piecemeal or en bloc [19]. Therefore, the surgical approach that should be selected for a patient should be capable of obtaining negative margins while simultaneously limiting patient morbidity [15].

While operable SNCs should generally be resected as primary therapy, several factors must be considered, including tumor histology and anatomic location. Certain tumor histologies, such as SNUC, are often not amenable to primary surgery compared with other tumor types due to rapidly destructive growth patterns, prominent neurotropism, and lymphovascular invasion [20]. Other histologies, such as melanoma, require specific surgical considerations such as wide margins [21]. On the other hand, sinonasal lymphomas are best managed with chemoradiation therapy, as surgical intervention does not significantly impact survival in these patients [22]. In general, the rarer histologies seen in SNC often have specific considerations in regard to primary surgical management.

Specific considerations for primary surgical therapy of SNC based on anatomical location should also be considered. For nasal vestibule cancers, surgery can yield a high control rate with acceptable cosmetic results in small superficial lesions where clear margins can be obtained. However, radiotherapy as primary therapy is generally preferred because of better cosmetic outcomes [23]. For tumors involving the nasal cavity, while stage II and operable stage III cancers are typically treated with surgery followed by adjuvant radiotherapy, stage I tumors can be treated with either radiation or surgery. As in nasal vestibule cancers, the decision regarding the type of therapy depends on the size and location of the tumor as well as projected cosmetic outcome. For example, posterior nasal septum lesions are generally treated with surgery. On the other hand, anterior septal lesions are often treated via radiation to avoid partial removal of the anterior nasal septum. Similarly, for cosmetic reasons, lateral wall lesions are also first evaluated for primary radiotherapy management [24].

Radiotherapy

In addition to the scenarios outlined above where primary radiation therapy is recommended, primary radiotherapy is also typically deemed appropriate for patients with locally advanced inoperable cancers or who are unfit for surgery. Postoperative radiation therapy is advised when adverse features are identified following surgery. These include advanced T stage, high tumor grade, high-risk histology, perineural or lymphovascular space invasion, positive lymph nodes, positive margins, and any surgeon concerns about the adequacy of the surgical resection. Postoperative doses typically range from fifty to sixty-six Gray (Gy), while higher doses in the 70–74.4 Gy range are often necessary to treat residual

or unresectable disease. Fraction size is typically 1.8–2.0 Gy for once-daily fractionation or 1.2 Gy for twice daily [25]. Advances in radiation oncology techniques have improved treatment outcomes, allowing for better coverage of disease and increased sparing of normal structures surrounding SNC. We will focus on these improvements and advances for the remainder of this section.

Intensity-modulated radiation therapy (IMRT) has been one of the most critical advances in radiation treatment planning and is currently the most commonly used technique for the treatment of SNC. IMRT utilizes computational mathematics and inverse radiation planning combined with multiple beams of varying shapes and intensities to create an ideal radiation plan that adapts around irregular targets and avoids critical anatomic structures. In fact, dosimetric studies have found that IMRT allows for better sparing of optic and brain structures and improved coverage of tumor compared with traditional three-dimensional conformal radiotherapy (3D-CRT) [26]. An institutional comparison of the two modalities by Dirix et al. showed that IMRT resulted in not only improved disease-free survival (72% vs. 60%) but also reduced incidence of toxicities including skin toxicity, mucositis, xerostomia, and dry-eye syndrome compared with 3D-CRT [27].

Despite these advances in photon therapy, overall outcomes in SNC remain poor, indicating the need for more effective treatment. In one recent meta-analysis, use of photon therapy in treatment-naïve patients resulted in 5-year OS of 47%, DFS of 41%, and locoregional control of disease in 64% [28]. Proton therapy presents an alternative form of treatment that may have the potential to improve outcomes. By taking advantage of the Bragg peak, proton therapy is able to concentrate the effect of light ion beams on the tumor being treated while minimizing the effect on the surrounding healthy tissue [29]. A systematic review by van de Water et al. analyzing data from available in silico planning comparative studies for the treatment of head and neck cancers showed that in comparison to traditional photon therapy, irradiation with protons generally results in a lower dose to normal tissues while simultaneously maintaining improved target dose distributions. This allows more opportunities for dose escalation, as well as an improvement in therapeutic ratio by risk reduction for radiation-induced side effects while keeping the same target dose or by target dose escalation without increased risk for radiation-induced toxicities [30].

