HUMAN PAPILLOMAVIRUS AND FACTORS ASSOCIATED WITH RECURRENCE IN SINONASAL INVERTED PAPILLOMAS FROM POLAND AND SPAIN

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ABSTRACT

Background: Sinonasal inverted papilloma (SNIP) is a benign but locally aggressive tumor that has a tendency toward recurrences and malignant transformation. The role of human papillomavirus (HPV) in SNIP is controversial.

Objective: to determine the HPV-DNA prevalence and type distribution in SNIP in two different geographical areas, and to assess the association of HPV infection and other factors to recurrence.

Methods: Two retrospective cohorts of SNIP patients from Poland and Spain were evaluated. Demographic, tobacco/alcohol use, clinical and follow-up data were collected. All samples were subject to histopathological evaluation, DNA quality control, and HPV-DNA detection by PCR. HPV-DNA positive samples and a random sample of HPV-DNA negative cases were further subject to $p16^{INK4a}$ analysis. Proportional-hazards models were used to evaluate the risk of recurrence by selected variables.

Results: Seventy-nine SNIP patients (46 from Spain diagnosed between 1995 and 2014, and 33 from Poland diagnosed between 2012 and 2017) were included in the study. HPV-DNA was detected in four patients (5.1%), two from each group, all four being positive for HPV11. Seventeen patients (21.5%) had recurrence, with a median time to recurrence of 14 months. HPV-DNA positivity, toxic habits, Krouse stage or malignant transformation during follow-up were not observed to be associated with a higher risk of recurrence.

Conclusion: The low prevalence of HPV-DNA found in SNIP suggests that HPV is not a main etiological factor for SNIP. The absence of association between the herein evaluated factors and recurrence may suggest the involvement of other factors, although further research with larger number of patients and additional biomarkers is warranted.

INTRODUCTION

The sinonasal inverted papilloma (SNIP) is a benign epithelial neoplasm that represents a 0.5-4% of primary sinonasal tumors and has an incidence of 0.2-0.7/100.000 people/year. It tends to present local aggressiveness and recurrences after surgical removal and may have a malignant transformation [1].

Within the sinonasal tract, SNIP is more frequently found on the lateral wall of the nasal fossae, although the localization at the ethmoidal and maxillary sinuses is also very frequent. Histologically, SNIP is characterized by invagination of the hyperplastic epithelium, ranging from squamous to ciliated columnar with goblet cells into the underlying stroma (figure 1 and 2).

SNIP is the most common type of sinonasal papillomas, which are classified according to their histological structure in exophytic or fungiform papilloma, inverted papilloma, and cylindrical or oncocytic papilloma [2]. All types may coexist. SNIPs represent 70% of all sinonasal papillomas [3].

Although histologically benign, SNIP shows a propensity for malignant transformation, most frequently to squamous cell carcinoma (SCC). The rate of malignant association is approximately 10% [4,5]. The factors responsible for malignant transformation are not yet fully elucidated due to the relative low prevalence of SNIPs as well as of SCC arising in the sinonasal tract [4]. SNIP is also particularly prone to recurrence [2] although the postulated factors associated with recurrence such as human papillomavirus (HPV) infection [6], tobacco smoking [7] or Krouse stage [8] have not been consistently corroborated.

The recommended treatment for SNIP is complete surgical excision by an endoscopic, open or combined approach [9]. Occupational exposures (organic solvents and welding fumes) have been reported to be implicated in the development of SNIP [2]. Chronic sinonasal inflammation may also have an etiologic relation with SNIP, but the mechanism is still unclear.

The establishment of the role of HPV in a fraction of head and neck cancers (HNC) raised interest on the etiologic and prognostic role of HPV in other benign head and neck lesions such as SNIP. In the last decades, several studies have explored the relationship between SNIP and HPV infection, obtaining conflicting results. The detection rates of HPV in SNIP range from 0 to 100% in the world literature [1,2,10]. Such differences have not been explained by differences in geographical regions or HPV detection methods [10].

Recently, last reports about the role of HPV in SNIP are proposing new theories postulating that the infection is not related to the initial pathogenesis of the SNIP but when there is an inflammatory and metaplastic mucosa, the virus is more susceptible to infect it [11]. Moreover, the presence of the virus in the SNIP has been related with a higher risk of recurrences [6] and malignant transformation (especially for high-risk genotypes 16 and 18) [1,12]. The unequivocal establishment of the prognostic HPV role in SNIPs, as well as other nasosinusal lesions, might have implications for tertiary prevention of recurrence or malignant transformation through HPV vaccination.

This study aimed to estimate the HPV-DNA prevalence and type distribution in SNIP in two series from two different geographical areas, Spain and Poland, and to analyse risk factors for recurrence and malignant transformation in both groups.

