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Original Research Article

Treatment outcomes of sinonasal tumours with neuroendocrine features

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ABSTRACT

Background: Sinonasal tumours with neuroendocrine immunophenotype include olfactory neuroblastoma (ONB), sinonasal neuroendocrine carcinoma (SNEC) and sinonasal undifferentiated carcinoma (SNUC). These neoplasms usually present in advanced stages and are associated with poor outcome. This study describes the clinical features of these tumours and analyzes treatment outcomes of patients with these malignancies.
Methods: Retrospective chart review of all patients with sinonasal tumours diagnosed from 2009 to 2019, in a tertiary cancer centre. Clinical and histopathological prognostic factors were determined by univariate analysis. Overall survival was estimated using Kaplan-Meier method.
Results: A total of 27 patients (77.8% male) with a mean age of 52.0±16.8 years were included in the study. ONB was diagnosed in 9 patients, SNEC in 10 patients and SNUC in 8 patients. TNM stage IV disease was found in 20 patients (74.0%) at presentation. According to staging and treatment results, curative therapy was attempted in 21 patients (77.8%), of whom sixteen (76.2%) received multimodality treatment. Overall mean survival was 49 months and 1-year, 3-years and 5-years overall survival rates were 70.5%, 47.3% and 37.8%, respectively. Patients with SNEC had worse overall survival (p=0.044). Regarding treatment options, patients with SNUC treated with surgery and adjuvant radiation therapy had improved overall survival (p=0.027), as well as patients with SNEC selected for endoscopic resection surgery (p=0.049).
Conclusions: Accurate histologic diagnosis, grading, and clinical staging are essential for characterization and treatment selection in this heterogeneous group of sinonasal tumours. Consensus in the management of these tumours is lacking due to their rarity, difficulties in diagnosis and diverse current treatment approaches.

Keywords: Olfactory neuroblastoma, Sinonasal cancer, Sinonasal neuroendocrine carcinoma, Sinonasal undifferentiated carcinoma

INTRODUCTION

Sinonasal malignancies with neuroendocrine differentiation are uncommon in the head and neck region, accounting for 5% of the tumours in this location.[1] This group of tumours is composed of heterogeneous neoplasms with either neuroectodermal origin, as olfactory neuroblastoma (ONB, previously known as esthesioneuroblastoma), or epithelial origin as sinonasal neuroendocrine carcinoma (SNEC) and sinonasal undifferentiated carcinoma (SNUC).[2,3]

These tumours can be classified based on their different cells of origin, since ONB arises from neuroectodermal cells of the olfactory epithelium and SNEC and SNUC have their origin in the respiratory epithelium of the sinonasal cavity.[4] Although the natural history and biological tumour behavior varies significantly between these entities, ONBs share some features of the other tumours and are often difficult to distinguish from SNECs.[5,6] SNUCs are regarded as a neuroendocrine tumour by some authors, due to the occasional presence of focal positivity for neuroendocrine markers, and must

be considered in the differential diagnosis due to overlapping morphology with high-grade ONBs and poorly differentiated SNECs.[7]

The limited evidence available, due to the rarity of these tumours, contribute to the lack of consensus regarding their behaviour, treatment options, response to therapy and prognosis. This study aims to report the experience with these entities in a tertiary cancer centre and review the existing literature, in order to improve treatment strategies and outcomes for affected patients.

METHODS

The authors performed a retrospective analysis, reviewing medical records of all patients with biopsy-proven sinonasal tumours with neuroendocrine immunophenotype treated at Portuguese Institute of Oncology of Oporto Francisco Gentil, between January 2009 and December 2019. Patient demographics, presenting symptoms, tumour location, pathologic and imaging data, staging and treatment modality were evaluated. Staging was performed using 8th American Joint Committee on Cancer (AJCC) TNM classification of the nasal cavity and paranasal sinuses, Dulguerov/University of California, Los Angeles (UCLA) staging system, modified Kadish stage, Hyam's grade and evaluation for orbital or dural/cerebral invasion.[8-11] Patients with missing clinical data or lost to follow up were excluded from the present study.