Although limited, the data available on proton therapy for SNC from single institutional studies has been promising. Dagan et al. reported disease outcomes after proton therapy for SNC at the University of Florida for 84 patients with non-metastatic disease, with 87% of those patients treated in the adjuvant setting. Three-year local control, neck control, freedom from distant metastasis, disease-free survival, and overall survival were 83%, 94%, 73%, 63%, and 68%, respectively. Gross disease was the only significant factor for local control on multivariate analysis, and late toxicity occurred in 24% of patients [31•]. Similarly, Russo et al. published data from Massachusetts General Hospital between 1991 and 2008 of 54 patients with stage III or IV sinonasal SCC that received proton beam therapy with a median dose of 72.8 Gy. The 2-year and 5-year actuarial local control rate was 80%, and overall survival rates were 67% (2 years) and 47% (5 years). Smoking was shown to be predictive for poorer locoregional control, with active smokers having a 5-year rate of 23% compared with 83% for non-active smokers. Karnofsky performance status ≤ 80 was the most significant factor predictive of worse OS in multivariate analysis [32•]. A

Japanese study by Zedna et al. incorporated findings for 39 patients with nonresectable SNC of varying histologies. Approximately 25% of patients received induction chemotherapy, and the most common dose and fractionation scheme was 65 Gy and 26 fractions, respectively. The 3-year overall survival was 59% and progression-free survival was 49%, with 23% of patients having local progression. Thirteen percent of patients experienced grade ≥ 3 late toxicity [33]. As more data becomes available, it is evident that additional prospective studies to compare IMRT with proton therapy, including in silico planning comparative studies with a focus on uniform accepted toxicity endpoints, in the treatment of SNC are indicated and necessary.

Systemic therapy

The use of systemic therapy for SNC is optimal when administered within a multimodal strategy. Careful determination of the sequence of the different modalities is essential to deriving the optimal outcome, as neoadjuvant chemotherapy is often designed to target distant metastasis and perhaps improve local control, while concomitant therapy is used primarily to increase locoregional control. Due to the rarity and heterogeneity of SNC, there is a paucity of RCT-based data for systemic therapy in SNC, and chemotherapy or chemoradiotherapy protocols are often derived by extrapolation from approaches used for more common tumors, such as larynx preservation protocols in traditional head and neck cancers. In fact, SNC is often an exclusion criterion for systemic therapy studies in traditional head and neck cancer clinical trials [34, 35]. In this section, we will review the use of systemic therapy in SNC, including treatment in the neoadjuvant, concurrent, and adjuvant settings, as well as briefly outline specific systemic therapy considerations for specific tumor histologies.

Neoadjuvant (induction) chemotherapy

Some of the earlier single institution studies from the late 1980s and early 1990s showed encouraging local control and survival rates when induction chemotherapy was combined with surgery and/or radiation in the treatment of SNC. In 16 stage III or stage IV SNC patients, in which a majority were SCC, LoRusso et al. demonstrated treatment with platinum-based chemotherapy followed by surgery and/or radiotherapy yielded a complete response rate of 44% and partial response rate of 38% [36]. This experience helped establish that cisplatin-containing regimens show promise in the treatment of SNC. In 1992, Bjork-Eriksson et al. treated 12 patients (advanced epithelial non-adenocarcinoma SNC) with cisplatin and 5-flurouracil (5-FU) induction chemotherapy followed by 48 Gy external radiotherapy and organ preservation surgery. This was the first reported pilot study in SNC using induction chemotherapy for organ preservation, and results were promising, with local control achieved in 11 of 12 patients and 10 patients were alive with no evidence of disease after a median follow-up of 27 months [37].