METHODS

Study Design

We carried out a retrospective study including two cohorts of all primary SNIPs diagnosed between 1995 and 2014 at the Department of otorhinolaryngology of the Hospital Universitari de Bellvitge (Spain) and between 2012 and 2017 at the Department of Otorhinolaryngology of the Czerniakowski Hospital in Warsaw (Poland). The pathologic diagnosis of the lesions was confirmed by biopsy. Demographic data and information about history of smoking and alcohol use, previous HPV-related pathology, tumor extent by Krouse

staging system [13] and follow-up was collected from medical records. Recurrent cases or cases previously undergoing nasal surgeries were excluded.

Protocols were approved by the ethics committee of the Catalan Institute of Oncology-ICO (Comité Ètic d'Investigació Clínica de l'Hospital Universitari de Bellvitge, Spain), which required no informed consent to use archived samples.

Formalin-fixed, paraffin-embedded (FFPE) blocks processing and histopathological evaluation

Protocols have been described elsewhere [14]. Briefly, FFPE blocks were processed under strict conditions to avoid contamination and were re-embedded at ICO whenever necessary. At least four paraffin sections were obtained for each block. First and last sections were used for histopathological evaluation (sandwich method) after hematoxylin and eosin (H&E) staining and the in-between ones for HPV testing and genotyping and expression of $p16^{INK4a}$. FFPE blocks were processed under strict pre/post polymerase chain reaction (PCR) physical separation, and blank paraffin blocks were systematically tested in parallel to serve as sentinels for contamination as previously published [14]. Pathology review was performed using a form specifically designed by two pathologists for the study (see supplementary material) and blind with respect to the original local diagnosis. It followed a pre-established algorithm for diagnostic consensus involving the two pathologists. First, all pathology slides were reviewed by a trained pathologist at ICO. Samples with discordant diagnosis were further reviewed by the two pathologists for a final evaluation and agreed diagnosis.

HPV-DNA Detection and Genotyping

The detailed methods used for HPV-DNA detection and genotyping have been reported elsewhere [14]. Briefly, we used SPF-10 PCR and a DNA enzyme immunoassay (DEIA) to test for the presence of HPV-DNA. Virus genotyping was performed using reverse hybridization line probe assay (LiPA25_v1) on all samples testing positive for viral DNA, targeting 25 HPV types with different oncogenic potential. DNA quality was evaluated in all

HPV-DNA negative samples by testing for the human tubulin gene [14]. All DEIA and LiPA25_v1 assays were performed at ICO.

p16^{INK4a} immunohistochemistry

p16^{INK4a} expression was evaluated on all HPV-DNA positive cases and a random sample of HPV-DNA negative cases using the CINtec histology kit (clone E6H4, Roche mtm laboratories AG, Germany), following the manufacturer's protocol. A pattern of diffuse staining of more than 70% stained cells (nuclear and cytoplasmic) is considered positive for malignant lesions [15], but in our study we assumed as positive a staining between 26 and 50% for premalignant lesions in a diffuse or continuous pattern [16,17].

Statistical analysis

Descriptive statistics were computed for each of the variables analysed. Fisher's exact test for categorical variables and t-test for continuous variables were used to detect statistically significant differences between the two centres for each variable. Median and range of months to recurrence and months of follow up variables were estimated. To compare medians between groups, qreg (quantile regression) test, equivalent to t-test for means, was employed. A survival analysis was conducted to identify variables associated with recurrence. Cox regression model was performed to estimate hazard ratios and their 95% CI. In order to avoid the possible bias due to the centre where the SNIPs were diagnosed and treated, centre was introduced as a strata variable allowing the baseline hazard function to differ for the different centre. Proportional hazard assumption was also verified. Due to the low number of cases progressing to invasive cancer during follow-up, survival analyses to identify variables associated with malignant transformation could not be performed. All the analyses were performed with STATA 13.1 software.

RESULTS

Figure 3 depicts the disposition of SNIP samples collected, processed and tested. The ICO laboratory received 63 samples from Bellvitge Hospital (Spain) and 68 samples from Czerniakowski Hospital (Poland). A total of 79 cases (46 from Spain and 33 from Poland) were included in the final analysis, respectively.

The characteristics of the patients are presented in Table 1. Most cases were males (67.1%) and non-drinkers (70.9%) with a mean age of 56.2 years. There was a higher proportion of ever-smokers in the Spanish group (67.4% vs 39.4%, p=0.010) whereas Polish cases were more frequently diagnosed with more advanced Krouse stages (p<0.001). Cases from both centres presented also differences regarding some histopathological variables, with more Polish cases presenting transitional epithelium (p=0.015) and more Spanish cases presenting squamous epithelium (p<0.001) and papillar or exophytic lesion adjacent to SNIP (p<0.001). The median time to follow-up was 76.63 months (range 0.23-174.3) for Spanish cases and 39.1 months (range 6.3-66.5) for Polish ones. Seventeen patients (21.5%) had recurrence, of which 12 were from Spain (26.1%) and 5 from Poland (15.2%), with a median time to recurrence of 14 months (range from 3 to 83). Only two cases (2.5%), both belonging to the Spanish series, progressed to invasive cancer during follow-up. HPV-DNA was detected in two samples (4.3%) in the Spanish series and in two samples (6.1%) in the polish series. All of them were positive for HPV11 and negative for $p16^{INK4a}$ high expression. All HPV-DNA negative cases tested for $p16^{INK4a}$ (20 cases, representing 27% of all HPV-DNA negative cases) were also negative for $p16^{INK4a}$ high expression.

