ACTA OTORHINOLARYNGOLOGICA ITALICA 2022;42:545-553; doi: 10.14639/0392-100X-N2087

Rhinology

Biphenotypic sinonasal sarcoma: European multicentre case-series and systematic literature review

Sarcoma bifenotipico nasosinusale: case-series europeo multicentrico e revisione sistematica della letteratura

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SUMMARY

Objective. Biphenotypic sinonasal sarcoma (BSNS) is a rare low-grade cancer that was included from the 4th edition of WHO classification of head and neck tumours. The purpose of this study is to analyse clinical behaviour, pattern of recurrences and survival outcomes of this neoplasm.

Methods. Retrospective review of patients affected by BSNS who were treated via an endoscopic-assisted approach in 6 European tertiary-care referral hospitals. Cases of BSNS described in literature since 2012 to date were fully reviewed, according to PRISMA guidelines.

Results. A total of 15 patients were included. Seven patients were treated via an endoscopic endonasal approach, 4 with endoscopic transnasal craniectomy, and 4 via a cranio-endoscopic approach. Adjuvant treatment was delivered in 2 cases. After a mean follow-up of 27.3 months, systemic metastasis was observed in 1 case; the 5-year overall survival and disease-free survival rates were 100% and 80 ± 17.9%, respectively.

Conclusions. BSNS is a locally aggressive tumour with a low recurrence rate and encouraging survival outcomes if properly treated with surgical resection and free margins followed by adjuvant radiotherapy for selected cases. Endoscopic-assisted surgery is safe and effective as an upfront treatment within a multidisciplinary care protocol.

KEY WORDS: anterior skull base, biphenotypic sarcoma, endoscopic endonasal surgery, low-grade sarcoma, sinonasal cancer

RIASSUNTO

Obiettivo. *Il sarcoma nasosinusale bifenotipico (SNSB) è un raro tumore a basso grado, incluso a partire dalla 4° edizione WHO dei tumori testa-collo. L'obiettivo di questo studio è analizzare i tassi di sopravvivenza e i pattern di recidiva di questa neoplasia.*

Metodi. *Revisione retrospettiva dei pazienti affetti da SNSB, trattati mediante approccio*

Received: May 3, 2022
Accepted: October 3, 2022

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How to cite this article: Turri-Zanoni M, Dalfino G, Lechner M, et al. Biphenotypic sinonasal sarcoma: European multicentre case-series and systematic literature review. Acta Otorhinolaryngol Ital 2022;42:545-553. https://doi.org/10.14639/0392-100X-N2087

endoscopico in 6 centri di riferimento europei. È stata condotta inoltre una revisione sistematica della letteratura dal 2012 ad oggi, secondo le linee guida PRISMA.
Risultati. *Sono stati inclusi 15 pazienti (approccio endoscopico endonasale in 7 casi, craniectomia endoscopica transnasale in 4 casi, approccio combinato transcranico in 4 casi). In 2 casi è stata somministrata radioterapia adiuvante. Dopo un periodo di follow-up medio di 27,3 mesi, è stato riscontrato un caso di metastasi a distanza; i tassi di 5-year Overall Survival e Disease-Free Survival erano 100% e 80 ± 17,9%, rispettivamente.*
Conclusioni. *Il SNSB è un tumore localmente aggressivo con un basso tasso di recidiva e tassi di sopravvivenza incoraggianti se trattato con asportazione chirurgica radicale con radioterapia adiuvante per casi selezionati. La chirurgia endoscopica ha dimostrato di essere sicura ed efficace come trattamento iniziale all'interno di un protocollo di cura multidisciplinare.*

PAROLE CHIAVE: *base cranica anteriore, sarcoma nasosinusale bifenotipico, chirurgia endoscopica endonasale, sarcoma basso grado, tumori maligni nasosinusali*

Introduction

Biphenotypic sinonasal sarcoma (BSNS) is a rare and recently introduced low-grade tumour that was initially described by Lewis et al. in 2012 as "low-grade sinonasal sarcoma with neural and myogenic differentiation," which remains a synonym for BSNS [1].

These cancers were first included in the fourth edition of WHO classification of head and neck tumours in 2017. The recognition of BSNS as a distinct neoplasm helps with the categorisation of a heterogeneous group of tumours that were previously classified together [2].

A variety of sinonasal neoformations, including cellular schwannoma, glomangiopericytoma, fibrosarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumour (MPNST), synovial sarcoma, solitary fibrous tumours, and fibromatosis may pathologically mimic BSNS. However, the diagnosis of BSNS based on pathological features alone is not possible due to the potential for pathological overlap. Therefore, immunophenotyping and immunofluorescence are essential for diagnosis [3]. Being rare and recently introduced, there is no available data, on survival outcomes and standard of care. The purpose of this study is to review a multicentre experience on patients treated at seven European tertiary-care referral centres, to report preliminary data on clinical behaviour, pattern of recurrences and survival outcomes of this rare clinical entity. Additionally, currently available protocols of multidisciplinary management were investigated, and the recent pertinent literature was reviewed.

