Cancer Treatment Reviews 41 (2015) 836–843

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

# The role of systemic therapy in the management of sinonasal cancer: A critical review

Paolo Bossi [a,*], Nabil F. Saba [b], Jan B. Vermorken [c], Primoz Strojan [d], Laura Pala [a], Remco de Bree [e], Juan Pablo Rodrigo [f], Fernando Lopez [f], Ehab Y. Hanna [g], Missak Haigentz [h], Robert P. Takes [i], Piet J. Slootweg [i], Carl E. Silver [h], Alessandra Rinaldo [j], Alfio Ferlito [k]

[a] Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[b] The Winship Cancer Institute of Emory University, Atlanta, GA, USA
[c] Antwerp University Hospital, Edegem, Belgium
[d] Institute of Oncology, Ljubljana, Slovenia
[e] UMC Utrecht Cancer Center, Utrecht, The Netherlands
[f] Hospital Universitario Central de Asturias, Oviedo, Spain
[g] The University of Texas MD Anderson Cancer Center, Houston, USA
[h] Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, USA
[i] Radboud University Medical Center, Nijmegen, The Netherlands
[j] University of Udine School of Medicine, Udine, Italy
[k] International Head and Neck Scientific Group, Italy

ARTICLE INFO

*Article history:*
Received 20 May 2015
Received in revised form 23 July 2015
Accepted 26 July 2015

*Keywords:*
Sinonasal cancer
Multimodality treatment
Chemotherapy
Targeted therapy

ABSTRACT

*Purpose:* Due to the rarity and the variety of histological types of sinonasal cancers, there is a paucity of data regarding strategy for their optimal treatment. Generally, outcomes of advanced and higher grade tumors remain unsatisfactory, despite the employment of sophisticated surgical approaches, technical advances in radiation techniques and the use of heavy ion particles.
In this context, we critically evaluated the role of systemic therapy as part of a multidisciplinary approach to locally advanced disease.
*Results:* Induction chemotherapy has shown encouraging activity and could have a role in the multimodal treatment of patients with advanced sinonasal tumors. For epithelial tumors, the most frequently employed chemotherapy is cisplatin, in combination with either 5-fluorouracil, taxane, ifosfamide, or vincristine. Only limited experiences with concurrent chemoradiation exist with sinonasal cancer.
The role of systemic treatment for each histological type (intestinal-type adenocarcinoma, sinonasal undifferentiated carcinoma, sinonasal neuroendocrine carcinoma, olfactory neuroblastoma, sinonasal primary mucosal melanoma, sarcoma) is discussed.
*Conclusions:* The treatment of SNC requires a multimodal approach. Employment of systemic therapy for locally advanced disease could result in better outcomes, and optimize the therapeutic armamentarium. Further studies are needed to precisely define the role of systemic therapy and identify the optimal sequencing for its administration in relation to local therapies.


## Background

Sinonasal cancer (SNC) is a rare disease, with an incidence of less than 1 case per 100,000 annually, representing 3% of all head and neck cancers [1]. Almost half of the tumors originate in the nasal cavity. The majority of other tumors originate in the maxillary or ethmoid sinuses, while tumors of the frontal and sphenoid sinuses are rare.

Tumors arising in the sinonasal tract usually remain asymptomatic for a long period. Therefore, patients more often present with extensive tumors with significant invasion of neighboring organs and tissues such as the eyes, optic nerves and chiasm, lacrimal glands, frontal and temporal lobes of the brain, brainstem, and pituitary gland. The usual clinical presentation of SNC includes symptoms that are indistinguishable from inflammatory sinus disease such as (unilateral) nasal obstruction, discharge and epistaxis. Depending on the origin and further extension in surrounding

* Corresponding author at: Head and Neck Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy. Tel.: +39 0223902765; fax: +39 0223903769.
*E-mail address:* paolo.bossi@istitutotumori.mi.it (P. Bossi).

http://dx.doi.org/10.1016/j.ctrv.2015.07.004
0305-7372/

structures, patients may have additional symptoms, including ocular symptoms (with proptosis, diplopia and visual loss), headache and nausea due to intracranial growth, or presence of an ulcerated intraoral palatal mass due to invasion of palatal bone [2].

Sinonasal cancers present highly heterogeneous histological features, and lesions with the same histology may show various degrees of differentiation. Epithelial malignancies are prevalent, with sinonasal squamous cell cancer (SCC) and intestinal type adenocarcinoma (ITAC) having the highest incidence, followed by minor salivary gland cancers (e.g. adenoid cystic carcinoma), sinonasal undifferentiated carcinoma (SNUC) and sinonasal neuroendocrine carcinoma (SNEC) [2,3]. Less frequent are sinonasal primary mucosal melanoma (SNPMM), olfactory neuroblastoma (ONB), also known as esthesioneuroblastoma, different types of sarcoma, hematolymphoid tumors, germ-cell tumors, and metastases from primary tumors in other parts of the body [4].

The etiology of most types of SNC is poorly understood. The appearance of non-keratinizing SCC has been etiologically linked to high-risk HPV [5]. Occupational exposure to wood and/or leather dust has been associated with development of ITAC [6]. Other possible risk factors include nasal polyposis, chronic sinusitis, allergies, as well as tobacco smoking [7,8].

