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Original Contribution

Sinonasal papillomas: A single centre experience on 137 cases with emphasis on malignant transformation and EGFR/KRAS status in "carcinoma ex papilloma"☆

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ABSTRACT

Among the three major histological subtypes of sinonasal papillomas, inverted (ISP) and oncocytic (OSP) sinonasal papillomas tend to undergo malignant transformation to carcinoma. However, criteria determining risk of recurrence and malignant progression have not been established. Recently, *EGFR* and *KRAS* mutations were detected to be characteristic for ISP and OSP, respectively. In this study, we analyzed 137 sinonasal papilloma cases (132 ISP and 5 OSP) for clinicopathological characteristics, frequency of recurrences/malignant transformation, and histological types and genetic features of *carcinoma ex Schneiderian papilloma*. OSP presented at a higher age than ISP (median, 75 vs. 57 years) and affected predominantly females. Overall frequency of recurrences and malignant transformation was 23.1% and 9.5%, respectively. Rates of recurrence (33.3% vs. 22.0%) and malignant transformation (33.3% vs. 8.8%) were higher in OSP compared to ISP, respectively. Carcinomas (n = 10) occurred mostly synchronously, more frequently in females and mainly associated with ISP (n = 9). Squamous cell carcinoma (SCC) was the most frequently associated malignancy. Concordant *EGFR* (in ISP/associated carcinoma) and *KRAS* (in the OSP/associated carcinoma) mutations were detected in all successfully analyzed matching papilloma/carcinoma pairs, confirming their shared clonal origin. Results of this large study are in line with recent studies showing frequent *EGFR* and *KRAS* mutations in sinonasal carcinoma ex Schneiderian papilloma. As the papilloma component might on occasion be missed on biopsy of synchronous *carcinoma ex papilloma*, *EGFR* and *KRAS* mutation testing represents a promising molecular surrogate for sinonasal "*carcinoma ex papilloma*", at the same time offering an opportunity for targeting mutant EGFR in this rare cancer type.

1. Introduction

Sinonasal papillomas (SP; synonym: Schneiderian papillomas) are uncommon neoplasms with three histologically distinct subtypes defined initially by Hyams et al. in 1971 [1]: inverted (ISP), exophytic (ESP) and oncocytic (OSP) sinonasal papillomas. ISP, the most common type, usually occurs in the 5th to 6th decades of life with a male predilection (2–3:1) [2]. In contrast, OSP, the least common type, does not show gender predilection. Due to clinicopathological overlap with the inverted type, OSP has been initially questioned as a distinctive subtype, but recognition of unequivocal oncocytes by Barnes and Bedetti in 1984 led to its acceptance as a distinctive subtype [3].

Due to their circumscribed exophytic growth enabling complete excision, ESPs carry minimal recurrence and minimal (if any) malignant potential. In contrast, both ISP and OSP tend to recur and may undergo malignant transformation [4]. "*Carcinomas ex sinonasal papillomas*" may occur either synchronously (both diagnosed in same specimen) or metachronously following primary or recurrent papilloma. Malignancies of different histological types have been described but the majority are squamous cell carcinomas (SCC) [5]. By 2014, 240 cases of "*carcinoma ex sinonasal papilloma*" have been reported in the literature [5]; Only 19 cases were associated with OSP [3,4,6-11]. Histological criteria to predict risk of malignancy have not been established. A higher malignancy risk was suggested for OSP, but remained undefined due to rarity

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Table 1
Study characteristics of the analyzed cohort (ISP vs. OSP).

	All tumors combined		ISP		OSP		p-Value
	n	(%)	n	(%)	n	(%)	
Total number of cases	137		132		5		
Age							
Minimum	21		21		63		0.004
Maximum	88		88		83		
Mean	57.43		56.76		75.2		
Median	57		57		75		
Gender							
Male	94	(68.6)	94	(71.2)	0	(0.0)	0.003
Female	43	(31.4)	38	(28.8)	5	(100.0)	
Location of papilloma							
Nasal cavity	16	(11.7)	16	(12.1)	0	(0.0)	0.22
Nasal cavity and paranasal sinuses	17	(12.4)	15	(11.4)	2	(40.0)	
Paranasal sinuses	104	(75.9)	101	(76.5)	3	(60.0)	
Recurrence							
No	80	(76.9)	78	(78.0)	2	(66.7)	0.60
Yes	24	(23.1)	23	(22.0)	1	(33.3)	
One recurrence			19		1		
Multiple recurrences			4		0		
Not available	33		31		2		
Malignant transformation							
No malignant transformation	95	(90.5)	93	(91.18)	2	(66.7)	0.24
Synchronous malignancy	8	(7.6)	7	(6.86)	1	(33.3)	
Squamous cell carcinoma	5		5				
Carcinoma in situ	1		1				
Transitional cell carcinoma	2		1		1		
Metachronous malignancy	2	(1.9)	2	(1.96)	0	(0.0)	
Low-grade mucin-forming (mucoepidermoid-like) adenosquamous carcinoma	1		1				
	1		1				
Transitional cell carcinoma							
No follow up available	32		30		2		

ISP, inverted sinonasal papilloma; OSP, oncocytic sinonasal papilloma.

of this subtype which precludes large scale studies [6,12].