Study design

Patients affected by BSNS, who were treated via endoscopic-assisted approaches between January 2013 and January 2021 in seven European tertiary-care referral University hospitals, were enrolled in this study. Inclusion criteria were as follows: (1) neoplasm treated with curative intent; (2) histology-proven BSNS; (3) at least 12 months of follow-up for surviving patients.

Pre-operative work-up

All patients underwent complete physical examination, nasal endoscopy, routine blood counts, biopsy with histological examination, neck ultrasound and total body contrast-enhanced CT scan. The local extension of disease was estimated using multiplanar computed tomography (CT) scan and contrast-enhanced magnetic resonance imaging (MRI) in all cases. All neoplasms were classified according to the WHO histologic classification (4th edition). BSNSs were staged using the AJCC cancer staging manual (8th edition).

Treatment

All patients were treated using an endoscopic-assisted approach tailored to the extension of disease and ranging from an exclusive endonasal resection (EER) to expanded resection including the ethmoidal roof and dura of the anterior skull base (ERTC, endoscopic resection with transnasal craniectomy). Transnasal skull base reconstruction was performed according to a multilayer technique using autologous materials such as fascia lata or the iliotibial tract. In cases of massive involvement of the dura over the orbital roof or brain parenchyma infiltration, the endoscopic endonasal technique was combined with an external transcranial approach (CER, cranio-endoscopic resection). No elective neck treatment was performed due to the low-grade of the neoplasm and the lack of evidence on this protocol. Adjuvant irradiation of the surgical field was administered in case of close or positive surgical margins or involvement of non-resectable areas (cavernous sinus, orbital apex).

Pathological diagnosis

Histopathological diagnosis was performed uniformly with centralised review and only those cases which had the following features were included in the present study: typical histopathological appearance, immunohistochemical analysis and fluorescence in situ hybridisation analysis. Haematoxylin-eosin staining showed a submucosal spindle cell proliferation with "herringbone" fascicular pattern of growth, uniform nuclei, lacking significant pleomorphism

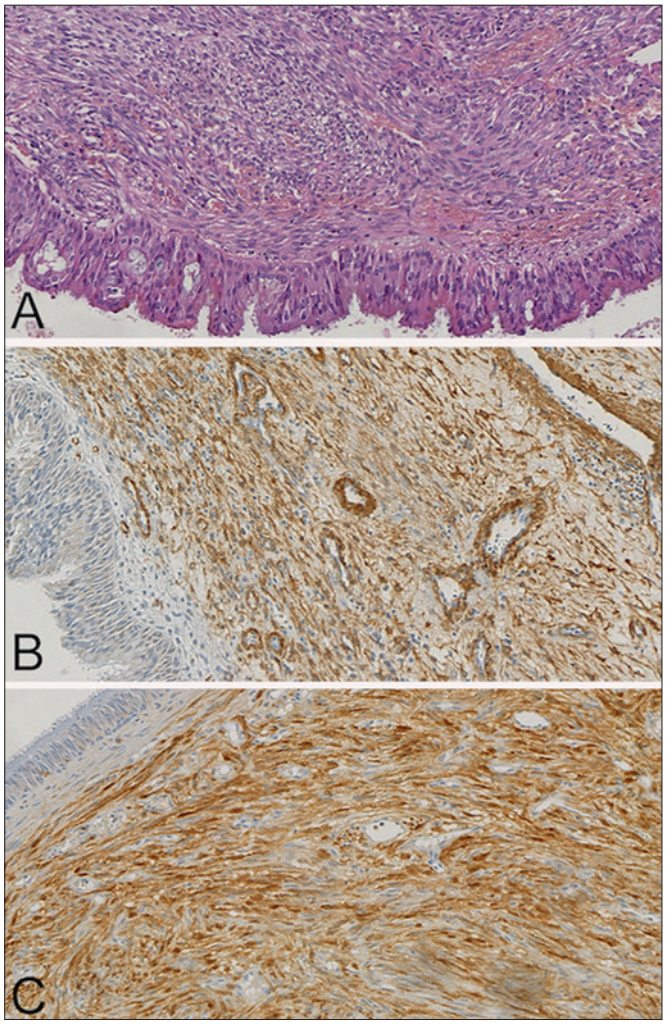

Figure 1. (**A**) Haematoxylin-eosin staining showing submucosal spindle cell proliferation with fascicular pattern of growth (20x); (**B**) Smooth muscle actin (SMA) staining showing concomitant expression of actin (20x); (**C**) S100 protein is positive with diffuse immunoreactivity (20x).

and increased mitotic activity. Immunohistochemical positivity for S100 protein (polyclonal AB) and smooth muscle actin (SMA, clone 1A4) was used to confirm the diagnosis (Fig. 1). Furthermore, fluorescence in situ hybridisation (FISH) analysis was performed to reveal the presence of PAX3-MAML3 fusion protein through t(2;4) translocation (q35; q31.1).