The presence of atypia adjacent to SNIP at diagnosis was the only statistically significant factor associated to recurrence with a crude hazard ratio (HR) of 18.83 (95%CI, 1.71-207.65) (Table 2). The recurrence rate was higher in higher Krouse stages (T2 and T3) compared to T1, although not statistically significant. No significant differences in risk of recurrence were found by smoking, alcohol drinking habits or HPV positivity. The four low

risk-HPV positive SNIPs were located in the nasal cavity (one in the septum, one in the vestibulum and two in the lateral wall, and among those, one in the lower turbinate and one in the middle turbinate and middle meatus). None of them presented dysplasia. In contrast, most HPV-negative SNIPs were located at the lateral wall (85%), the maxillary sinus (15%) and the ethmoid sinus (20%), some of them affecting more than one location. HPV-positive patients were two males and two females, with a mean age of 37.8 years old at the moment of diagnosis. SNIPs recurred in 25% (1/4) of HPV-positive vs 22.2% (16/72) of HPV-negative lesions (crude HR=3.70, 95%CI 0.44–31.37). Recurrence univariate Cox models for tobacco use and Krouse stage were also performed stratified by centre, and statistically significant differences between both groups were not found.

DISCUSSION

The etiologic and prognostic role of HPV in SNIP remains unclear, with previous studies reporting HPV detection rates ranging from 0 to 100% [1,2,10,11] as well as contradictory results on the role of HPV infection in recurrence and malignant transformation of SNIP [1,6,12].The differences have not been explained by differences in geographical regions or HPV detection methods [10]. However, to the best of our knowledge, any study has evaluated cases from different geographical regions with the same sample processing and HPV detection protocol. Thus, our results add to current data from a systematic review [10], the only previous publication pooling results of studies from different geographical regions, since systematic reviews and meta-analyses are not exempt from limitations [18].

We herein evaluated the prevalence and prognostic role of HPV in two retrospective cohorts of primary SNIPs from Spain and Poland, as well as additional factors associated to recurrence. We tested the SNIPs cases following a previously validated robust, standardized and international protocol designed to provide estimates of HPV-attributable fractions in HPV-related cancers [14].

Our study is the first to evaluate SNIPs from two different geographical regions which have previously shown marked differences in HPV-AFs in OPC [14]. Our data demonstrates a low HPV-DNA detection (5.1%) in primary SNIPs, similar to the 4.9% estimated at the oral cavity of healthy population [19] or the 4% and 7% estimated at inflammatory nasal polyps and normal sinonasal mucosa, respectively [10], suggesting that HPV is not a main etiological factor for SNIP in either setting herein evaluated. Our HPV prevalence estimates are in accordance with those of previous studies with equivalent number of cases [10,11] although lower than others [7,10,20,21]. The only type found was HPV11, as reported by others [1,7,20]. No high risk types were found in our sample.

The prevalence of HPV in SNIP with dysplasia or with SCC adjacent to the lesion is estimated to be higher than in SNIP without dysplasia [1], and more common in recurrent lesions [1]. We only included primary lesions, and only one case from Spain had dysplasia adjacent to the SNIP at diagnosis, and it was HPV positive. Three out of four HPV-positive patients in our series were ever smokers, although the association between the two variables was not statistically significant (p-value=0.631). The low HPV prevalence rates found in our series prevented us to further explore factors associated with HPV positivity. However, we noted a trend for HPV positive cases to affect the nasal cavity rather than the sinus and to involve younger people, in accordance with other studies [22].

We observed some differences between the two groups of patients, with Polish cases diagnosed at more recent periods (due to case selection), more advanced Krouse stages, and presenting a lower proportion of ever-smokers. Differences in some histopathological features were also observed between Polish and Spanish cases. However, due to the low number of cases, we decided to combine both groups to evaluate factors associated with recurrence and to address the differences between groups with the use of the strata function in Stata. Moreover, when accounting for such differences by stratifying the recurrence univariate Cox models for tobacco use and Krouse stage by centre, we did not find

statistically significant differences between both groups. Although showing marked differences in HPV-AF in OPC for SNIPs, both series showed similar HPV prevalences, confirming that the variability in HPV detection rates in SNIPs is not explained by their different geographic origins, as it was already hypothesized in a previous metanalysis [10]

The presence of dysplasia adjacent to the SNIP at diagnosis was the only factor associated with recurrence (HR: 18.83, 95%CI: 1.71-207.65), as it has been shown in previous studies [23], although only one case contributed to the estimation. A HR of 3.70 (95%CI 0.44-31.37) was observed for recurrence in HPV-positive cases, although not statistically significant. Other factors such as tobacco smoking or Krouse stage did not show any prognostic value for recurrence. However, tobacco use [1,7] and T3 vs T2 Krouse stages [8] have been previously reported to be related to recurrence. The low number of cases evaluated in this study could explain these discrepancies with the literature. A slight decreasing trend for recurrence in more recent years was observed, although it was not statistically significant.