Recent studies reported frequent *EGFR* (in ISP) and *KRAS* (in OSP) mutations and linked presence of Human Papillomavirus (HPV) and absence of *EGFR* mutations to risk of progression of ISP to SCC [13-17]. We herein describe our institutional experience with a large series of ISP and OSP with focus on frequency of malignant transformation and the histological patterns and genetic alterations in "*carcinomas ex sinonasal papillomas*".

2. Material and methods

2.1. Study cohort

All cases encoded as "sinonasal papilloma" in the data bank of the Department of Pathology, University Hospital of Erlangen, over a 10-year period from 1 January 2001 to 31 December 2010, have been retrieved via computerized search. After review of the reports, exophytic variants were excluded due to their minimal malignant potential and rarity. The remainder (ISP and OSP) were reviewed histologically to confirm diagnosis and subtypes and are enrolled in this study. Patients with recurrent tumors whose primary lesions were treated elsewhere were included as well. Histological consultation cases were excluded to avoid statistical bias.

Investigated parameters were gender, age at first diagnosis, location of the lesion, frequency of and time until recurrence, associated malignancy, time until progression, locoregional tumor recurrences or distant metastases, treatment and follow-up data including the last documented survival status of the patient. Reference time of follow up period was first diagnosis of the sinonasal papilloma according to histological finding or, if not available, patients´ information in clinical records. All histopathological reports of the selected cohort were reviewed carefully. Histological slides were re-examined in all cases. Histological subtype of the papilloma and the carcinoma were classified according to the current WHO classification [18]. Clinical data and follow-up information were obtained from medical records of the ENT Department, University Hospital of Erlangen, and included all documented information until December 2016. The location of the lesion was divided into three categories: nasal cavity, paranasal sinuses and nasal cavity plus paranasal sinuses. Recurrences were defined according to clinical reports and discussed with the ENT Department to exclude residual tumor versus genuine recurrence. Recurrences within 3 to 12 months after surgery were labelled as "recurrence with possibility of residual tumor". Out of the 159 patients identified by initial search, microscopic review led to exclusion of 8 patients: six malignancies could not be confirmed to originate from or be associated with a papilloma and two had no available slides for re-review. In addition, 14 cases without available clinical data were excluded as well. The final cohort consists of 137 patients.

2.2. Statistical analysis

Fisher's and Kruskal Wallis tests were appropriately used to compare different groups. Log-rank test was used to compare survival variables. All p-values < 0.05 were considered significant. Statistical analyses were performed using R version 3.4.3. The "survminer" package included in the R environment was used to plot survival curves.

2.3. Molecular genetic analysis

Molecular genetic analysis was performed in all cases of *carcinoma ex sinonasal papilloma* (n = 10). DNA was extracted from areas of invasive carcinoma and – if possible - matching papilloma separately. After manual microdissection of the tumor cells and DNA isolation (Maxwell 16 system, Promega, Madison, USA), amplicon based massive parallel sequencing was performed using a commercial 15 gene panel (TruSight Tumor 15 (TST15) panel, Illumina, San Diego, USA) and a

MiSeq system according to the manufacturer's instructions (Illumina). The 15 gene panel is focused on the detection of hot-spot mutations within the coding regions of 15 genes (*AKT1, BRAF, EGFR, ERBB2, FOXL2, GNA11, GNAQ, KIT, KRAS, MET, NRAS, PDGFRA, PIK3CA, RET, TP53*) frequently altered by mutations in solid tumors. This gene panel includes the most frequently mutated genes in sinonasal papillomas: *EGFR* and *KRAS*. Raw sequencing data was automatically aligned to the human genome (hg19), and the reported variants were annotated using Variant Studio 3.0 (Illumina).

3. Results

3.1. Clinical data

Out of 137 patients, 132 (96.4%) were diagnosed with ISP and 5 (3.6%) with OSP. Table 1 summarizes the characteristics of the analyzed cohort. Age at first diagnosis was significantly higher in OSP (median: 75 years; range, 63–83 years) than ISP (median, 57 years; range, 21–88 years) (p = .004). The patients included 94 (68.6%) men and 43 (31.4%) women. All 5 OSPs occurred in females, whereas ISP predominated in men (n = 94; 71%) with a male to female ratio of 2.5: 1. Sex predilection of the subtypes reached statistical significance (p = .003). Majority of ISP involved the paranasal sinuses (76.5%), followed by the nasal cavity (12.1%) or both (11.4%). Three OSPs were centered in the paranasal sinuses and two affected the sinuses as well as the nasal cavity. No OSP limited to the nasal cavity was found.