Follow-up

All patients were followed in accordance with a specific protocol which included endoscopic nasal examination, contrast-enhanced MRI of the head, neck US, and total body CT scan at scheduled intervals, as previously described [4]. Follow-up data were available for all patients.

Statistical methods

The main endpoints analysed were overall survival (OS) and disease-free survival (DFS). OS was defined as the time from surgical treatment to death from any cause. DFS was defined as the time from surgical treatment to the first observation of recurrence at any site or death from any cause. The Kaplan-Meier method was used to estimate the probability of OS and DFS. All analyses were performed using IBM-SPSS statistical software, version 1.0.0.1347.

Literature review

Currently available clinical studies were selected through searching on online English-language electronic databases (Pubmed, Scopus, Web of Science, and Cochraine Library) from January 2012 to January 2021, under Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The Population, Intervention, Comparator, Outcome, and Study (PICOS) design was utilised for this review. The keywords and search terms included the following: biphenotypic sinonasal sarcoma OR low-grade sinonasal sarcoma with neural and myogenic differentiation OR low-grade sinonasal sarcoma. In addition, we manually scanned the reference lists of the articles included to identify the other potential studies. The articles included in this review of the literature met the following inclusion criteria: confirmed histopathological diagnosis with immunohistochemical and molecular studies; available data on clinical presentation, treatments, follow-up period and oncological status.

Case-series

A total of 15 patients, aged between 34 to 75 years (mean, 54 years) were analysed. The female gender was more often affected, with a male to female ratio of 1:4 (Tab. I). The clinical symptoms reported by patients were unilateral nasal airway obstruction in 14 cases, unilateral epistaxis in 9 cases, olfactory disfunction in 6 cases, and facial pain in 3 cases. Only one patient presented with diplopia and ocular motility impairment.

Only one patient (1/15, 6.7%) has been formerly treated via trans-facial surgery 10 years earlier in Peru for a sinonasal sarcoma not otherwise specified (NOS) and this was also the diagnosis on the pre-operative biopsy when the patient was sent to our tertiary care referral centre. However, the histology slides relating to both the previous surgical procedure and the pre-operative biopsy were examined by our expert pathologists who were able to confirm a diagnosis of BSNS.

The histological result of the preoperative biopsy was in line with the final diagnosis of BSNS in six cases (6/15,

Table I. Clinico-pathological features of the study population.

		BSNS
Gender	Male	3/15 (20%)
	Female	12/15 (80%)
Age	Range	34-75 years
	Mean	54 years
Previous treatments	Yes	1/15 (6.7%)
	No	14/15 (93.3%)
Site of origin	Ethmoid	13/15 (86.7%)
	Frontal sinus	2/15 (13.3%)
Surgery	ER	7/15 (46.6%)
	ERTC	4/15 (26.7%)
	CER	4/15 (26.7%)
Surgical margins	R0	13/15 (86.7%)
	R1	2/15 (13.3%)
pT classification	T2	1/15 (6.7%)
	T3	2/15 (13.3%)
	T4a	9/15 (66.7%)
	T4b	3/15 (20%)
Adjuvant therapy	None	13/15 (86.7%)
	IMRT	2/15 (13.3%)
Recurrence		1/15 (6.7%)
Follow-up	Range	6-80 months
	Mean	27.3 months
	Median	18 months
Status	NED	13/15 (86.7%)
	AWD	2/15 (13.3%)
OS	3-year	100%
	5-year	100%
DFS	3-year	80%
	5-year	80%

BSNS: biphenotypic sinonasal sarcoma; ER: endoscopic resection; ERTC: endoscopic resection with transnasal craniectomy; CER: cranio-endoscopic resection; R0: free margin resection; R1: microscopic residual disease; IMRT: intensity modulated radiotherapy; IMPT: intensity modulated proton therapy; NED: no evidence of disease; AWD: alive with disease; OS: overall survival; DFS: disease-free survival.

40%), while a misleading diagnosis was found on pre-operative biopsy in other cases: glomangiopericytoma (2/15, 13.3%), malignant peripheral nerve sheath tumour (MPNST) (1/15, 6.7%), NOS sarcoma (1/15, 6.7%), neurofibroma (1/15, 6.7%), synovial sarcoma (2/15, 13.3%) and inverted papilloma (1/15, 6.7%). Of note, in one case (1/15, 6.7%) two preoperative biopsies of the sinonasal lesion were performed, but the histological result was negative for cancer and compatible with inflammatory tissue in both cases. Pre-operative neck ultrasound and contrast-enhanced total body CT scan ruled out the presence of satellite lymphadenopathies (N0) and distant metastasis (M0) in any patient.