Only two cases (2.6%) progressed to invasive cancer during follow-up, and none of them were HPV-positive. Thus, we could not evaluate further the prognostic value of HPV positivity or other factors for malignant transformation. Different risk factors are suspected to be involved in malignant transformation of SNIPs and include HPV infection, tobacco smoking and occupational exposure [24]. In contrast, EGFR mutations have been observed to be a protective factor for malignant transformation of SNIPs [21,24]. However, many previous studies suggesting that HPV infection may play a role as a co-factor in the development of carcinoma ex-SNIP did not use biomarkers of biological activity of HPV such as the presence of E6/E7 mRNA transcripts or $p16^{INK4a}$ expression. Indeed, studies evaluating E6/E7 mRNA transcripts [25] or $p16^{INK4a}$ expression [26] in SNIPs did not find HPV as an etiological driver of SNIP development or progression to SCC. We did not observe $p16^{INK4a}$ expression in any HPV-DNA positive samples as expected, since all of them were positive for low risk genotypes. However, we did not test all HPV-DNA negatives

samples for $p16^{INK4a}$ expression. We did neither evaluate further biomarkers of biological activity of HPV on HPV-DNA positive samples such as E6/E7 mRNA positivity nor do use techniques like laser capture microdissection, which combined with highly sensitive PCR allow assignment of a particular HPV genotype to an area of normal or abnormal epithelium [27].

The major limitation of the study was its relatively small sample size, which hampered us to evaluate factors associated with HPV-positivity, recurrence and malignant transformation. However, given the fact that SNIP is a relatively rare entity, few studies have reported results for series with equivalent number of primary SNIP cases consecutively diagnosed in two decades, like ours. Not all HPV-DNA negative cases were evaluated for $p16^{INK4a}$ expression and no evaluation of further biomarkers such as E6/E7 mRNA or EGFR was performed. A recent study showed that EGFR mutations and HPV infection represent essential, alternative oncogenic mechanisms in SNIP and SNIP-associated sinonasal SCC [21]. The study observed that SNIP progression was significantly associated with the presence of HPV infection and the absence of an EGFR mutation. We did not evaluate the prognostic value of the treatment received by the SNIP patient. However, a previous study did not find differences in recurrence by different types of interventions [9].

The low prevalence of HPV-DNA found in SNIPs from two different countries suggests that HPV is not a main etiological factor for SNIP. The absence of association between HPV and the rest of herein evaluated factors and recurrence may suggest the involvement of other factors. Further research with larger number of patients and additional biomarkers is warranted to unequivocally assess the aetiology and prognosis of SNIP.

TITLE'S LEGENDS

Figure 1. Sinonasal inverted papilloma. Inverted growth pattern and absence of seromucinous glands (hematoxylin-eosin 0'5x)

Figure 2. High power image shows non-keratinizing transitional epithelium covered by a layer of ciliated columnar epithelium. Infiltration by neutrophils is seen (hematoxylin-eosin 10 x)

Figure 3. Flow chart of cases included in the study

DISCLOURE

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HISTOLOGICAL EVALUATION

Identification number _____ Date _____ Pathologist _____

1. HISTOLOGICAL DESCRIPTION OF THE LESION

1.1. Types of epithelium in the sinonasal inverted papilloma (SNIP)

□ Transitional

□ Squamous

□ Columnar

□ Presence of oncocytic cells

□ Hyper-parakeratosis

□ Presence of exophytic or papillary lesion adjacent to SNIP

□ Dysplasia □ Mild □ Moderate □ Severe/Carcinoma *in situ*

Others:

1.2. Intralesional polymorphonuclear infiltrate:

□ No

□ Yes □ Mild □ Moderate □ Severe

Inflammatory Perilesional infiltrate:

□ No

□ Yes □ Mild □ Moderate □ Severe

1.3. Subepithelial stromal tissue

□ Lax □ Dense

1.4. Other findings:

2. DEFINITIVE DIAGNOSIS OF THE LESION

□ Inverted

□ Oncocytic.