3.2. Papilloma recurrence

Due to unavailable follow-up data of 33 cases (31 ISP, 2 OSP), the analyzed group for survival and outcome consisted of 104 patients. Overall, recurrences developed in 24 patients (23.1%) with a rate of 22.0% (n = 23) and 33.3% (n = 1) for ISP and OSP, respectively. Risk of recurrence according to the subtype was not statistically significant (Table 1). Majority of the detected recurrences were singular (83.3%), while multiple recurrences were found in four cases (16.7%) with a maximum of three recurrences noted in one patient. In our series, all multiple recurrences were associated with ISP. Two recurrences occurring in ISP after 4 and 10 months, respectively, were marked as “recurrence with possibility of residual tumor”. Median time until first recurrence was 3.75 years (range, 4 to 189 months) with most recurrences (71%) presenting within 5 years following initial diagnosis (Fig. 1).

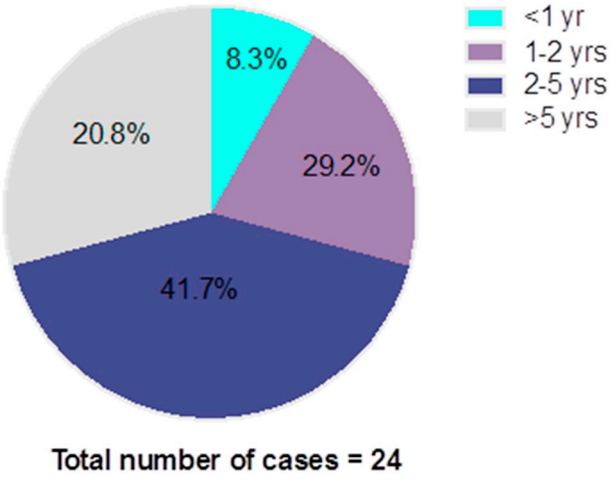

Fig. 1. Time until first papilloma recurrence for inverted (ISP) and oncocytic (OSP) sinonasal papilloma sorted by years.

3.3. Malignant transformation

Malignant changes were found in ten sinonasal papillomas (9.5%) with a frequency of 8.8% (n = 9) in ISP and 33.3% (n = 1) in OSP. Eight (7.6%) carcinomas were synchronous and two (1.9%) metachronous. While synchronous malignant changes existed in association with both ISP and OSP, we detected no metachronous malignancy arising in OSP. Rate of malignant transformation was statistically not significantly different in ISP versus OSP (p = .24). At the time of initial diagnosis of the malignancy, median age was 62.5 years (range, 46 to 83 years). The two metachronous carcinomas presented at the age of 52 and 65, respectively. The most frequently encountered synchronous malignancy associated with ISP was SCC (n = 5), followed by one case each of transitional cell carcinoma and carcinoma in situ (CIS). Metachronous malignancies consisted of a transitional cell carcinoma and a low-grade mucin-forming (mucoepidermoid-like) adenosquamous carcinoma occurring after 12 and 14 years, respectively. Both tumors developed in papillomas with history of singular recurrence. A papillary transitional cell carcinoma was the type detected synchronously in an OSP. None of the malignancies presented with metastasis at the time of first diagnosis. Half of the tumors involved the paranasal sinuses and half the nasal cavity plus sinuses. Patients with malignant transformation were 3 years older when their primary lesion (papilloma or synchronous carcinoma) was diagnosed than those without malignancy (median, 59 vs. 56 years). In addition, risk of malignant transformation was significantly increased in female subjects (Table 2) with seven malignancies occurring in women and three in men (p = .012).

3.4. Treatment and follow up

Endoscopic approach was the treatment of first choice regarding sinonasal papillomas. Excluding those with synchronous malignancies, all but one papilloma (n = 128) underwent endoscopic surgery. The remaining one was isolated to the nasal cavity and was removed by an excisional biopsy. Therapy of carcinomas was discussed individually and varied depending on extent and location of the lesion. In this series, malignant primary tumors were either treated by surgery only (40%) or combined with adjuvant irradiation (30%) or adjuvant concurrent chemoradiation (30%). Follow up data existed in 104 cases (101 ISP, 3 OSP) and varied from 2 to 215 months (median, 28 months). Recurrence-free survival is presented in Fig. 2 and was 47 months in median. Median follow up of patients with malignant lesions was 57 months (range, 7 to 215 months). While we found no distant metastases in our series, four malignancies (40%) presented locoregional recurrences commonly occurring within the first year (range, 7 to 61 months with a median of 8 months). The metachronous low-grade mucin-forming (mucoepidermoid-like) adenosquamous carcinoma was the only lesion developing two locoregional recurrences, one of them a submandibular lymph-node metastasis. This tumor was the locally most aggressive one in our study and infiltrated surrounding tissue as bone, skin and orbital cavity. The patient died from the consequences of his disease 3.6 years following first clinical signs of his malignancy. Of the remaining patients, 93 (89.4%) were alive without clinical evidence of disease (five of them in status post carcinoma), 8 (7.7%) individuals including three suffering from a carcinoma were alive with disease and two (1.9%) died of unrelated causes.