In our sample, seven patients were treated with EER (7/15, 46.6%, Fig. 2), four patients were treated with ERTC (4/15, 26.7%, Fig. 3) and four patients with CER (4/15, 26.7%). Free-margin tumour excision was obtained in all cases except two (2/15, 13.3%), where the resection margins were microscopically infiltrated (R1). The epicentre of the tumour was most frequently the ethmoid sinus (13/15, 86.7%), followed by the frontal sinus (3/15, 20%). Based on the final histology report, most cases were classified as locally advanced tumour (pT4, 12/15 cases, 80%, Tab. I). Adjuvant irradiation was performed in cases (2/15, 13.3%) with positive surgical margins using intensity modulated radiation therapy (IMRT, 62 Gy).

During follow-up, only one patient (1/15, 6.7%) experienced recurrence. This patient's tumour was initially resected with negative surgical margins, but she developed local recurrence at the level of anterior skull base and orbit after 35 months of follow-up. The patient was treated via CER with curative intent obtaining a free margin resection of the local recurrence. After 47 months of follow-up, she developed a second local recurrence involving the orbital apex and cavernous sinus and was submitted to intensity modulated proton therapy (IMPT, 70 Gy). Surprisingly, lung metastasis was observed after 56 months of follow-up, which was treated with lobectomy. The final histology report on the lung confirmed the diagnosis of BSNS, and confirmed by both immunohistochemical and FISH analyses. The patient is currently alive with stable persistence of disease (cavernous sinus) after 80 months. After a mean follow up of 27.3 months (median, 18 months; range, 6-80 months), 13/15 (86.7%) patients are alive without evidence of disease. The 5-year OS rate was 100%, since no deaths occurred during follow-up. Conversely, the 5-year DFS was 80 ± 17.9% (Fig. 4).

Literature review

A total of 19 clinical studies were identified through searches on online electronic databases, of which 16 were selected (Fig. 5). A total of 122 cases were described in the selected studies (Tab. II). However, the large majority of studies were focused on histological diagnosis and, therefore, clinical data (age, stage of disease, treatment strategy, follow-up, recurrence) were not fully available. Stage of disease was available for 7/122 cases in the literature and most were classified as locally advanced tumour (T4a-T4b). Among cases with reported surgical technique, 29.4% (5/17) underwent EER, 17.65% (3/17) ERTC and 17.65% (3/17) lateral rhinotomy. The most widely used surgical technique was CER in 35.3% (6/17) of cases.

Adjuvant treatments were performed in 17/122 (20.75%) of cases. In 13 cases (76.5%) adjuvant radiotherapy was

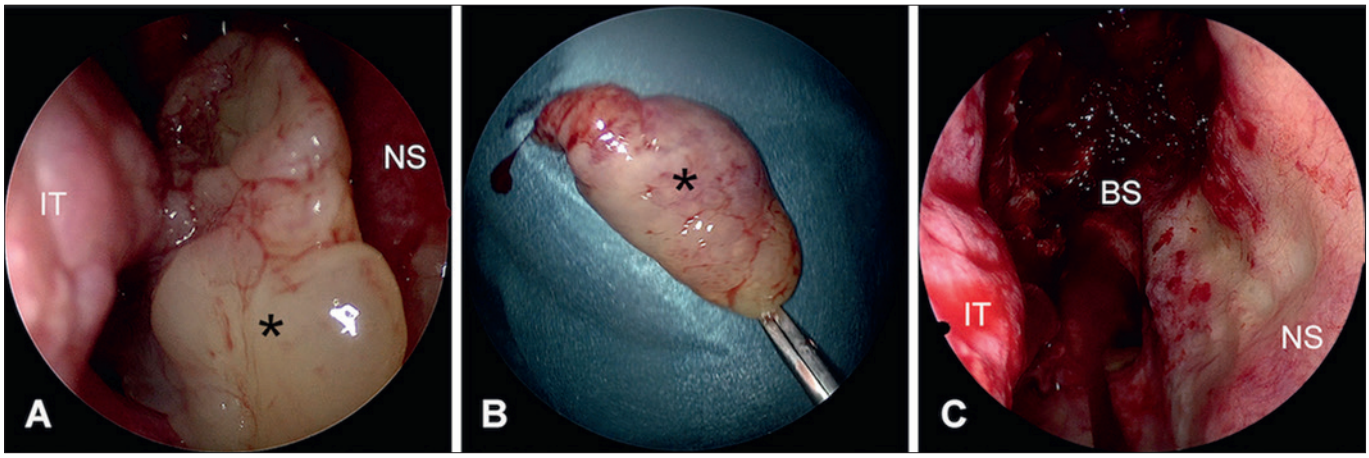

Figure 2. Endoscopic appearance of BSNS in right nasal fossa (**A**). Tumour mass after removal (**B**). Right nasal cavity after endoscopic resection (**C**). BS: basisphenoid; IT: inferior turbinate; NS: nasal septum; black asterisk: tumour.