An initial observation was performed in all patients, including a complete physical examination, head and neck computed tomography (CT) and magnetic resonance imaging (MRI) in selected cases. In patients with nodal disease, positron emission tomography was requested to allow the detection of distant metastasis. The institution's routine follow-up schedule includes appointments every 1-2 months in the first year, 2-3 months in the second year, 4-6 months from the third to fifth year and annually beyond. CT scan and/or MRI were performed between 8-12 weeks after treatment conclusion.

Treatment modality was chosen after case discussion in a Multidisciplinary Head and Neck Tumour board, based on patient age, comorbidities, tumour extension and stage, and in accordance with the patient's informed decision. The main end point of this study was overall survival (OS). Follow-up time was calculated from the date of primary treatment to either death, with or without disease, or last follow-up visit.

Statistical analyses were conducted using the Statistical Package for Social Sciences software, version 19.0 for Windows (SPSS, Chicago, Illinois, USA). Differences in proportions between groups were tested with Fisher's exact test and Chi-square test. Actuarial OS was estimated using Kaplan-Meier method and statistical significance was determined by log-rank test. Univariate analysis to define independent prognostic factors for OS was performed by Cox regression. All statistical tests were 2-sided, and significance was defined as $p<0.05$.

RESULTS

We identified 27 cases, which were classified as SNEC in 10 patients (37.0%), followed by ONB in 9 patients (33.3%) and SNUC in 8 patients (29.7%). Mean age at presentation was 52.0±16.8 years and the majority of patients were male (77.8%). Patients with ONB were mostly females, compared to SNEC and SNUC types (p=0.011) (Table 1).

Table 1: Patients characteristics compared by different histologic subtypes.

Variable	All (n=27)	SNEC (n=10)	ONB (n=9)	SNUC (n=8)	P value
Age (mean, SD)	52.0 (16.8)	54.0 (12.0)	47.6 (21.8)	54.8 (16.6)	0.695
Gender (male, %)	21 (77.8)	10 (100)	4 (44.4)	7 (87.5)	0.011
Symptoms (N, %)					
Nasal obstruction	15 (71.4)	4 (57.1)	6 (100)	5 (62.5)	0.182
Recurrent epistaxis	12 (57.1)	5 (71.4)	4 (66.7)	3 (37.5)	0.356
Rhinorrhea	7 (33.3)	3 (42.9)	2 (33.3)	2 (25.0)	0.765
Anosmia	5 (23.8)	2 (28.6)	2 (33.3)	1 (12.5)	0.621
Kadish classification (N, %)					
B	7 (25.9)	2 (20.0)	2 (22.2)	3 (37.5)	0.730
C	15 (55.6)	5 (50.0)	6 (66.7)	4 (50.0)	
D	5 (18.5)	3 (30.0)	1 (11.1)	1 (12.5)	
Dulguerov T stage (N, %)					
1	1 (3.7)	0	1 (11.1)	0	0.791
2	8 (29.6)	3 (30.0)	2 (22.2)	3 (37.5)	
3	8 (29.6)	3 (30.0)	2 (22.2)	3 (37.5)	
4	10 (37.0)	4 (40.0)	4 (44.4)	2 (25.0)	
TNM stage (N, %)					
II	4 (14.8)	0	2 (22.2)	2 (25.0)	0.422

Continued.

Variable	All (n=27)	SNEC (n=10)	ONB (n=9)	SNUC (n=8)	P value
III	3 (11.1)	1 (10.0)	1 (11.1)	1 (12.5)	
IVA	13 (48.1)	6 (60.0)	3 (33.3)	4 (50.0)	
IVB	5 (18.5)	1 (10.0)	3 (33.3)	1 (12.5)	
IVC	2 (7.4)	2 (20.0)	0	0	

Abbreviations: SD, standard deviation; SNEC, sinonasal neuroendocrine carcinoma; ONB, olfactory neuroblastoma; SNUC, sinonasal undifferentiated carcinoma.