3.5. Pathologic findings

ISP were identified by an endophytic growth into the underlying stroma and were composed of a multi-layered squamous-like transitional cell epithelium alternating with respiratory epithelium with variable usually limited goblet cell-like component. In contrast, OSP provides both exophytic and endophytic growth. It consists of a multilayered epithelium composed of columnar cells with eosinophilic granular cytoplasm, intraepithelial mucin-filled microcysts and

Table 2
Study characteristics of the analyzed cohort (no malignant transformation vs. malignant transformation).

	All tumors combined		No malignant transformation		Malignant transformation		p-Value
	n	(%)	n	(%)	n	(%)	
Total number of cases	137		95*		10*		
Age at presentation of primary lesion							
Minimum	21		21		40		
Maximum	88		88		83		
Mean	57.43		55.8		60.2		
Median	57		56		59		
Gender							
Male	94	(68.6)	68	(71.6)	3	(30.0)	0.012
Female	43	(31.4)	27	(28.4)	7	(70.0)	
Location of lesion							
Nasal cavity	16	(11.7)	10	(10.5)	0	(0.0)	
Nasal cavity and paranasal sinuses	17	(12.4)	10	(10.5)	5	(50.0)	0.0097
Paranasal sinuses	104	(75.9)	75	(79.0)	5	(50.0)	

* Numbers related to those cases with available clinical data/follow-up

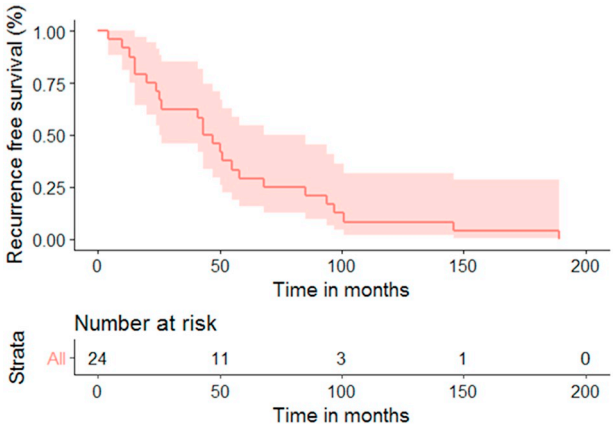

Fig. 2. Kaplan-Meier representation of recurrence-free survival of sinonasal papillomas. Reference time was first diagnosis of the papilloma.

microabscesses. Table 3 summarizes the detected malignancies and their characteristics. SCC (n = 5) was the most commonly encountered type (Fig. 3), followed by transitional cell carcinoma (n = 3), low-grade mucin-forming (mucoepidermoid-like) adenosquamous carcinoma (n = 1; Fig. 4A–C) and CIS (n = 1). All but one carcinoma presented in association with ISP. The remaining one was a papillary transitional cell carcinoma associated with an OSP (Fig. 4D–F). Histologically, malignant transformation was characterized by architectural disorder, signs of stromal invasion with desmoplasia and cellular features of frank malignancy as nuclear pleomorphism, prominent nucleoli, increased mitotic activity with frequent atypical mitoses and necrosis. CIS was diagnosed based on severe full thickness dysplasia in the absence of evident stromal invasion. Two SCC showed focal keratinization. One non-keratinizing SCC demonstrated transitional cell like features and a focal undifferentiated component. The low-grade mucin-forming (mucoepidermoid-like) adenosquamous carcinoma contained transitional, squamous and mucinous component as well as areas with glandular morphology and was in part closely mimicking mucoepidermoid carcinoma (Fig. 4A–C). This tumor lacked the *MAML2* gene fusion characteristic of low-grade mucoepidermoid carcinoma (data not shown). Overall, four malignancies infiltrated the orbital cavity (three of them within recurrences), two presented with bone invasion and one carcinoma extended to the lacrimal ducts. Both benign and malignant tumors commonly were accompanied by variable degree of mainly neutrophilic inflammation.