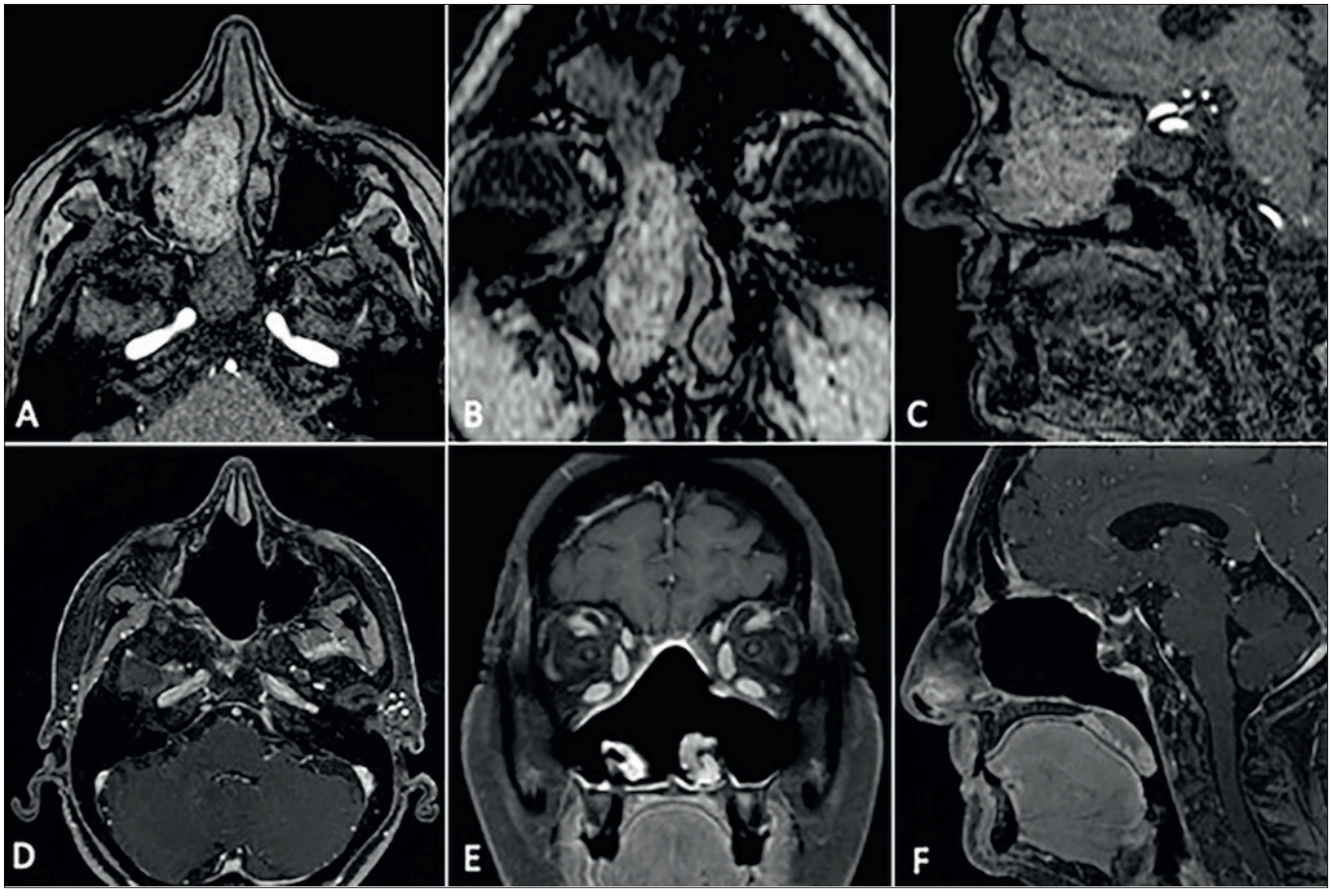

Figure 3. Preoperative MR angiography in axial (**A**), coronal (**B**) and sagittal (**C**) views revealed a mass arising from the right ethmoid. At 45 months, postoperative MRI in axial (**D**), coronal (**E**) and sagittal (**F**) views revealed no recurrence of disease.

administered, while the remaining four (23.5%) received chemo-radiotherapy. Follow-up information was provided for 73/122 cases. In detail, the mean follow-up period was 54.6 months (range 2-336 months). Recurrences were ob-

