RESEARCH ARTICLE

Application of new WHO classification on malignancies of sinonasal tract: correlation with epidemiology and survival in Pakistani population

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Abstract

Objective: To analyse the clinicopathological characteristics of sinonasal malignancies in the light of the updates regarding head and neck tumours.

Method: The retrospective study was conducted at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data of patients diagnosed with primary malignant tumours of the sinonasal tract between 2015 and 2020. Slides related to biopsies and resection specimens were retrieved from the institutional database and reviewed by two pathologists. Follow-up data was also obtained. Data was analysed using SPSS 20.

Results: Of the 245 samples, 144(58.7%) were epithelial tumours, 46(18.7%) neuroectodermal tumours, 41(16.7%) haematolymphoid tumours and 14(5.7%) were malignant soft tissue tumours. A heavy reliance was placed on immunohistochemical stains to diagnose poorly-differentiated tumours. Survival was dismal, especially with early and frequent spread to the brain (33.3% in cases of Sinonasal Undifferentiated Carcinoma).

Conclusion: A wide array of sinonasal malignancies was seen. Updated knowledge of the malignancies prevalent in the region is imperative for timely diagnosis and treatment.

Key Words: Sinonasal tract, Squamous cell carcinoma, Sinonasal undifferentiated carcinoma, NUT c, Survival, Pakistani. (JPMA 73: 1603; 2023) **DOI: 10.47391/JPMA.7060**

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Introduction

The recently updated World Health Organisation (WHO) Classification of Head and Neck Tumours (5th edition) has included and elaborated on novel entities, like Human Papilloma Virus (HPV)-related multiphenotypic sinonasal carcinoma, SMARCA4-deficient carcinomas, and DEK-AFF2 carcinomas[1]. The 7th edition of Mill's and Sternberg's Diagnostic Surgical Pathology emphasises the paradox of sinonasal tumours as faced by a practicing pathologist: these tumours are neither so rare as to avoid them completely, nor are they so common as to diagnose them without any difficulty[2]. Furthermore, the confined anatomy of the sinonasal region, coupled with its proximity to the essential organs of special senses, makes the early diagnoses of malignant tumours exceptionally important. However, since the presenting complaints are usually obstruction and discharge, the differential diagnoses are broad, leading to late presentations[3].

To the best of our knowledge, no study has been conducted in Pakistan, compiling the clinicopathological characteristics of malignant tumours of the sinonasal tract. The current study was planned to analyse the clinicopathological characteristics of sinonasal malignancies occurring in the Pakistani population, in the light of WHO updates regarding head and neck tumours.

Materials and Methods

The retrospective study was conducted at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan. After exemption from the institutional ethics review board, data was retrieved from January 1, 2015, to December 31, 2020, of mucosal biopsies and resection specimens diagnosed with malignant tumours primary to the area. Data related to cases where fixation was suboptimal was excluded, and so were tumours of odontogenic origin occurring in the bones of paranasal sinuses. The blocks had been fixed in 10% buffered formalin and embedded in paraffin. The tissues had then been sectioned at 0.5um thickness and stained with haematoxylin and eosin (H&E). The slides were retrieved from the institutional archives and reviewed by two pathologists. Follow-up data was obtained from the medical records of patients admitted to the hospital. Data ws analysed using SPSS 20, and 2-year survival data was used to plot the survival graph using the Kaplan Meier Curve.

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Results

Of the 245 samples, 144(58.7%) were epithelial tumours, 46(18.7%) neuroectodermal tumours, 41(16.7%) haematolymphoid tumours and 14(5.7%) were malignant soft tissue tumours. All the subtypes were noted and malignant tumours were divided by virtue of their origin (Table 1). The epidemiological characteristics and survival data were summarised separately (Table 2).

A heavy reliance was placed on immunohistochemical (IHC) stains to diagnose poorly differentiated tumours, including sinonasal undifferentiated carcinoma (SNUC), INI-deficient carcinoma and NUT carcinoma (Table 3). All three carcinomas showed patternless growth of cells with marked pleomorphism. The striking feature of SNUC was that no obvious line of differentiation could be discerned upon initial histological assessment, and a variable morphology was noted within the same tumour (Figure 1). Focal spindling was seen in 10 (58.8%) cases. INI-deficient Carcinomas showed cells with considerably more basophilic cytoplasm; nuclear hyperchromasia was seen in 3 (60%) cases and necrosis in 4 (80%). INI (SMARCB1) was negative in all cases. The 2-year survival rate of SNUC and INI-deficient carcinoma showed overlapping, coinciding lines, representing equally dismal prognosis (Figure 2). NUT carcinomas showed frequent mitoses (>10 per 10 high-power fields [HPFs]) and necrosis; abrupt keratinisation was seen in 2 (66.6%) cases.