3.6. Molecular genetic analysis

Five of the ten malignant cases were successfully analyzed using the TST15 gene panel. (Table 3). *EGFR* mutations were identified in four carcinomas ex ISP (three SCC and one low-grade mucin-forming (mucoepidermoid-like) adenosquamous carcinoma, while a *KRAS* mutation was present in the carcinoma ex OSP case. Corresponding papilloma DNA could be extracted and analyzed in all 5 cases. The same *EGFR* mutation was identical in each ISP and its associated SCC. A *KRAS* mutation (p.Val14Ile) was found additionally in one of these papillomas, but could not be re-identified in the matching SCC. The low-grade mucin-forming (mucoepidermoid-like) adenosquamous carcinoma harbored two different EGFR mutations in both components.

Table 3
Pathological characteristics of carcinomas ex sinonasal papillomas.

Malignancy	Occurrence	Associated type of papilloma	Grading	Locoregional recurrence	Mutated gene	Mutation
Squamous cell carcinoma	Synchronous	ISP	G3	Yes		
Squamous cell carcinoma	Synchronous	ISP	G2	No		
Squamous cell carcinoma	Synchronous	ISP	G1	Yes	*EGFR*	p.Ser768_Asp770dup
Squamous cell carcinoma	Synchronous	ISP	G2	No	*EGFR*	p.Asn771_His773dup
Squamous cell carcinoma	Synchronous	ISP	G2	No	*EGFR*	p.Ser768_Asp770dup
Transitional cell carcinoma	Metachronous	ISP	G2	No		
Transitional cell carcinoma	Synchronous	ISP	G2	No		
Papillary transitional cell carcinoma	Synchronous	OSP	G2	Yes	*KRAS*	p.Gly12Cys
Low-grade mucin-forming (mucoepidermoid-like) adenosquamous carcinoma	Metachronous	ISP	G1	Yes	*EGFR*	p.Glu746_Thr751delinsIle
					EGFR	p.Ser768_Asp770dup
Carcinoma in situ	Synchronous	ISP	-	No		

ISP, inverted sinonasal papilloma; OSP, oncocytic sinonasal papilloma; n.a., not available.