Table 2: SNEC clinical characteristics and treatment outcomes.

Age (years)	Sex	Kadish stage	Dulguerov/ UCLA stage	TNM stage	Treatment	Recurrence	Recurrence treatment	Status	F/U (months)
55	Male	C	T3N0M0	IVA	OSR + RT	Local	Supportive	DOD	6
45	Male	B	T2N0M0	IVA	EEA + chemo/RT	-	-	NED	16
58	Male	B	T2N0M0	III	EEA + chemo/RT	Distant	RT	DOD	17
47	Male	C	T4N0M0	IVA	OSR + chemo/RT	Distant	Supportive	DOD	13
55	Male	D	T2N0M1	IVC	Palliative chemo	-	-	DOD	2
79	Male	C	T3N0M0	IVA	Palliative chemo/RT	-	-	DOD	11
38	Male	D	T4N1M0	IVB	Chemo/RT	Regional, distant	ND + Chemo	DOD	45
67	Male	C	T4N0M0	IVA	OSR + chemo/RT	-	-	DOD	4
52	Male	D	T3N0M1	IVC	Palliative chemo	-	-	DOD	6
44	Male	C	T4N0M0	IVA	OSR + chemo	-	-	DOC	2

Abbreviations: AJCC, American Joint Committee on Cancer; chemo, chemotherapy; DOC, dead of other causes; DOD, dead of disease; EEA, endoscopic endonasal approach resection; F/U, follow-up from the last day of treatment in months; LR, lateral rhinotomy; ND, neck dissection; NED, no evidence of disease; OSR, open surgical resection; RT, radiotherapy; SNEC, sinonasal neuroendocrine carcinoma; TNM, TNM classification of malignant tumours; UCLA, University of California, Los Angeles.

Table 3: ONB clinical characteristics and treatment outcomes.

Age (years)	Sex	Hyam's Grade	Kadish stage	Dulguerov/ UCLA stage	TNM stage	Treatment	Recurrence	Recurrence treatment	Status	F/U (months)
52	Male	IV	B	T2N0M0	II	EEA + RT	Local	OSR + Chemo	DOD	10
62	Male	IV	C	T4N0M0	IVA	Palliative chemo/RT			AWD	18
27	Female	II	D	T4N1M0	IVB	Chemo/RT			NED	28
50	Female	I	B	T1N0M0	II	EEA			NED	31
65	Male	II	C	T2N0M0	III	OSR			DOC	28
74	Male	Uncertain	C	T3N0M0	IVA	OSR	Local	OSR + RT	DOC	94
54	Male	III	C	T3N0M0	IVA	OSR	Local	Supportive	DOD	20
20	Female	II	C	T4N0M0	IVB	Chemo/RT			NED	9
64	Female	III	C	T4N0M0	IVB	OSR + RT	Local, distant	RT	DOD	106

Abbreviations: AJCC, American Joint Committee on Cancer; AWD, alive with disease; chemo, chemotherapy; DOC, dead of other causes; DOD, dead of disease; EEA, endoscopic endonasal approach resection; F/U, follow-up from the last day of treatment in months; NED, no evidence of disease; ONB, olfactory neuroblastoma; OSR, open surgical resection; RT, radiotherapy; TNM, TNM classification of malignant tumours; UCLA, University of California, Los Angeles.

Most frequently reported symptoms included nasal obstruction (71.4%), recurrent epistaxis (57.1%), rhinorrhea (33.3%) and anosmia (23.8%). Presenting symptoms preceded primary diagnosis by a median of 3 months (interquartile range 2-5 months). It was not possible to reliably ascertain primary tumour location since the majority of patients presented with advanced disease. There were no significant differences in the remaining clinical variables between the different subtypes (Table 1).