□ Exophytic

□ Non-papillary lesion:

□ Dysplasia □ Mild □ Moderate □ Severe/Carcinoma *in situ*

3. Slides A&B

□ Same □ Different

4. Control

□ Tissue: _____

5. Final evaluation

□ Adequate for HPV analysis

□ Repeat sandwich technique

□ Doubtful/Uncertain

□ Discard for HPV analysis

6. External quality control

□ Pathologist _____

7. Internal quality control

□ Pathologist _____

Comments

Figure

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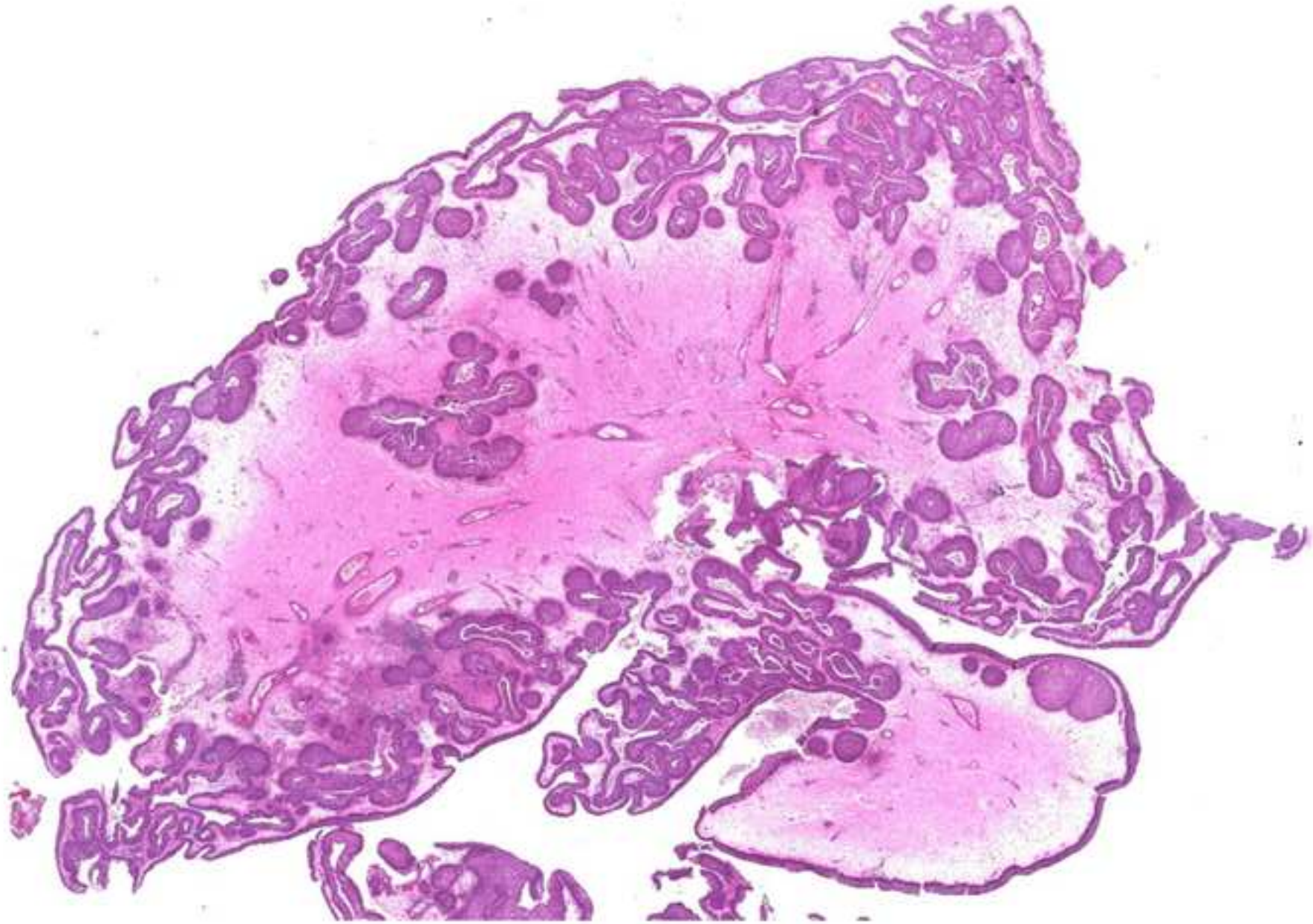