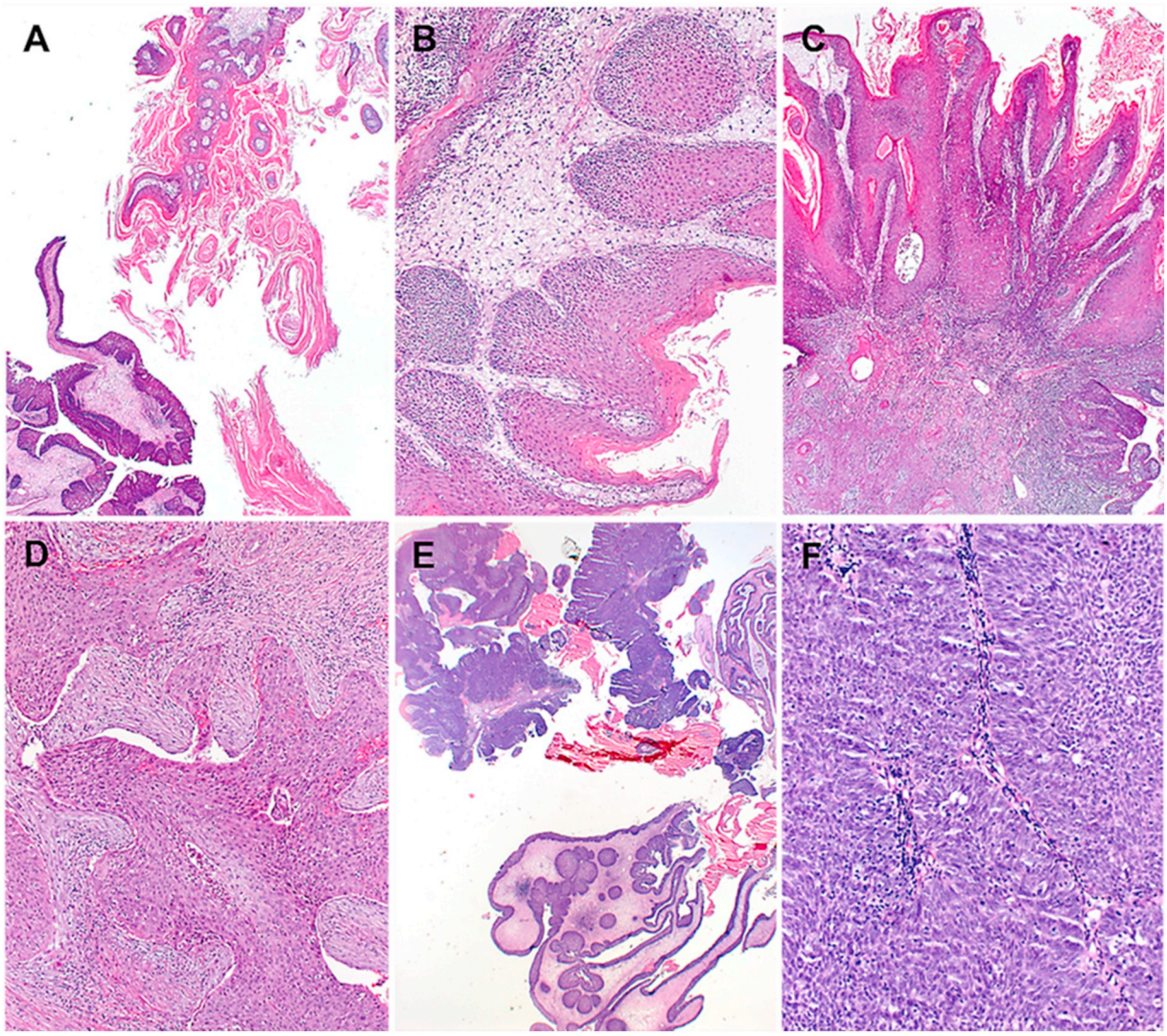

Fig. 3. Pathological characteristics of *carcinomas ex sinonasal papillomas*. Hematoxylin and eosin stain. A: Coexisting inverted sinonasal papilloma (lower left) and keratinizing squamous cell carcinoma (upper right). B: Higher magnification of keratinizing dysplastic papilloma component at the interphase to carcinoma. C: Papillary-verrucous differentiated part of squamous cell carcinoma. D: Non-keratinizing infiltrating squamous cell carcinoma. E: Coexisting inverted sinonasal papilloma (lower field) and poorly differentiated non-keratinizing basaloid squamous cell carcinoma (upper field). F: Higher magnification of the carcinoma in E.

Predominant mutation type in *EGFR* was an S768_D770dup mutation, present in three carcinomas. The papillary transitional cell carcinoma and its matched OSP showed the same *KRAS* mutation.

4. Discussion

In this study we investigated a large series of ISP and OSP to identify differences in behavior and malignant potential related to the respective subtype. With a cohort size of 137 cases (96.4% ISP and 3.6% OSP), this series is one of the more extensive studies compared to previous studies addressing sinonasal papillomas [12,19]. The part of ISP compared to OSP in our study (26:1) is much higher compared to previous reports with ratios up to 15:1 [1,3,6,9,12]. This significant variation in the frequency of OSP among different series could be due to variations in the criteria used for classification of sinonasal papillomas in different studies and the variety of terms available for the oncocytic subtype in the literature.

Age distribution (median, 57 years) and predilection for men in our study are in accordance with the literature [18]. ISPs tend to arise from the nasal cavity and maxillary sinus. In our series, about three-quarters were located in the paranasal sinuses, the remainder were equally distributed between nasal cavity and nasal cavity plus paranasal sinuses. On the other hand, OSP commonly originates from the lateral nasal wall or the paranasal sinuses with more frequent presentation in patients older than 50 years equally distributed between men and women. In the present study, OSP occurred at a later median age than ISP (75 vs. 57 years) with a predilection for women, as all tumors affected females. Gender predominance in our OSP series may however be biased by the limited number of cases.

Reported recurrence rates of sinonasal papillomas varied greatly from 6% to 46% for ISP and 6% to 40% for OSP [1,3,6,12,19,20]. In the present series, the recurrence rates of 22% in ISP and 33.3% in OSP are within these reported ranges. Statistical analysis did not confirm an increased risk of recurrence in OSP, but case number is low to allow for conclusive results. Risk factors for recurrence are addressed by several previous studies [19,21-24]. Recurrence seems to be a result of incomplete resection, as most tumors recur at the same site as the original lesion [1,19]. Furthermore, the presence of HPV in ISP has been linked to development of recurrence [22].

Role of recurrence in the malignant transformation is still controversial. While Hyams et al. [1] suggested no relation between the aforementioned factors, Kristensen et al. [25] found papilloma