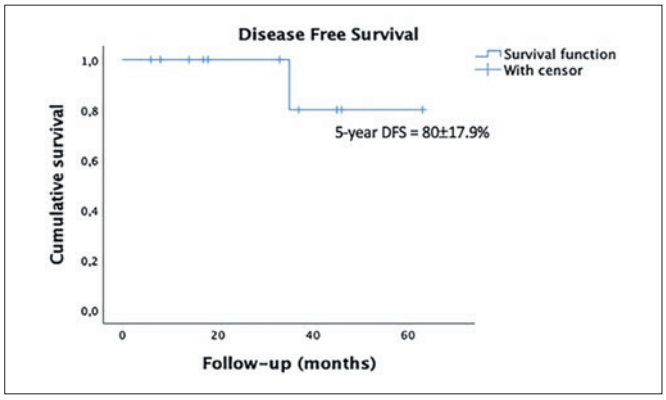

Figure 4. Kaplan-Meier disease-free survival analysis.

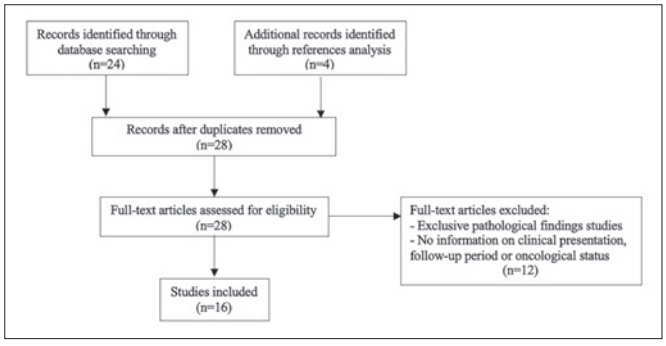

Figure 5. Review process according to PRISMA guidelines.

served in 33.8% (25/74) of cases. None of these patients were reported to have distant metastases. At the time of the last follow-up, most of these patients (64/77, 83.1%) had no evidence of disease (NED); eight patients (8/77, 10.4%), however, were alive with disease (AWD); in addition, four patients (4/77, 5.2%) died for other diseases (DOD) and one patient (1/77, 1.3%) died for other complications (DOC).

Discussion

The BSNS, also referred to as low-grade sinonasal sarcoma with neural and myogenic differentiation, is a rare and recently described low-grade sarcoma that exhibits both neural and myogenic differentiation [1]. BSNS typically arises along the sinonasal tract, especially in the ethmoid sinus and nasal cavity. Clinically, it mainly affects women (M:F ratio 1:3) and presents with non-specific symptoms such as nasal airway obstruction, nasal congestion and epistaxis. BSNS demonstrates a slowly progressive growth with local invasion and potential for local recurrences [5,6]. Conversely, distant metastasis is rare, as shown by the fact that no cases have been described in the literature thus far.

Histologically, BSNS is characterised by a "herringbone" fascicular pattern, "staghorn" vessels and consistent immunohistochemical positivity for S100, smooth muscle actin (SMA), calponin and b-catenin. Moreover, it can also show variable expression of desmin, myogenin and factor XIIIa, while it is negative for cytokeratin and SOX10 [7]. The double phenotype stems from rearrangements in PAX3 gene, a transcription factor that normally promotes neural crest and skeletal muscle differentiation and which is particularly important in the normal development of nasal structures. The original and predominant translocation identified in BSNS is t(2;4) (q35; q31.1), which results in a PAX3-MAML3 that appears to be specific for BSNS [8,9].

Given its rarity, BSNS is often misdiagnosed, resulting in improper treatment planning. Unfortunately, endoscopic appearance and imaging of this tumour do not allow for adequate differential diagnosis. In some cases, it is possible to suspect a sinonasal malignant tumour, and in selected cases to postulate the possibility of sinonasal sarcoma based on endoscopic endonasal examination and specific radiological patterns. However, a specific diagnosis of BSNS can be only defined by an expert pathologist. In this regard, immunohistochemical analysis and fluorescence in situ hybridisation (FISH) are mandatory for appropriate characterisation of this rare sinonasal sarcoma, which is crucial for an appropriate histology-driven multidisciplinary treatment [10].

From a histological viewpoint, the differential diagnosis for BSNS includes cellular schwannoma, low-grade malignant peripheral nerve sheath tumour (MPNST), leiomyosarcoma, fibrosarcoma, synovial sarcoma and glomangiopericytoma [7].

Compared to other sinonasal sarcomas, BSNS shares a similar clinical presentation, with aspecific symptoms, and a high propensity for local recurrence, while it differs in terms of clinical course and overall prognosis, especially from high grade sarcomas which are characterized by increased rates of distant metastasis and poor prognosis.