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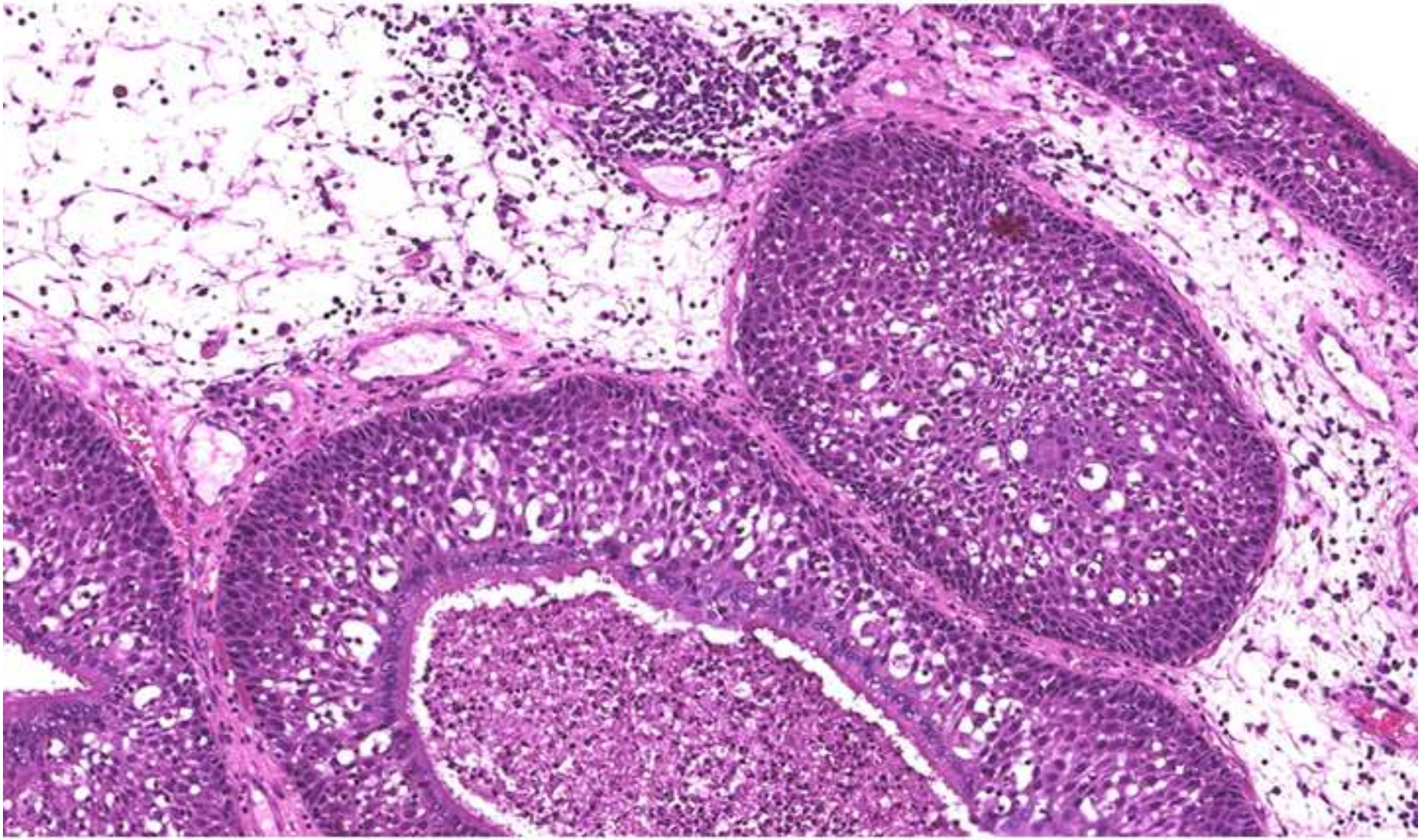

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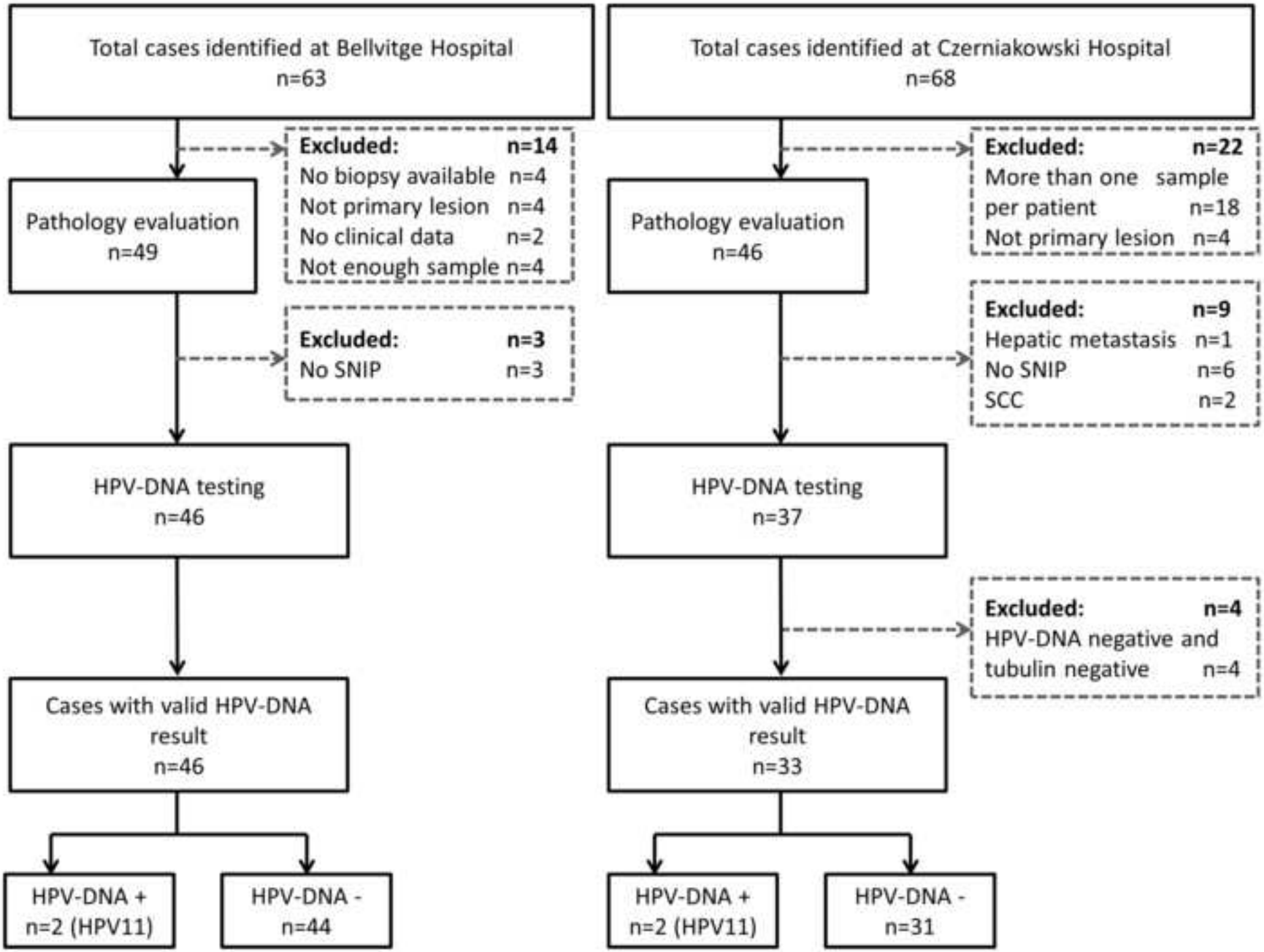