More recently, Hanna et al. evaluated data on 46 advanced SNC patients treated with induction chemotherapy at the MD Anderson Cancer Center. Twenty-six percent of patients had clinical evidence of nodal metastases, 67% had

orbital invasion, and 80% had stage IV disease. Chemotherapy regimens used included platinum and taxane in the majority (alone or in combination with a third agent such as ifosfamide or 5-FU), with the remaining 20% of patients receiving the combination of taxane and 5-FU. Treatment following induction chemotherapy included either surgery followed by radiation (or chemoradiation) or by definitive radiation (or chemoradiation), with salvage surgery for residual disease. Results were favorable, including a high rate of local control, a 2-year overall survival of 67%, and achievement of conservative surgery with orbital preservation in 87% of patients. Overall, response to induction chemotherapy was obtained in two-thirds of the patient population, with tumor response to induction chemotherapy being predictive of treatment outcome and prognosis independently of the ensuing methods of locoregional control [38].

Theoretical advantages of induction chemotherapy include the ability to optimize drug delivery through an intact tumor blood supply, as it allows higher chemotherapy doses/dose intensities compared with chemotherapy given during or after local therapy [39]. Additionally, toxicities are more often transient in the neoadjuvant setting. On the other hand, a primary disadvantage is the possible delay of locoregional therapy, which remains the most critical treatment intervention. Several questions remain in regard to creating a more definitive role for induction chemotherapy in the treatment of SNC. Given the heterogeneity in tumor histology, a definitive regimen has not yet been established. Studies thus far have primarily utilized a platinum-based regimen with the addition of either 5-FU, taxane, ifosfamide, or vincristine [36–38, 40, 41]. Further evaluation is necessary and randomized trials are needed to produce practice-changing results. ECOG-ACRIN 3163 is a randomized phase II study evaluating the effect of preoperative chemotherapy using platinum with docetaxel on organ preservation and overall survival in patients with resectable SCCs of the nasal and paranasal sinuses.

Concurrent chemotherapy

Unlike the management of traditional head and neck cancers, for which platinum-based chemotherapy has shown to be an impactful radiosensitizer, concurrent chemoradiation (CCRT) has been much less studied in SNC. Data is largely limited to retrospective analyses. While surgical resection followed by radiation is generally preferable to definitive radiotherapy, available retrospective data thus far is conflicting as to whether management with surgery followed by radiotherapy (with or without chemotherapy) is superior to definitive CCRT [42, 43]. Specifically, Kang et al. analyzed retrospective data of patients with maxillary sinus tumors treated with either one of these methods, and the patients who had undergone surgery had better progression-free survival (hazard ratio 2.363, 95% confidence interval 1.098–5.085, $p = 0.028$) and overall survival (hazard ratio 4.989, 95% confidence interval 1.646–15.118, $p = 0.004$) [44]. Conversely, a retrospective review by Kim et al. of 30 patients with non-metastatic stage III and stage IV sinonasal SCC showed that locoregional recurrence-free, distant metastasis-free, disease-specific, and overall survival

Table 1. Current Phase II trials involving treatment of sinonasal malignancies (Clinicaltrials.gov)

Name	Sponsor	Primary investigator	Therapy
Phase II randomized trial of neo-adjuvant chemotherapy followed by surgery and post-operative radiation versus surgery and post-operative radiation for organ preservation of T3 and T4a nasal and paranasal sinus squamous cell carcinoma (NPNSCC)	ECOG-ACRIN Cancer Research Group	Nabil F Saba	Neo-adjuvant chemotherapy
Phase II trial of induction therapy with docetaxel, cisplatin, and fluorouracil in previously untreated patients with locally advanced squamous cell carcinoma and/or poorly differentiated carcinoma of the nasal cavity and/or paranasal sinuses	M.D. Anderson Cancer Center	Ehab Y Hanna	Induction chemotherapy
A Phase II study of intensity-modulated or proton radiation therapy for locally advanced sinonasal malignancy	Massachusetts General Hospital	Annie W Chan	Radiation therapy
A Phase II, single-arm trial assessing local control of near total endoscopic resection followed by concurrent chemotherapy and proton radiation in the treatment of unresectable sinonasal tumors	Memorial Sloan Kettering Cancer Center	Marc Cohen	Endoscopic surgery

rates did not differ between patients receiving surgery and postoperative radiotherapy versus CCRT. In addition, there were no significant differences in occurrence rates of acute and chronic toxicities between the treatment groups [45].