Histological review of squamous cell carcinomas (SCCs) showed sheets and/or trabeculae of large, syncytially

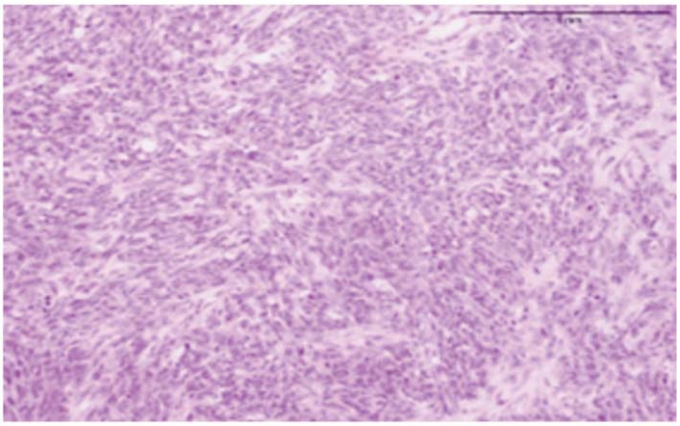

Figure-1: High-powered view of sinonasal undifferentiated carcinoma (SNUC). The cells are markedly pleomorphic, spindled to ovoid with vesicular nuclei.

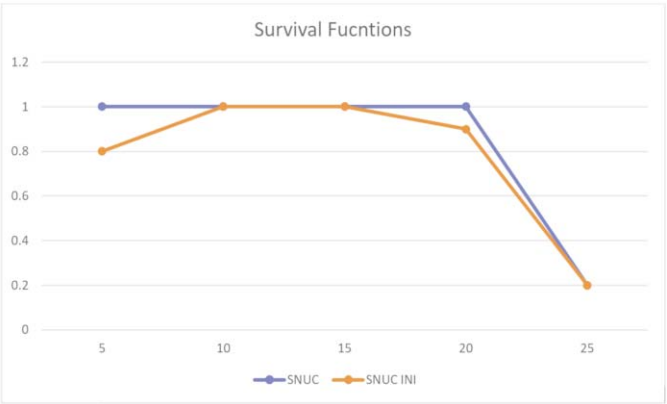

Figure-2: Two-year survival of sinonasal undifferentiated carcinoma (SNUC) and INI-deficient carcinoma (SNUC INI).

Table-1: Summary of the malignant tumours of sinonasal tract.

Epithelial tumours n=144(58.7%)	Hematolymphoid tumours n=41(16.7%)	Neuroectodermal tumours n=46 (18.7%)	Malignant soft tissue tumours n=14 (5.7%)
Squamous Cell Carcinoma n=82 (56.9%) KSCC n=53 NKSCCn=29	Diffuse large B-cell lymphoma n=17 (41.4%)	Ewing Sarcoma n=4 (8.6%)	Leiomyosarcoma n=1(7.1%)
Adenocarcinoma n=37 (25.7%) ITAC n=20 NITAC n=17	Burkitt lymphoman=3 (7.3%)	Neuroblastoma n= 23 (50%)	Alveolar Rhabdomyosarcoma n=2 (14.3%)
Sinonasal Undifferentiated Carcinoma (SNUC) n=17 (11.8%)_	Extranodal NK-T cell lymphoma n=7 (17%)	Mucosal Melanoma n=19 (41.3%)	Embryonal Rhabdomyosarcoma n=5 (35.7%)
NUT Carcinoma n=3(2.1%)	Mantle Cell lymphoma n=2 (4.8%)		Angiosarcoma n=2 (14.3%)
INI-deficient Carcinoma n=5 (3.5%)	Follicular lymphoma n=1 (2.4%)		Biphenotypic sinonasal sarcoma n=4 (28.6%)
	Plasmacytoma n=11(26.8%) Kappa restricted n=10 90.9%) Lambda restricted n=1 (9.1%)		

KSCC: Keratinising squamous cell carcinoma, NKSCC: Non-keratinising squamous cell carcinoma, ITAC: Intestinal-type adenocarcinoma, NITAC: Non-intestinal type adenocarcinoma, NUT: Nuclear Protein in Testis, INI (SMARCB1): SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily B, Member 1, NK-T cell: Natural Killer-T cell
NOTES: The percentages of individual tumour subtypes are a function of the total number of tumours in that particular subtype.