Table 1. Demographic and clinical characteristics of SNIP patients included in the study

Characteristics	Total SNIPs (n = 79) No. (%)[a]	Spanish SNIPs (n = 46) No. (%)	Polish SNIPs (n = 33) No. (%)	p-value[a]
Age at diagnosis				0.460
Mean (SD)	56.2 (16.1)	55.0 (15.0)	57.8 (17.7)	
Range	19-91	19-85	23-91	
Gender				0.150
Male	53 (67.1)	34 (73.9)	19 (57.6)	
Female	26 (32.9)	12 (26.1)	14 (42.4)	
Period of diagnosis				**<0.001**
1995-2000	7 (8.9)	7 (15.2)	0 (0.0)	
2001-2006	17 (21.5)	17 (37.0)	0 (0.0)	
2007-2012	24 (30.4)	22 (47.8)	2 (6.1)	
2013-2017	31 (39.2)	0 (0.0)	31 (93.9)	
Tobacco use				**0.010**
Never smoker	33 (41.8)	13 (28.3)	20 (60.6)	
Ever smoker	44 (55.7)	31 (67.4)	13 (39.4)	
Missing	2 (2.5)	2 (4.3)	0 (0.0)	
Alcohol use				0.616
Never drinker	56 (70.9)	33 (71.7)	23 (69.7)	
Ever drinker	21 (26.6)	11 (23.9)	10 (30.3)	
Missing	2 (2.5)	2 (4.3)	0 (0.0)	
Previous history of HPV-related pathology				1.000
Yes	3 (3.8)	2 (4.3)	1 (3.0)	
No	74 (93.7)	42 (91.3)	32 (97.0)	
Missing	2 (2.5)	2 (4.3)	0 (0.0)	
Krouseclassification				**<0.001**
1	33 (41.8)	28 (60.9)	5 (15.2)	
2	23 (29.1)	11 (23.9)	12 (36.4)	
3	16 (20.3)	3 (6.5)	13 (39.4)	
4	4 (5.1)	1 (2.2)	3 (9.1)	
Missing	3 (3.8)	3 (6.5)	0 (0.0)	
Transitionalepithelium				**0.015**
Absence	19 (24.1)	16 (34.8)	3 (9.1)	
Presence	60 (75.9)	30 (65.2)	30 (90.9)	
Squamousepithelium				**0.001**
Absence	45 (57.0)	19 (41.3)	26 (78.8)	
Presence	34 (43.0)	27 (58.7)	7 (21.2)	
Columnarepithelium				0.316
Absence	23 (29.1)	11 (23.9)	12 (36.4)	
Presence	56 (70.9)	35 (76.1)	21 (63.6)	
Hyper-parakeratosis				1.000
Absence	76 (96.2)	44 (95.7)	32 (97.0)	
Presence	3 (3.8)	2 (4.3)	1 (3.0)	
Papillar or exophytic lesion adjacent to SNIP				**<0.001**
Absence	61 (77.2)	44 (95.7)	17 (51.5)	
Presence	18 (22.8)	2 (4.3)	16 (48.5)	
Polymorphonuclear neutrophil inflammatory intralesional infiltrate				1.000
Absence	2 (2.5)	1 (2.2)	1 (3.0)	
Presence	77 (97.5)	45 (97.8)	32 (97.0)	
Polymorphonuclear neutrophil inflammatory perilesional infiltrate				0.418
Absence	1 (1.3)	0 (0.0)	1 (3.0)	
Presence	78 (98.7)	46 (100.0)	32 (97.0)	
Recurrence				0.268
No	59 (74.7)	31 (67.4)	28 (84.8)	
Yes	17 (21.5)	12 (26.1)	5 (15.2)	
Missing	3 (3.8)	3 (6.5)	0 (0.0)	
Months of follow up				
Median	52.83	76.63	39.1	0.003 [b]
Range	0.23-174.33	0.23-174.33	6.27-66.47	
Months to recurrence				0.469[b]
Median	14	17	4	
Range	3-83	9-83	3-36	
Progression to invasive cancer				0.502
No	74 (93.7)	41 (89.1)	33 (100.0)	
Yes	2 (2.5)	2 (4.3)	0 (0.0)	
Missing	3 (3.8)	3 (6.5)	0 (0.0)	
HPV positivity				1.000
No	75 (94.9)	44 (95.7)	31 (93.9)	
Yes	4 (5.1)	2 (4.3)	2 (6.1)	