When considering unresectable patients, Hoppe et al. reported survival data of 39 patients with stage IVB paranasal sinus cancer. A total of 35 of these patients were treated with primarily platinum-based CCRT, and the remaining 4 received radiation alone. The patient population had a median follow-up of 90 months, and reported outcomes included 5-year local progression-free survival, regional progression-free survival, distant metastasis-free survival, disease-free survival, and overall survival of 21%, 61%, 51%, 14%, and 15%, respectively. Local relapse (64%) was primarily within the irradiated field, and the only significant factor predictive of improved local progression-free survival and overall survival was a biologically equivalent dose of radiation greater than or equal to 65 Gy [46]. Overall, further evaluation of CCRT is necessary, in both the resectable and unresectable settings, and data obtained through randomized control trials would limit the selection bias seen in choice of therapy in the available retrospective data.

Adjuvant chemotherapy

While the optimal combination and sequencing of treatment interventions in locally advanced SNC remains controversial, surgery, when feasible, remains the mainstay of treatment for patients with these tumors [47]. In general, a

multimodal approach has been shown in the literature to yield improved survival outcomes [40, 48–50]. In the adjuvant setting following surgery for head and neck cancer, chemotherapy is traditionally utilized in combination with radiotherapy for its radiosensitization properties [51]. In locally advanced SNC, it is not clear that the addition of chemotherapy to radiotherapy in the adjuvant setting improves overall survival, and radiotherapy alone may be sufficient for the eradication of microscopic disease in this setting. Adjuvant chemotherapy is not an accepted current standard and will require evaluation in prospective trials [52••]. While each patient must be evaluated on a case-by-case basis, it is of our opinion that those patients receiving adjuvant radiotherapy should be considered for adjuvant concurrent chemotherapy only if they have high-risk pathologic features.

Systemic therapy considerations for specific tumor histologies

Systemic therapy has shown efficacy in specific tumor histologies for SNC. We will focus on these specific tumor types in this section. Tumor types where chemotherapy does not have a clear role (such as adenoid cystic carcinoma) will not be discussed in this section.

Squamous cell carcinoma

Despite being the most common histological subgroup in SNC, a lack of prospective data exists on the management of SCC of the sinonasal tract due to the overall low incidence of SNC. Small cohort studies dating back to the early 1990s have suggested the use of platinum-based doublet therapy, most commonly cisplatin and 5-FU, in the neoadjuvant setting for stage III and stage IV SCC SNC [37, 53]. Over two decades later, the neoadjuvant regimen has not drastically changed, based on a recent retrospective single institution review of 68 cases by Pare et al. from France. In this review, neoadjuvant chemotherapy was administered in patients with locally advanced (T3 or T4) and/or rapidly growing tumor (58.8% of cases in total). The regimen consisted of 3 cycles of cisplatin with 5-FU until 2006 and TPF thereafter (cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2 on days 1, 5 and 5-FU on days 1–4). Depending on the patient's comorbidities, carboplatin could be used instead. Tumor downsizing with neoadjuvant chemotherapy was observed in 82.5% of cases. 27.9% of patients received adjuvant chemoradiation therapy with cisplatin 100 mg/m^2 on days 1, 22, and 43 of radiation. The decision to give adjuvant treatment with radiation or radiation with chemotherapy was dependent on initial staging and pathological risk factors [54•].

Adenocarcinoma

Adenocarcinoma of the sinonasal tract is classically treated with surgery with adjuvant radiation therapy in the setting of positive margins or high-grade

disease [55, 56]. In general, chemotherapy has not been shown to provide a survival advantage. In a specific subset of patients with advanced sinonasal intestinal-type adenocarcinoma with functional p53 status, two Italian studies have shown some efficacy of cisplatin, 5-FU, and leucovorin in the neoadjuvant setting [57, 58].