Table 2: Clinicopathological characteristics of tumours.

Tumour type	Gender (M:F)	Age range(years)	Follow up data
SCC	M:F=3.5:1	21-85; median=55	37 patients admitted; 2-year survival 16.2%; 20 patients had metastases to brain
Adenocarcinoma	M:F=3:1	25-100; median=55	16 patients admitted; 2-year survival 62.5%
SNUC	M:F=1.8:1	19-100; median=50	15 patients admitted; 2-year survival 33.3%; 7 had brain metastases
INI-deficient Carcinoma	M:F= 3:2	23-55; median=40	4 patients admitted; 2-year survival 50%; 1 had brain metastases
NUT Carcinoma	All females	38-56; median=49.6	1 patient admitted with brain and lymph node metastases and died within 8 months
Diffuse Large B cell Lymphoma	M:F=3:1	5-85	9 patients admitted; 2-year survival 33.3%
Extranodal NK-T cell Lymphoma	M:F=5:3	11-80	4 patients admitted; 2-year survival 100%
Mantle Cell Lymphoma	All males	43-78	No data available*
Follicular lymphoma	Male (single patient)	60	No data available*
Burkitt lymphoma	All males	5-51	No data available*
Plasmacytoma	M:F=1.2:1	19-55	3 patients admitted; 2-year survival 33.3%; 2 with brain i*nvolvement (one with bilateral blindness due to pituitary involvement); all three with osseus involvement**
Ewing Sarcoma	All males	18-30; median= 21.3	3 patients admitted; 2-year survival 33.3%
Neuroblastoma	M:F=2.3:1	1-70; median=35.9	13 patients admitted; 2-year survival 53.8%; 1 patient with metastases to brain and 1 to liver
Mucosal Melanoma	M:F=10:9	35-80; median=55.2	7 patients admitted; 2-year survival 14.3%; 1 patient with osseus, pulmonary and hepatic metastases
Leiomyosarcoma	Male (single patient)	37 years	No data available*
Alveolar Rhabdomyosarcoma	All females	16-30	No data available*
Embryonal rhabdomyosarcoma	M:F=3:2	3-17	4 patients admitted; 2-year survival 50%
Angiosarcoma	All males	25-42	No data available*
Biphenotypic Sinonasal Sarcoma	All males	5-53; median=29.3	All 4 patients admitted; 2 year survival=100%

SCC: Squamous Cell Carcinoma, SNUC: Sinonasal undifferentiated carcinoma, M:F: Male:female. *Follow-up lost due to non-compliance of patients; **Plasmacytomas are by definition diagnosed in the absence of multiple myeloma and osseus involvement, which could not be reliably established in the study.

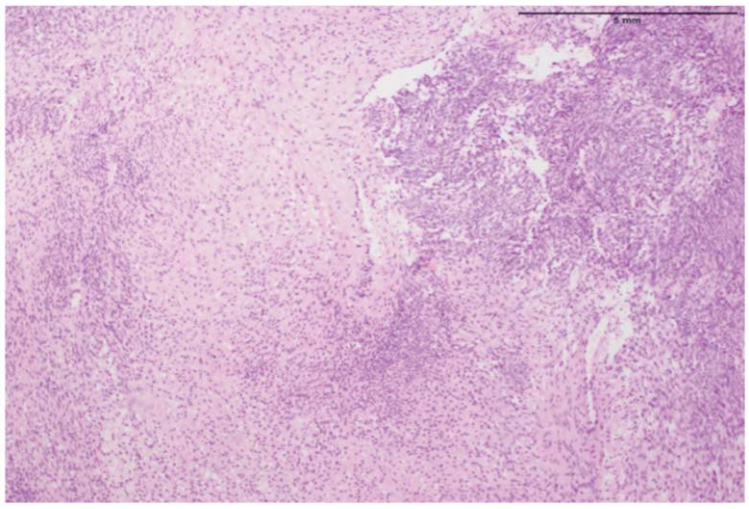

Figure-3: Biphenotypic sinonasal sarcoma in a 28-year-old male, showing mass maxillary sinus.