In the literature, the treatment of choice for BSNS is free-margin surgical excision [11]. Endonasal endoscopic surgery has been described as a safe, effective and minimally invasive surgical approach in the management of sinonasal malignant tumours [4]. This was confirmed also by this multicentre European experience for the treatment of BSNS. The endonasal endoscopic surgical approach, either exclusive or extended to the ethmoidal roof and dura of the anterior cranial fossa, allows appropriate excision of the disease since the most frequently involved site in the origin of this tumour is the ethmoid sinus. An effective option for extended tumours with anterior or lateral involvement of the frontal sinus, infiltration of the dura far over the orbital roof, or presenting with an infiltration of the brain is a combined

Table II. Review of literature and analysis of described cases.

Author, year	No. of cases	No., location	Staging	Surgical treatment	Adjuvant treatment	Follow-up (number of patients with available information)	Recurrence	Status
Lewis, 2012 [1]	28	19, ethmoid 8, nasal cavity 1, sphenoid sinus	NA	NA	NA	Range 12-336 months (16)	7/16 12 NA	14 NED 2 DOD
Powers, 2015 [5]	1	1, ethmoid and nasal cavity	T3	ERTC	None	10 months (1)	None	1 NED
Rooper, 2016 [14]	11	4, ethmoid 3, frontal sinus 3, nasal cavity 1, ethmoid and nasal cavity	NA	NA	NA	Range 12-312 months (7)	2/7 4 NA	6 NED 1 DOD 4 LOST
Cannon, 2016 [15]	3		NA	1 ERTC 1 CER	None	Mean 25 months (3)	1/3	2 NED 1 AWD
		3, frontal, ethmoid and orbit		1 None				
Wong, 2016 [6]	1	1, ethmoid and sphenoid sinus	T4a	ER	CH-RT	5 months (1)	None	1 NED
Huang, 2016 [7]	7	2, frontal sinus 3, ethmoid and nasal cavity 1, nasal septum 1, upper nasal meatus	NA	NA	1 CH-RT	Range 3-132 months (4)	1/4 3 NA	4 NED 3 LOST
Fritchie, 2016 [16]	9	7, ethmoid and nasal cavity 1, ethmoid and frontal sinus 1, nasal cavity, oropharynx, skull base	NA	NA	NA	12 months (2)	1/2 7 NA	1 NED 1 AWD 6 LOST
Lin, 2017 [17]	1	1, ethmoid, sphenoid, frontal and maxillary sinus with skull base and frontal lobe involvement	T4b	CER	None	NA	NA	1 DOC
Hockstein, 2018 [18]	1	1, frontal sinus	T4b	CER	None	NA	NA	1 NED
Kakkar, 2018 [19]	6	2, ethmoid and nasal cavity 1, maxillary sinus 1, maxillary and ethmoid sinus 1, maxillary, ethmoid, sphenoid sinus with intracranial extension 1, maxillary, ethmoid sinus with dura involvement	NA	3 Only biopsy 3 Lateral rhinotomy	None	Range 10-56 months (3)	2/3 3 NA	1 NED 2 AWD 1 DOD 2 LOST
Chitguppi, 2018 [20]	1	1, ethmoid, nasal cavity and orbit	T4a	ER	RT	NA	None	1 NED
Andreasen, 2018 [21]	3	2, ethmoid sinus 1, ethmoid and nasal cavity	NA	NA	2 RT	Range 64-72 months (3)	1/3	3 NED
Miglani, 2019 [22]	5		NA	3 CER 1 ER	1 RT	Range 2-97 months (5)	2/5	4 NED 1 AWD
		5, ethmoid and nasal cavity		1 ERTC				
Alkhunder, 2019 [23]	1	1, ethmoid sinus	NA	ER	None	24 months (1)	None	1 NED
Le Loarer, 2019 [24]	41	14, nasal cavity 11 ethmoid sinus 10 ethmoid and frontal sinus or skull base 6 NA	NA	NA	8 RT	Range 11-185 months (25)	8/25 16 NA	22 NED
Sethi, 2021 [25]	3	3, ethmoid, maxillary and frontal sinuses and nasal cavity	3 T4a	3 ER	1 RT	Mean 22.5 months (2)	None	2 NED
Present series	15		1 T2 2 T3		2 CH-RT 1 CH	Range 6- 80 months (15)	1/15	3 AWD 16 LOST
		13, ethmoid 2, frontal sinus	9 T4a 3 T4b					

ER: endoscopic resection; ERTC: endoscopic resection with transnasal craniectomy; CER: cranio-endoscopic resection; RT: radiotherapy; CH-RT: chemoradiotherapy; NED: no evidence of disease; AWD: alive with disease; DOC: dead of other causes; DOD: dead of disease; NA: not available.

approach, consisting in performing an endoscopic endonasal procedure in conjunction with an external transcranial approach (i.e., CER).