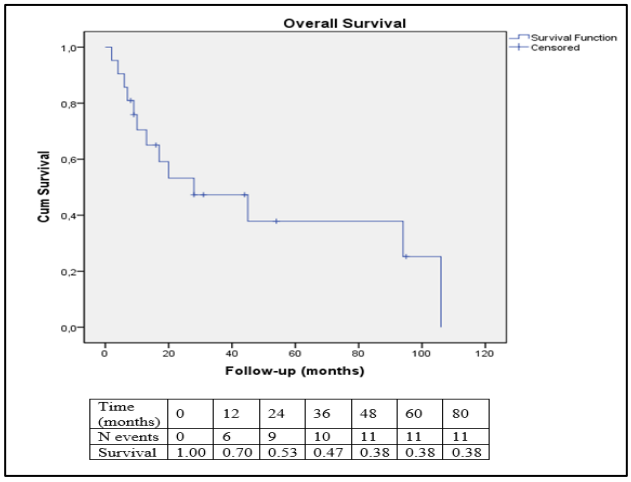
Most patients, in all different histological subtypes, presented with advanced disease. Twenty (74.1%) patients were classified as stage C or D, according to the modified Kadish stage, Dulguerov/UCLA stage T3 or T4 was observed in 18 (66.0%) patients and TNM stage IV tumour in 20 (74.0%). There were no differences between the histological subtypes, regarding the different staging systems (Table 1). Tumours affected the orbita in eleven (40.7%) cases, while dural and/or cerebral invasion was observed in twelve (44.4%) patients. At the time of diagnosis, cervical node metastases were observed just in one patient in each tumour subtype (n=3; 11.1%). Two (7.4%) patients with SNEC presented distant metastases in bone or liver. Tumour characteristics are summarized in Table 2, 3 and 4, respectively.

Table 4: SNUC clinical characteristics and treatment outcomes.

Age (years)	Sex	Kadish stage	Dulguerov/ UCLA stage	TNM stage	Treatment	Recurrence	Recurrence treatment	Status	F/U (months)
61	Male	B	T2N0M0	III	EEA + chemo/RT			NED	8
37	Male	B	T2N0M0	II	EEA + RT			NED	44
41	Male	B	T2N0M0	II	EEA + RT			NED	54
61	Male	D	T3N1M0	IVA	Supportive			DOD	2
57	Female	C	T4N0M0	IVA	OSR	Local, distant	Chemo	DOD	9
44	Male	C	T3N0M0	IVA	OSR + chemo/RT			NED	95
89	Male	C	T4N0M0	IVB	Supportive			DOD	4
48	Male	C	T3N0M0	IVA	OSR + chemo/RT	Local, distant	Chemo	DOD	7

Abbreviations: AJCC, American Joint Committee on Cancer; chemo, chemotherapy; DOD, dead of disease; EEA, endoscopic endonasal approach resection; F/U, follow-up from the last day of treatment in months; NED, no evidence of disease; OSR, open surgical resection; RT, radiotherapy; TNM, TNM classification of malignant tumours; UCLA, University of California, Los Angeles

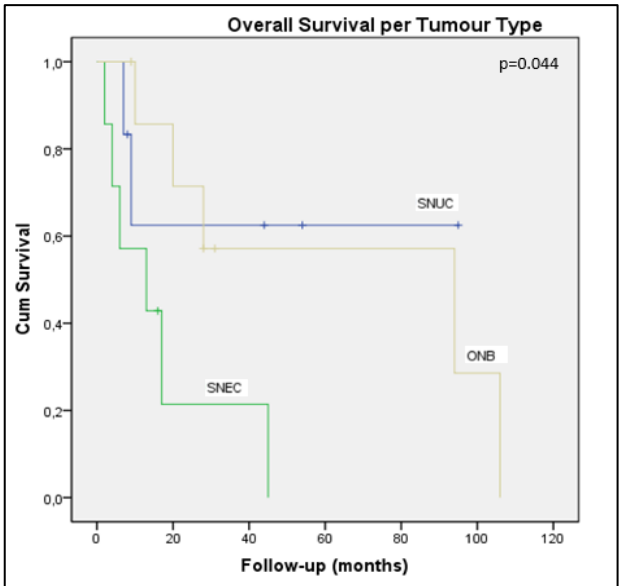
Treatment with curative intent was decided in 21 (77.8%) patients, which consisted of multimodality therapy in most cases (n=16; 76.2%). Overall, surgery was the most frequently selected modality, in 18 (85.7%) patients, followed by radiotherapy in 15 (71.4%) and chemotherapy in eleven (52.4%). Trimodality therapy was selected for seven (33.3%) patients, the association of surgery with radiotherapy in five (23.8%) and combination of radiotherapy and chemotherapy in three (14.3%). Surgery was performed as a single treatment in five patients (23.8%) and one patient was treated with a combination of surgery and chemotherapy (4.8%). Six (22.2%) patients received palliative treatment.