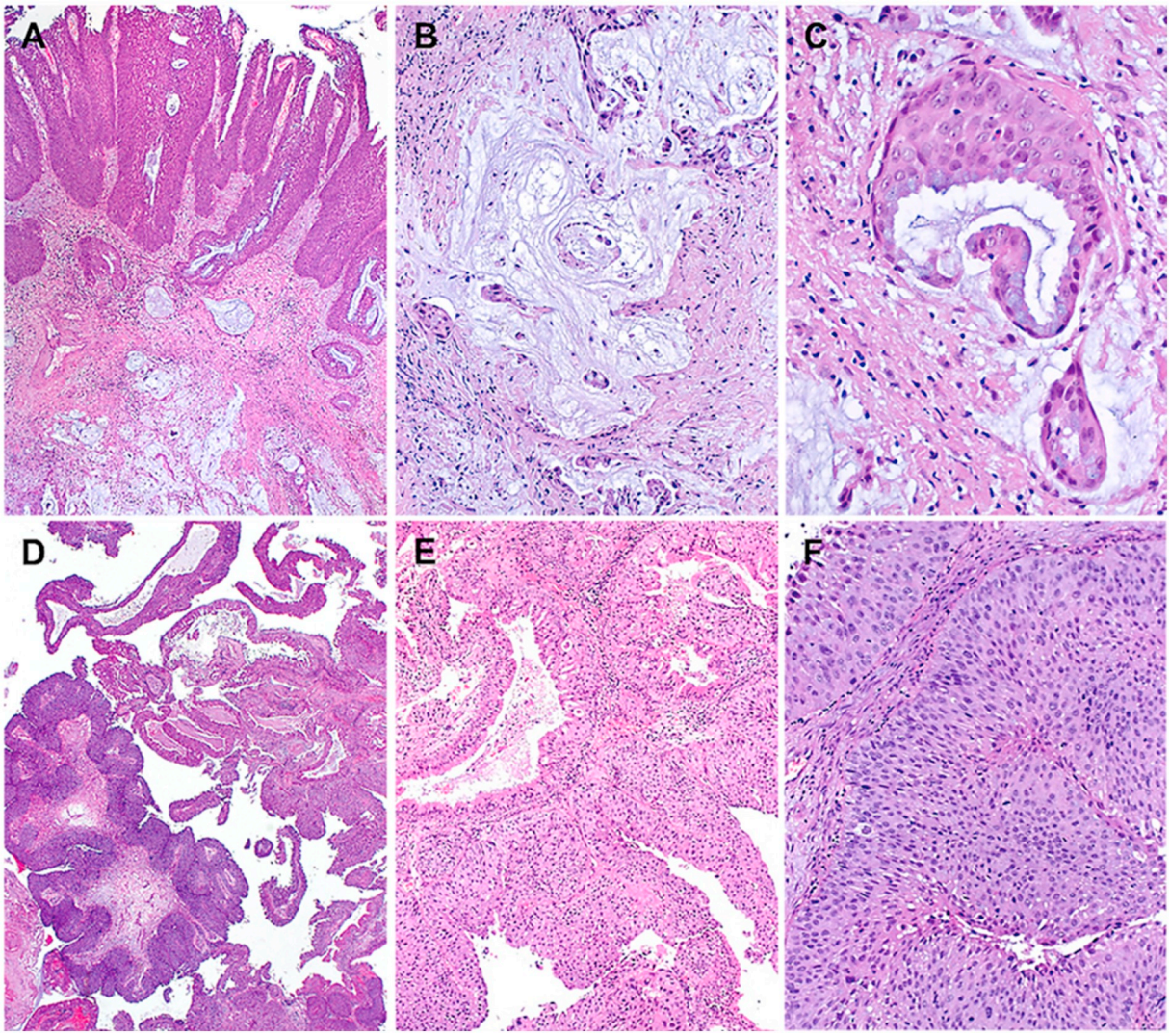

Fig. 4. Pathological characteristics of *carcinomas ex sinonasal papillomas*. Hematoxylin and eosin stain. A: This aggressive transformed inverted papilloma showed atypical squamoid papillary surface growth associated with prominent mucoepidermoid-like mucinous component in the deeper part (B and C: higher magnification). D: Overview of carcinoma (lower field) ex oncocytic papilloma (upper field). E: Higher magnification of the oncocytic papilloma. F: Higher magnification of the carcinoma shows solid transitional cell-like morphology.

recurrence to be a predisposing factor for malignancy. Furthermore, Mirza et al. [26] observed carcinomas arising in recurrent inverted papillomas in 11% of their cases. In our series, both metachronous carcinomas developed in papillomas with history of recurrence. This is in accordance with the findings of Nudell et al. [5].

Our finding of 9.5% frequency of malignant transformation is in line with a previous review of literature showing 10% of sinonasal papillomas undergoing malignant transformation on average [27]. However, Nudell et al. [5] reported a rate of malignancy of 1.9% in their presumably bias-free data. Median age at first presentation of the malignancy was 62.5 years and majority (70%) of malignancies occurred in females. In contrast, Nachtigal et al. [28] reported a similar male predominance in benign and transformed sinonasal papillomas.

Synchronous occurrence of malignancy was observed in 7.6% and metachronous occurrence in 1.9% in our current study. A thorough review of literature [26] investigating recurrence and malignancy in ISP noted a comparable prevalence of 7.1% synchronous and 3.6% metachronous carcinomas. However, these rates reported in the literature and also in our study might be overestimated due to referral bias to tertiary care centers. Metachronous carcinomas occurred at a mean interval of 63 months after first papilloma diagnosis (range, 6 months to 13 years) [29]. We observed even a longer interval for development of metachronous carcinomas (12 and 14 years). The longest reported interval for metachronous malignancy arising after sinonasal papilloma was 17 years [11].