According to our literature review, data on surgical treatment were available only for 17/122 cases (Tab. II), who were treated using an endoscopic endonasal technique in 14/17 cases (82.3%), obtaining free-margin tumour resection in 12/17 patients (70.6%). In our series, patients treated with an endoscopic-assisted approach achieved free-margin tumour resection in 13/15 cases (86.7%). In most (11/15, 73.3%), the surgical technique was exclusively endonasal with minimal impact on the quality of life of the patient.

Adjuvant treatment is a matter of debate in the literature since, to date, there are no universally accepted protocols for BSNS. Given their rarity, its low-grade biological behaviour and the absence of prospective studies, the indications for adjuvant treatments, at present, might be comparable to those used for low-grade mesenchymal tumours [12]. Adjuvant irradiation can be administered in case of positive microscopic surgical margins and in case of perineural spread and/or lymphovascular invasion. Postoperative radiation can be delivered using conventional photon radiotherapy (e.g., IMRT) or by particle beam therapy (IMPT), especially for cases with positive surgical margins. Moreover, this innovative irradiation form has shown excellent local disease control rates not only in the postoperative setting but also for inoperable cases. However, the use of heavy ion particle radiotherapy in the anterior skull base should be considered with caution, given the potential for toxicity (e.g. osteoradionecrosis) even after several years [13]. The role of chemotherapy in this cancer subtype is controversial. Adjuvant cisplatin-based chemotherapy might be delivered concomitant to irradiation in cases of macroscopic persistence of disease in unresectable critical sites. In our experience, adjuvant radiotherapy was indicated in two cases (2/15, 13.3%) due to microscopic infiltration of the tumour resection margins, while adjuvant chemotherapy was never administered. In the studies examined in our literature review, 17/122 (20.75%) patients were subjected to adjuvant treatment. The indication for adjuvant radiotherapy in 10 cases (10/17, 58.8%) was for positive surgical margins. In four cases (4/17, 23.5%) adjuvant chemo-radiotherapy was indicated, but no specific details on indications and drugs were provided.

The recurrence patterns of this cancer are far from being completely elucidated due to the rarity of the neoplasm. Data emerging from the literature seem to support that this sarcoma often relapses locally (33.8%) during follow-up, while it is rarely associated with distant metastases. Conversely, in our series, we observed a very low recurrence rate (1/15, 6.7%) and the only patient who relapsed had experienced multiple recurrences: two local recurrences and one pulmonary metastasis, after 35, 47 and 56 months of follow-up, respectively. This anecdotal clinical case represents the first case of a systemic metastasis from BSNS so far reported in literature. The difference observed between our case series and the literature in local recurrence rate might be explained by a limitation of this study, which is the short mean follow-up period of 27.3 months of our case series, compared to 54.6 months of mean follow-up for the patients reported in the studies selected through the literature review. On the other hand, only case reports or retrospective studies based on the review of histological slides are available in the literature which resulted in a lack of complete data on each patient's medical history. In the absence of reliable data, at present, it would be prudent to follow all patients closely, based on a follow-up protocol which includes contrast-enhanced MRI of the head every 6 months and an annual total body CT scan, in order to detect possible recurrences as early as possible.

Conclusions

BSNS is a rare and a locally aggressive tumour, mostly involving the nasal cavity and paranasal sinuses. BSNS may invade the skull base and result in intracranial extension. Endoscopic-assisted surgery proved to be safe and effective as an upfront treatment within a multidisciplinary care protocol. Adjuvant irradiation should be delivered in case of positive surgical margins and in case of persistence or recurrence of disease in non-resectable areas. A low mortality rate was found in our series, as confirmed by data in literature. Although distant metastases are extremely rare, they are theoretically possible. Immunohistochemical analysis and molecular studies by expert pathologists are mandatory to confirm the correct diagnosis. Further clinical and molecular studies on larger case-series will be needed to better decipher the biological behaviour of this disease and improve treatment strategies for this rare subtype of sarcoma.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

MT-Z and GD conceptualised and designed the review, performed the literature search, collected and analyzed data and drafted the work. PC conceptualised the review, coor-

dinated the data collection and data analysis and critically revised the manuscript. ID, PB, GG, MF realised the figure and performed the statistical analysis. CF, FF took care of histopathological diagnosis, through a centralised case review. ML, DT, CG, AJ, ALA, MDF, PH, PN, MB and VJL shared their clinical cases and experience to analyze all study data. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical consideration

This study was performed in compliance with the Helsinki Declaration and approved by the Institutional Review Board (Insubria Board of Ethics, approval number 0033025/2015).

Written informed consent was obtained from all patients prior to any diagnostic or therapeutic procedure.

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