Time (months)	0	12	24	36	48	60	80
N events	0	6	9	10	11	11	11
Survival	1.00	0.70	0.53	0.47	0.38	0.38	0.38

Figure 1: Overall survival Kaplan Meier curve for 21 patients with sinonasal tumours, after treatment of choice.

Mean OS of all tumour groups was 49 months and 1-year, 3-years and 5-years OS rates were 70.5%, 47.3% and 37.8%, respectively (Figure 1). The univariate analysis for OS is presented in Table 5. Longer time intervals before diagnosis negatively impacted OS (odds ratio (OR) 1.546; p=0.009). Considering different tumour subtypes, patients with SNEC had worse overall survival (p=0.044) (Figure 2).



Tumour type / Time (months)		0	12	24	36	48	60	80
ONB	N events	0	1	2	3	3	3	3
	Survival	1.00	0.86	0.71	0.57	0.57	0.57	0.57
SNUC	N events	0	2	2	2	2	2	2
	Survival	1.00	0.62	0.62	0.62	0.62	0.62	0.62
SNEC	N events	0	3	5	5	6	6	6
	Survival	1.00	0.57	0.21	0.21	0	0	0

Figure 2: Overall survival Kaplan Meier curve of sinonasal cancers according to tumour type.

Surgical treatment, using either an open or endoscopic approach, was used in accordance with tumour extent, selecting endoscopic approaches for more localized tumours. This approach improved overall survival in SNEC cases (p=0.049). Patients with SNUC selected for treatment with surgery and adjuvant radiation therapy had improved overall survival, compared with patients treated with surgery and chemotherapy or surgery alone (p=0.027).

A total of 7 (33.3%) patients presented local recurrence, 1 (4.8%) patient had nodal recurrence and 6 (28.6%) showed distant metastases during a mean follow-up period of 26 months.

Table 5: Univariate analysis of factors influencing the overall survival of sinonasal tumours.

Factor	OR (95% CI)	P value
Age	1.013 (0.975-1.052)	0.498
Gender (male as reference)	0.320 (0.068-1.505)	0.149
Symptoms duration (months)	1.546 (1.115-2.142)	0.009
Tumour type		
ONB	1 (reference)	
SNUC	0.837 (0.152-4.598)	0.837
SNEC	3.961 (1.023-15.334)	0.044
SNUC Treatment (decoupled, no as reference)		
endoscopic surgery	0.015 (0-1327.440)	0.471
surgery and radiotherapy	0.408 (0.025-6.621)	0.027
SNEC Treatment (decoupled, no as reference)		
Endoscopic surgery	0.014 (0-52.476)	0.049
Surgery and radiotherapy	1.607 (0.168-15.373)	0.681
ONB Treatment (decoupled, no as reference)		
Endoscopic surgery	1.943 (0.174-21.685)	0.589
Surgery and radiotherapy	0.691 (0.068-7.071)	0.755

Abbreviations: OR, odds ratio; CI, confidence interval; ONB, olfactory neuroblastoma; SNEC, sinonasal neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma. Reported odds ratios for patients dying of disease.