Divided by subtype, malignancies arose in 8.8% of ISP and 33.3% of OSP. While carcinomatous transformation in ISP is addressed by several studies and commonly documented with rates between 5% and 14% [1,3,19,20,28,30,31], malignant behavior of the oncocytic subtype remains debatable. Kapadia et al. [9] performed the largest study of OSP in the literature including 150 cases; 6 (4%) of them were associated with malignancies. Karligkiotis et al. [6] in the second largest series detected one malignancy among 33 OSP, concluding that the oncocytic type per se is not a negative prognostic factor in terms of recurrence or malignant transformation. In contrast, Kaufman et al. [12] reported a malignancy rate of 17% and suggested OSP to be associated with aggressive behavior. In line with this, the present study noted higher rates of recurrence and malignant transformation in OSP than ISP. The carcinoma frequency of 33.3% in our series is the highest reported yet. However, differences did not reach statistical significance and the number of carcinoma ex OSP cases is too low to allow for statistical analysis.

Corresponding to the literature [5], the majority of malignancies occurred synchronously and SCC was the most frequently encountered carcinoma type in this study. Less common types are papillary transitional cell carcinoma, low-grade mucin-forming (mucoepidermoid-like) adenosquamous carcinoma and CIS. A similar case of low-grade mucin-forming (mucoepidermoid-like) adenosquamous carcinoma has been illustrated in a recent review [2]. In analogy to carcinoma ex pleomorphic adenoma of salivary glands, the phenotypic spectrum of *"carcinoma ex sinonasal papilloma"* seems highly heterogeneous. Unfortunately, this topic has been omitted in the current WHO classification (probably for brevity). This might however negatively impact the precise classification of these uncommon tumors. In our opinion, *"carcinoma ex sinonasal papilloma"* represents a category and not a diagnostic entity. Thus, the biology of the carcinoma would significantly be influenced by the histological type of the malignancy and not the presence of the papilloma itself. Accordingly, it is important to precisely subtype the carcinoma component which is usually not a problem in cases of conventional SCC. However, there seems to be inconsistency in diagnosing and reporting other less common carcinoma variants. Due to lack of reproducible criteria for diagnosis and consensus terminology, some tumors for which we used the terminology "transitional cell carcinoma" might have been classified as low-grade Schneiderian carcinoma or as a variant of non-keratinizing SCC by other authors. In our view, these transitional cell-like tumors and other less common low-grade carcinoma variants need more defined diagnostic criteria for proper classification. The mere expression of squamous line markers (high molecular weight cytokeratins, p40, etc.) should not justify lumping them with conventional SCC. Likewise, low-grade mucin-forming (mucoepidermoid-like) adenosquamous carcinoma is currently not well-defined and might have been misnamed as mucoepidermoid carcinoma of salivary type in the past. The case we described herein lacked of *MAML2* gene fusion and instead harbored two different *EGFR* mutations. This is in line with a distinct adenosquamous carcinoma variant unrelated to genuine mucoepidermoid carcinoma of salivary type.

The role of molecular biomarkers in sinonasal papillomas along with HPV and tumor suppressor genes alterations (e.g. p16 and p53) were the focus in recent literature [13,22,31-33]. *EGFR* mutations are reported to be disease-defining molecular features of ISP and ISP-associated SCC [13,16,17], whereas *KRAS* mutations seem to be specific to OSP and its associated malignancies [10,14,15]. Consistent with this, all analyzed ISP-associated carcinomas and matched ISP in our study showed concordant *EGFR* mutations, while the OSP and its associated carcinoma harbored same *KRAS* mutation. We observed identical genotypes in all these cases, indicating that the carcinoma is indeed derived from the papilloma as reported recently [14,16,17]. The prognostic relevance of these findings is debated recently. Presence of *EGFR* mutations in ISP was suggested to be associated with a lower risk of malignant transformation [13,15,17]. Furthermore, EGFR inhibitors may proof promising as targeted therapy option for ISP-associated SCC [16,17].

In conclusion, our data showed an overall rate of malignant transformation in sinonasal papillomas of 9.5% and suggest OSP to occur at a later age than ISP with female predilection and possibly higher rate of malignancy compared to ISP, but this did not reach statistical significance. Although conventional SCC is the most common malignancy encountered *ex sinonasal papilloma*, other less common variants exist and they still are in need for diagnostic and nosologic clarity. Molecular genetic analysis identified concordant *EGFR* mutations in all ISP-associated carcinomas and concordant *KRAS* mutation in the OSP-associated carcinoma indicating clonal origin and confirming the "*carcinoma ex papilloma concept*".

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Declaration of competing interest

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