arranged cells with abundant cytoplasm, vesicular nuclei and prominent nucleoli. Keratinisation ranged from focal cytoplasmic keratinisation to large pearls. Non-keratinising variants were composed of sheets and trabeculae of basaloid cells with marked nuclear pleomorphism. A single case of NKSCC was re-diagnosed as HPV-related multiphenotypic sinonasal carcinoma upon review. The tumour occurred in a 55-year-old woman who presented with a mass involving maxillary sinus, nasal cavity and orbit. Histologically, cribriform arrangement of basaloid cells surrounded by distinctive myoepithelial cells were seen. P63 and p16 were positive. The patient died in 2015 after developing T4 disease.

Cases of ITAC showed tubulo-papillary architecture lined by columnar cells with

Table-3: Immunohistochemical (IHC) stains performed in cases of SNUC, INI-deficient carcinoma and NUT carcinoma.

Diagnosis	Immunostain	Cases performed	Positive	Negative
SNUC	CK	14	12	2
	p40	8	0	8
	NUT	17	0	17
	INI	17	17 (RETAINED)	0
	EBER	11	1	10
	CD56	1	0	1
	CHROMOGRANIN	7	1	6
	p63	9	0	9
	DESMIN	2	0	2
	CAM5.2	3	3	0
	SYNAPTOPHYSIN	10	6	4
	LCA	12	0	12
	NSE	1	0	1
	CD99	10	0	10
	S100	6	0	6
	CK7	5	3	2
	CK20	2	0	2
	Melan A	1	0	1
	P16	3	0	3
INI-Deficient Carcinoma	CK	5	4	1
	CK7	1	0	1
	EMA	1	1	0
	CD34	1	0	1
	p63	3	0	3
	DOG1	1	0	1
	S100	1	0	1
	SMA	1	0	1
	p16	2	0	2
	INI	5	0	5
	NUT	5	0	5
	NSE	1	0	1
	p40	3	0	3
	LCA	1	0	1
	CD56	1	0	1
	SALL-4	2	0	2
	CHROMOGRANIN	2	0	2
	SYNAPTOPHYSIN	1	0	1
	EBER	3	0	3
	DESMIN	2	0	2
NUT Carcinoma	CK	3	2	1
	NUT	3	3	0
	INI	3	3 (RETAINED)	0
	P63	3	1	2
	P40	2	2	0
	EBER	2	0	2
	CK5/6	1	1	0
	INSM1	1	0	1
	SYNAPTOPHYSIN	1	0	1
	LCA	1	0	1
	CD20	1	0	1
	CD5	1	0	1
	CALRETININ	1	0	1

SNUC: Sinonasal undifferentiated carcinoma, CK: cytokeratin, LCA: leukocyte common antigen, NSE: Neuron-specific enolase, DOG1: Discovered on GIST-1, SMA: Smooth Muscle Actin, INSM1: insulinoma associated protein 1, EBER: EBV-encoded RNA

cytoplasmic mucin, pleomorphic nuclei and prominent goblet cells. There were 11 (55%) cases that showed large mucin pools. All tumours were positive for CK7 and CK20. NITAC were composed of cribriforming tubuloglandular structures lined by columnar cells, with 15 (88.2%) cases showing nuclear hyperchromasia. An absence of goblet cells was conspicuous in all cases. CK7 was invariably positive. CK20 was performed on 10 (58.8%) cases out of which 3 (17.6%) showed focal positivity. Focal p63 positivity was seen in 1 (5.9%) case.