DISCUSSION

A wide variety of benign and malignant tumours are located in the sinonasal tract, due to the unique diversity of histologic tissues present in this region. Notwithstanding, these tumours are infrequent comprising less than 1% of all neoplasms with an estimated incidence of approximately 8 cases per million.[12]

The majority of these tumours are squamous cell carcinomas and their variants (55%), followed by nonepithelial subtypes (20%), glandular (15%), undifferentiated (7%) and miscellaneous tumours (3%).[4] Among the malignancies of the sinonasal tract, olfactory neuroblastoma, sinonasal neuroendocrine carcinoma and sinonasal undifferentiated carcinoma form a specific group of tumours with neuroendocrine differentiation that represent around 5% of all sinonasal malignancies.[13]

The definition of neuroendocrine neoplasms is still controversial, since some neuroendocrine markers are nonspecific and their expression may be present in non-neuroendocrine malignancies.[2] This group of tumours share similar clinical and radiological findings, and their histopathology often present poorly differentiated morphology with overlapping features, which leads to increased diagnostic difficulties, especially in small biopsy specimens.

Patients with neuroendocrine differentiation sinonasal tumours typically present in the fifth decade of life.[14,15] With the exception of ONB which is reported to affect both sexes equally, remaining tumour types are reported to have a slight male predominance.[4,14,16] These tumours most commonly affect the nasal cavity and ethmoid sinuses and patients often report nasal obstruction, epistaxis and nasal drainage, as described in this study.[17,18] These complaints overlap those of rhinosinusitis and other benign sinonasal diseases, which frequently delays diagnosis and appropriate treatment. Changes in visual acuity or diplopia, facial pain and swelling, and facial numbness are uncommon.[17] No geographic, environmental or lifestyle risk factors are associated with these tumours.[19]

The initial diagnostic work-up should include a thorough physical (including neurological) examination and a combination of sinus CT and MRI is usually required to assess the degree of local invasion. CT of the neck is also paramount to evaluate for nodal involvement. Additional imaging like chest CT or positron emission tomography (PET-CT) to screen for nodal or distant metastases may be performed, although this practice is not uniform.[20,21]

Histopathologic assessment is essential to diagnosis, since sinonasal malignancies with neuroendocrine features cannot be distinguished only based on clinical presentation or radiological studies. Tumours with neuroendocrine differentiation show common ultrastructural and immunohistochemical features, including dense core secretory granules, staining for chromogranin, synaptophysin and other markers.[18] Accurate diagnosis has profound impact on therapy selection and outcome, but can be particularly challenging between poorly differentiated variants of ONBs, SNECs or SNUCs, frequently requiring expert review.[22] Detailed description of typical histopathologic findings is outside the scope of this review and can be found elsewhere.[23-25]

Once the diagnosis is established, tumours may be stratified by histological and clinical staging systems. Patients are usually staged according to the American Joint Committee on Cancer (AJCC) staging system for paranasal sinus tumours. However, other systems originally developed to classify ONB tumours, as the Kadish staging system, later modified by Morita, and the Dulguerov classification systems, have been used by some authors to describe the extent of either SNUC or SNEC.[8-10,26-28] Hyams histologic grading system has been used to predict disease-free and overall survival in patients with ONB.[11,15] In this series no staging system was related with overall survival.

Most patients present with locally advanced disease, including invasion of the skull base, orbit or brain, which

seems to predict poor outcomes.[14,17,29] Cervical lymph node metastasis at presentation are found in 10-30% of patients with SNUC, 18% in SNEC and between 5-8% in ONB; distant metastases are uncommon initial findings.[4,17,27,30] In our series, 20 (74%) patients presented in stage IV disease, 3 (11.1%) had regional disease and 2 (7.4%) had distant metastases at presentation.