Sinonasal undifferentiated carcinoma

SNUC have been demonstrated in studies to be chemosensitive, the most significant of which was a meta-analysis by Reiersen et al. of 167 SNUC patients that indicated improved patient survival with the addition of systemic therapy to surgery [59]. These tumors are known to be highly aggressive, and composed of uncertain histologies with or without neuroendocrine differentiation [60]. Given the often-advanced stage of disease at presentation, high rate of distant failure, along with its noted chemosensitivity, induction chemotherapy followed by either chemoradiation or surgery followed by postoperative IMRT is a promising optimal treatment strategy for SNUC [61, 62]. The regimen of choice requires further evaluation, as a variety of induction regimens have been previously used, ranging from the traditional platinum-based regimens to a combination of cyclophosphamide, doxorubicin, and vincristine, which showed a relatively favorable outcome in a study by Musy et al. [63]. A recently published study by Amit et al. of 95 patients with SNUC treated with induction platinum-based doublet (cisplatin or carboplatin with etoposide or docetaxel) chemotherapy before definitive locoregional therapy showed that in patients who achieved a favorable response to induction chemotherapy, definitive CCRT resulted in improved survival (5-year disease-specific survival (DSS) probability 81%) compared with patients who underwent definitive surgery (5-year DSS probability 54%). On the other hand, in patients who did not achieve a favorable response to induction chemotherapy, surgery when feasible followed by radiotherapy or CCRT seemed to provide a better chance of disease control and improved survival, with a 5-year DSS probability of 39%, compared with 0% in patients who were treated with CCRT after induction chemotherapy [64].

Sinonasal primary mucosal melanoma

Arising from melanocytes within the nasal cavity, sinonasal primary mucosal melanomas often present at an advanced stage and carry a worse prognosis compared with cutaneous melanomas [65]. In the adjuvant setting, a phase II trial by Lian et al. showed significant improvement in median relapse-free survival for patients treated with temozolomide plus cisplatin after surgery compared with those treated with either high-dose interferon alfa-2b or observation alone after surgery (48.7, 40.4, and 21.1 months, respectively) [66]. More recently, targeted therapies, such as c-KIT inhibitors (imatinib, sunitinib), have

demonstrated potential promise in specific subsets of patients with sinonasal mucosal melanoma [67, 68]. Immune checkpoint blockade therapies such as anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) monoclonal antibodies and anti-programmed death-1 (anti-PD1) antibodies are undergoing evaluation in clinical trials for patients with mucosal melanoma. National Cancer Database data has already shown that immunotherapy use was a significant predictor of improved survival in patients with sinonasal mucosal melanoma with distant metastases [69].

Olfactory neuroblastoma/esthesioneuroblastoma

Olfactory neuroblastoma (ONB) arises from the olfactory neuroepithelium and is typically associated with an overall better prognosis than other SNC [70]. Surgery followed by radiation therapy and frontline CCRT with planned or surgical salvage are the most commonly employed treatment options [71]. Neoadjuvant systemic therapy has been studied, most recently by a team at the University of Virginia, who treated 50 patients with ONB with neoadjuvant vincristine and cyclophosphamide and achieved 5-year and 15-year disease-free survival rates of 87% and 83%, respectively [72]. Systemic therapy in the neoadjuvant setting is not yet commonly practiced, however, likely due to the locally but not systemically aggressive nature of ONBs compared with other SNC.

Sarcoma

Sarcomas involving the sinonasal tract are managed with systemic therapy as part of multimodal therapy based on the histologic subtype identified. While chemotherapy has a defined role in certain histologies, such as sinonasal osteosarcoma and rhabdomyosarcomas, a definitive role for chemotherapy has yet to be established in other histologies, such as adult soft tissue sarcomas and sinonasal chondrosarcoma [73–77].

Conclusions

Sinonasal malignancies remain one of the most challenging malignances to treat, often requiring a multidisciplinary approach with surgery, radiation, and systemic therapy. Given that these tumors are surrounded by critical structures, often present at advanced stages due to nonspecific symptoms, and vary significantly in histology, they are best treated at large academic centers that have multidisciplinary head and neck cancer teams. Further, randomized studies in the management of SNC are urgently needed, yet lacking (in Table 1 we have outlined notable Phase II clinical trials that are currently open to enrollment). While a multimodal therapy approach is essential, significant questions remain in regard to the combination, timing, and sequence of these regimens.

Contributions

Dr. Mody contributed as a primary author and Dr. Saba contributed as senior author and editor.

Compliance with Ethical Standards

Conflict of Interest

Mayur D. Mody declares that he has no conflict of interest. Nabil F. Saba has received research funding from Bristol-Myers Squibb, Exelixis, and Champions Oncology; has served on advisory boards for Merck, Bristol-Myers Squibb, Rakuten, and GlaxoSmithKline; and has served on a data safety monitoring committee for Amgen.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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