Ewing Sarcoma was composed of sheets of small cells with scant cytoplasm, round nuclei and inconspicuous nucleoli. 1 (25%) case showed pseudorosettes. CD99 and FLI1 (Friend leukaemia integration 1) were invariably positive by IHC and EWSR1(EWS RNA binding protein 1) rearrangements were observed. There were 12 (52.2%) cases of neuroblastoma that showed lobular growth of small, uniform cells with stippled chromatin and absent nucleoli, and 11 (47.8%) cases that showed sheet-like growth with focal necrosis and increased pleomorphism. Synaptophysin and calretinin were positive. Squamous differentiation was seen in 1 (4.3%) case. Mucosal melanomas were composed of sheets of large ovoid to spindled cells with large nuclei and single prominent nucleolus and prominent melanin pigment in 5 (26.3%) cases. Pleomorphism was striking. Necrosis was seen in 15 (78.9%) cases.

Leiomyosarcoma showed sheets of spindled cells with large nuclei and 25 mitoses per 10HPFs. Necrosis was seen in 30% of the tumour area. The tumour cells were positive for SMA and Desmin and negative for CK and S100. Rhabdomyosarcomas were composed of trabeculae of small round to spindled cells with hyperchromatic nuclei. Alveolar subtypes showed fibrous septae between nests of cells. Focal necrosis was seen in 3 (60%) of the 5 cases of embryonal rhabdomyosarcoma. Mitoses and apoptotic bodies were frequent in both subtypes. Both cases for alveolar rhabdomyosarcoma showed FOXO1(KHR - forkhead in rhabdomyosarcoma) gene rearrangements by FISH (Fluorescence in sityu hybridization). Angiosarcoma showed vascular channels lined by highly atypical cells. Both cases were positive for CD34, ERG and FLI1.

Biphenotypic sinonasal sarcomas (Figure 3) were composed of sheets of small spindled to ovoid cells with an infiltrative growth pattern and low-grade nuclei. Nucleoli were absent. Mitoses was not seen. All cases were positive for S100 and SMA, 2 (50%) cases were focal positive for TLE1, and 1 (25%) case was focally positive for Desmin. Beta-catenin, CD34, EMA (Epithelial Membrane Antigen) and Stat6 were negative in all cases.

Discussion

An extremely wide array of malignant tumours occurs in the sinonasal region, although the overall incidence is quite low at approximately 5% of all head and neck malignancies[4]. In the current study, the most common presenting complaint was unilateral obstruction, followed by discharge, epistaxis and pain, all of which remain relatively nonspecific. Early diagnosis is, therefore, crucial to the survival and maintenance of quality of life of the patient.

Epidemiologically, the results seen in Pakistani population were like the ones in Western population. The most common epithelial malignancy diagnosed in Pakistani population was squamous cell carcinoma (SCC), KSCCs more common than NKSCCs ones. This was in line with Western reports[5,6]. Adenocarcinomas were the second most common malignancy, which is in agreement with the established incidences of tumours as per the WHO classification[1].

One case was re-diagnosed as HPV-related multiphenotypic sinonasal carcinoma. The tumour lacks Myb translocations characterising the adenoid cystic carcinomas of salivary glands[7]. Although deaths from the disease are not documented[8], the patient in the current study did not survive 12 months post-diagnosis. Studies have reported that HPV association does not improve the tumour's prognosis[7,8]. The matter requires a more comprehensive study with a larger sample size in various populations.

SNUCs were 11.8% in the current study compared to 3% in earlier studies[9]. The difference can be explained by the relatively more undifferentiated tumours seen in Pakistani population. It may be attributed to different genetic lineage and the war-studded history of the region, which, in our speculation, must have led to genetic havoc at some level.

The tumour can show partial neuroendocrine differentiation (focal synaptophysin positivity was seen in the current study) and positivity for keratins (CK, EMA positivity in the current study); an obvious lack of squamous or glandular cells remains the main clue[10]. Focal CK7 positivity was also seen[11]. This is a major pitfall since high-grade squamous cell and adenocarcinomas may lose expression of the conventional markers. A study observed that all SNUCs were positive for at least one low molecular weight keratin (EMA, Cam5.2 in the current study), and negative for CK5/6, which would be useful in distinction with high-grade SCC[12]. Furthermore, a paucity of aetiological factors has long been considered one of the helpful criteria for diagnosis[13]. In contrast, one of the cases in the current study was positive for EBER stain: Lopatequi et al. stated that EBER association of SNUC existed in Asian patients, but not in Western patients[14]. In the light of the current findings, all high-grade tumours should be evaluated by an extended panel of IHC stains before giving a definitive diagnosis of SNUC or any other entity, thus making it essentially a diagnosis of exclusion[15]. In the current study, differential diagnoses included lymphoepithelial carcinoma, poorly-differentiated squamous cell and adenocarcinomas, NUT carcinoma, INI-deficient carcinoma, rhabdomyosarcoma, high-grade lymphoma, malignant melanoma, and neuroendocrine carcinoma. Recently, IDH2 mutations have been described in SNUC, although the exact implication of this mutation has yet to be delineated[16].