Treatment outcomes and survival rates have been shown to differ significantly between the different subtypes, as has been shown in this study, leading to the distinction between ONB and non-ONB subtypes, namely SNUC and SNEC.[5] Nevertheless, treatment multimodalities combining surgery, radiotherapy and/or chemotherapy has been selected for the majority of patients (n=16; 76.2%) with tumours with neuroendocrine differentiation treated in our institution, as recommended in the literature.[7,17,28]

For olfactory neuroblastoma, traditionally considered to have a better prognosis and survival compared with the other malignancies, a well-defined treatment strategy has been defined.[31] Except for very early and limited disease, the standard of care involves multimodality treatment with surgery followed by radiotherapy, with reported 5-year disease-free survival rates of 45%.[32,33] Surgical resection of these tumours often involves an open craniofacial approach; however, recent advances have led to an increased use of endoscopic resection techniques in lower-stage ONBs (Kadish A or B) with similar outcomes.[34-36] Although chemotherapy as primary option for ONBs has shown inferior outcomes, the role of neoadjuvant therapy in advanced disease is still debated.[37] The impact of elective neck dissection or nodal irradiation in patients with a clinically-negative neck is also controversial; however neck dissection should be performed when nodal disease is present.[33]

Since sinonasal neuroendocrine carcinoma (SNEC) is a rare neoplasia with less than 300 cases reported, uniform management protocols are lacking and treatment outcomes remain both variable and poor.[7,17] In a recent meta-analysis, SNEC differentiation grade was the most important predictor of survival, which can be used to guide the management strategy.[14] Surgery is considered the cornerstone of every management strategy, being associated with an improved overall survival in this series, as shown in our study, and can be used alone in resectable well-differentiated tumours.[14] Due to limitations in the existing data, the role of neoadjuvant or adjuvant treatments is still under debate.[14,28,38]

Sinonasal undifferentiated carcinoma (SNUC) is an aggressive malignancy and original reports described poor survival outcomes.[39] Therefore, multimodality therapy is generally used either with surgery followed by adjuvant radiotherapy/chemoradiation, or definitive chemoradiation with or without neoadjuvant chemotherapy. The preferred management approach varies between institutions, with several protocols reported in the literature.[27,30,40,41] Both surgery and radiotherapy were associated with significant better outcome among 459 patients with SNUC, included in a meta-analysis of existing studies.[14] In our institution, standard treatment modality involved surgical resection followed by chemoradiation or radiotherapy. This approach, reported by Tanzler et al, was associated with better local control, reduced risk of long-term complications and improved overall survival.[30] However, the use of primary surgery as initial treatment may be conditioned due to unresectable local disease at presentation. The role of non-surgical treatment has been supported by some authors, reporting improved survival rates.[5,42,43] Recently, the use of neoadjuvant chemotherapy was associated with significant improvement of recurrence-free survival and has been advocated as a promising approach.[44]

The prognosis of these tumours is limited by the high rates of locoregional recurrence and distant metastases. Particularly, SNUC shows a 10-30% rate of locoregional recurrence, and distant metastases, often involving the lungs and bone, occur in 10-30% of cases.[5,27,30,45] SNECs have a poor prognosis due to frequent local recurrences, in around 45% of cases and distant metastases in 35% of patients, mainly in the lungs, liver, bone marrow and vertebrae.[4,13] The results of long-term follow-up in ONB patients also show an incidence of overall recurrence and distant metastases of 46% and 15%, respectively.[31] These recurrences have been reported beyond ten years of follow-up, warranting these patients long-term surveillance.[32,46]

CONCLUSION

Olfactory neuroblastoma, sinonasal neuroendocrine tumours and sinonasal undifferentiated tumours are rare and heterogeneous sinonasal neoplasms. In this study, patients presented frequently in the fifth decade of life with non-specific complaints of nasal obstruction, epistaxis and nasal drainage. These tumours originate in the nasal cavity and ethmoid sinuses, but, at diagnosis, 74% of patients had locally advanced disease and cervical lymph node metastasis were found in 11%.

These tumours represent a spectrum of neuroendocrine histologic characteristics, therefore histopathological differentiation is essential to define appropriate management strategies. Treatment outcomes and survival rates differ significantly between tumour groups, with SNEC tumours presenting the worse overall survival. Regarding treatment selection, treatment multimodalities are recommended in the literature and were selected in 76% of patients.

Although several advances have been reported in the last decades, there is still no consensus on an ideal treatment strategy, which reinforces the need for long-term multicenter clinical trials to improve survival outcomes of these rare neoplasms.

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