Nasal cavity is the most frequent site of origin of SNEC (superior and posterior part), melanoma (lateral walls, septum) and olfactory neuroblastoma (roof), while SNUC is usually diagnosed when it already involves multiple adjacent areas and is not limited to a single sinus. Primary mucosal melanoma characteristically exerts at high frequency c-KIT overexpression, RAS-mitogen-activated protein kinase pathway alterations, CDKN2A mutations, loss of p16 expression (mainly related to 9p21deletions) and loss of heterozygosity; contrary to cutaneous melanoma, BRAF gene mutations are uncommon in mucosal counterpart [9]. In ONB a complex pattern of gene alterations were described, although no specific mutations have been reported [10]. As the most frequent tumor of the small salivary glands, adenoid cystic carcinoma shows a wide range of genetic and molecular alterations, with possible prognostic role or with potential therapeutic implications (EGFR, TrkC/NTRK3, PI3K/AKT pathway) [11]. Next-generation sequencing recently suggested that EGFR mutations is detectable in the majority of patients with sinonasal SCC related to Inverted Sinonasal Papilloma (ISP). Since identical genotypes were found in matched pairs of ISP and their associated SNSCC, these findings strongly pointed to a biologic link between these tumors [12]. Clinically relevant activating genomic mutations in selected genes were not identified in a series of SNUC, underlining the importance and complexity of a more comprehensive evaluation in such a disease [13].

In addition to varied tumor histology and molecular characterization, the anatomy of the region, with the proximity of several important structures, adds further complexity to the treatment planning. A multimodality therapeutic approach is mandatory, which is in general based on complete surgical resection with postoperative radiotherapy [14]. Outcomes may have improved with the use of new endoscopic surgical approaches [15,16] and the employment of new radiation techniques such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) [17,18] and proton and heavy ion therapy enabling the achievement of a well-defined and steep dose gradients close to the target volumes [19,20]. Despite these observed advances, the prognosis of patients with locally advanced SNC is generally poor, with a 5-year survival rate of approximately 30% [3]. In addition to surgery and radiotherapy, the inclusion of systemic therapy may offer improvement of locoregional control rates and reduction of the frequency of distant metastasis, as well as better survival for patients with unresectable disease. In this review, we discuss the role of systemic therapy in the management of SNC.

## Locoregionally advanced disease

Systemic therapy of SNC is best delivered within a multimodal strategy. In this regard, the appropriate sequencing of different modalities may be important in determining the optimal outcome with neoadjuvant chemotherapy intended to ameliorate distant metastasis and possibly improve local control, and concomitant therapy to increase locoregional control.

### *Neoadjuvant (induction) chemotherapy*

Incorporating neoadjuvant chemotherapy in the multimodality treatment of locally advanced cancers of the paranasal sinuses and nasal fossa has had promising results. However, due to the rarity of disease, only limited experiences with small number of patients have been reported, and no prospective, randomized trials have been performed to date. Moreover, most phase III induction chemotherapy studies in head and neck squamous cell carcinoma (HNSCC) have excluded patients with SNC [21–24]. Therefore, chemotherapy or chemoradiotherapy protocols are usually administered based on extrapolation from the approaches used for more-common tumors, such as the larynx preservation protocols. Another factor complicating the interpretation of published series is that most sinonasal cancer reports describe a mixture of different histological types.

A possible advantage of giving chemotherapy before the locoregional treatment is a more optimal drug delivery, permitting higher chemotherapy doses and dose intensities compared with chemotherapy given during or after the local therapy. Moreover, in that setting toxicities most often are only transient. Possible disadvantages include a slow recovery from toxicity. When the interplay between different modalities is less than optimal, delay of locoregional treatment, which still is the cornerstone of the intervention, may be fatally counterproductive.

In various single institution studies, induction chemotherapy combined with surgery and/or (chemo)radiation showed encouraging local control and survival rates (Table 1). One of the earliest reported experiences of this approach was a small study by Lorusso et al. in which 16 untreated patients with advanced SNC, mostly of the squamous cell type, were treated with platinum-based chemotherapy followed by surgery and/or radiotherapy [25]. An overall response rate of 82% (complete response, (CR) = 44% and partial response, (PR) = 38%) was observed following induction therapy. The authors concluded that patients with sinonasal cancers are responsive to cisplatin-containing combinations and the quality of the response to chemotherapy correlated with overall survival.

A pilot study in 1992 evaluated the impact of induction chemotherapy with cisplatin and 5-fluorouracil (PF) on tumor control and organ preservation in 12 patients with advanced epithelial non-adenocarcinoma of the paranasal sinuses and nasal fossa. After induction chemotherapy, patients received external radiotherapy with 48 Gy and "limited" surgery. Histopathologic analysis of resected specimens showed no vital tumor in 8 patients, minimal microscopic disease in 3 patients, and infiltrating tumor in 1 patient. Local control was achieved in 11 of 12 patients. After a median follow-up of 27 months, 10 patients were alive with no evidence of disease. This was the first reported pilot study in SNC using induction chemotherapy for organ preservation [26].

In 1999, Lee et al. reported on the experience in 19 patients with stage III and IV SNC receiving multimodality treatment of whom 16 had 3 cycles of PF followed by resection or debulking