Only 3.5% of the tumours were INI-deficient carcinomas in the current study. Bishop, et al.[17] observed a 5% incidence, and reported a 50% survival rate, which was similar to that in the current study. The pathogenesis of the tumour lies in the inactivation of INI gene on chromosome 22, leading to a relatively rhabdoid/round blue cell morphology. INI stain should be included in IHC panel of all undifferentiated and round blue cell tumours of the sinonasal region, ideally followed by FISH. A single case report in Taiwan[18] reported favourable outcome, as opposed to Bishop et al[15] and our study. The current study showed overlapping Kaplan Meier curves for both SNUC and INI-deficient carcinomas.

NUT carcinomas are rare (2.1% in the current study), with a female predominance[19]. The median age was 49.6 years in the current sample, which was considerably older than that reported by Chau N.G. (21.9 years). The increasing age of diagnosis was also noted by Bauer D, et al.[20] in the United States. The change in different parts of the world can only be explained by reporting bias. The issue is under-recognised, not every case is subjected to NUT antibody during diagnosis, and some might have been reported as SCCs. Ideally, NUT rearrangement by FISH or RT-PCR (reverse transcription polymerase chain reaction) should be done, but because of the paucity of these facilities in Pakistan and the high sensitivity of NUT antibody (87%)[21], the IHC stain is currently used as a

diagnostic tool. Differential diagnoses considered in the current cases included lymphoma, poorly-differentiated SCC, undifferentiated nasopharyngeal carcinoma, small and large cell neuroendocrine carcinomas, and INI-deficient sinonasal carcinoma, making it a diagnosis of exclusion.

Biphenotypic sinonasal sarcoma is a rare and recent phenomenon[22], characterised by fusions of PAX3 (paired box gene 3) with a wide array of other genes, most commonly MAML3 (Mastermind Like Transcriptional Coactivator 3). Only 4 cases have been diagnosed at the current study site so far, underlining its rarity, recent inclusion in WHO Classification and lack of widespread genetic testing in Pakistan. In the current study, 2 out of the 4 cases showed focal TLE1 positivity, which may be considered a potential pitfall, especially with morphology resembling synovial sarcoma. However, TLE1 is known to express in other soft tissue sarcomas as well. Moreover, diffuse strong staining of TLE1 supports a diagnosis of synovial sarcoma[23], rather than a focal, weak expression. Characteristically, biphenotypic sinonasal sarcoma shows a mixture of myogenic and neural differentiation, shown by S100 and SMA positivity. Keratins are negative. In the study, Beta-catenin was consistently negative, in contrast to focal positivity seen in most cases. The most important differential diagnoses were malignant peripheral nerve sheath tumours and synovial sarcomas. Both entities showed high-grade morphology, absence of myogenic differentiation (SMA negative) and focal SOX10 (SRY-related HMG box) expression. Kang et al[24] described positivity of SOX10 in synovial sarcoma and malignant peripheral nerve sheath tumour, whereas biphenotypic sinonasal sarcoma is consistently negative.

The current study has limitations. There was a major follow-up bias. Illiteracy in Pakistani population, coupled with belief in quackery and faith-healers, were major contributors to this bias. Therefore, an adequate follow-up data could not be obtained from the patients who were not admitted and treated at the study site. Besides, the study lacked widespread genetic and molecular testing, mostly due to non-availability of most such services, and partly due to the high costs of these tests. Confirmation of newer entities, like SMARCA4 (Switch/sucrose non-fermentable-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4)-deficient sinonasal carcinoma, could not be reliably done. Finally, the data relates to a single centre.

Conclusion

SCCI was found to be the most common sinonasal malignancy in the studied population, followed by adenocarcinomas. A heavy reliance was placed on IHC stains to diagnose poorly-differentiated tumours. Survival was dismal, especially with early and frequent spread to the brain.

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Conflict of Interest: None.

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