SNIP: Sinonasal Inverted Papilloma; SD: Standard deviation; [a]Fischer exact test with the exception of age and months to recurrence. where t-student test has been used to compare the median values between populations. [b]: qreg (quantilte regression): test for equality of medians, equivalent for t-test for medians.

Table 2. Hazard ratios for recurrence in SNIP patients included in the study

Characteristics	Total SNIPs (n = 76) No. (%)	Recurrences No. (%)	Crude HR (95%CI)
Hospital			
Bellvitge (Spain)	43 (56.58)	12 (27.91)	Ref.
Czerniakowski (Poland)	33 (43.42)	5 (15.15)	0.81 (0.27–2.39)
Age at diagnosis[b]			
Mean (SD)	56.34 (16.40)	-	1.01 (0.98–1.04)
Gender			
Male	51 (67.11)	14 (27.45)	Ref.
Female	25 (32.89)	3 (12.00)	0.45 (0.13–1.58)
Year of diagnosis			
Range	1995-2017	-	0.96 (0.86–1.08)
Tobacco use			
Never smoker	32 (42.11)	7 (21.88)	Ref.
Ever smoker	44 (57.89)	10 (22.73)	0.97 (0.35–2.64)
Alcohol use			
Never drinker	55 (72.37)	12 (21.82)	Ref.
Ever drinker	21 (27.63)	5 (23.81)	1.32 (0.46–3.78)
Previous history of HPV-related pathology			
No	73 (96.05)	16 (21.92)	Ref.
Yes	3 (3.95)	1 (33.33)	0.91 (0.12–7.06)
Krouse classification			
1	33 (43.42)	8 (24.24)	Ref.
2	23 (30.26)	6 (26.09)	1.70 (0.54–5.29)
3	16 (21.05)	3 (18.75)	1.27 (0.28–5.75)
4	4 (5.26)	0 (0.00)	-
Transitional epithelium			
Absence	18 (23.68)	2 (11.11)	Ref.
Presence	58 (76.32)	15 (25.86)	3.01 (0.67–13.56)
Squamous epithelium			
Absence	43 (56.58)	11 (25.58)	Ref.
Presence	33 (43.42)	6 (18.18)	0.49 (0.17–1.43)
Columnar epithelium			
Absence	22 (28.95)	3 (13.64)	Ref.
Presence	54 (71.05)	14 (25.93)	1.90 (0.54–6.69)
Papillar or exophytic lesion adyacent to SNIP			
Absence	58 (76.32)	14 (24.14)	Ref.
Presence	18 (23.68)	3 (16.67)	0.85 (0.20–3.55)
Polymorphonuclear neutrophil inflammatory intralesional infiltrate (present in 74 cases)			
Low	67 (90.54)	16 (23.88)	Ref.
Moderate	7 (9.46)	1 (14.29)	0.52 (0.07–3.96)
Polymorphonuclear neutrophil inflammatory perilesional infiltrate (present in 75 cases)			
Low	56 (74.67)	12 (21.43)	Ref.
Moderate	18 (24.00)	5 (27.78)	2.59 (0.79–8.52)
Severe	1 (1.33)	0 (0.00)	-
Dysplasia at diagnosis adyacent to SNIP			
Absence	75 (98.68)	16 (21.33)	Ref.
Presence	1 (1.32)	1 (100.00)	**18.83 (1.71–207.65)**
Progression to cancer during follow-up			
No	74 (97.37)	16 (21.62)	Ref.
Yes	2 (2.63)	1 (50.00)	1.69 (0.22–13.24)
HPV positivity			
No	72 (94.74)	16 (22.22)	Ref.
Yes	4 (5.26)	1 (25.00)	3.70 (0.44–31.37)

SNIP: Sinonasal Inverted Papilloma; [a]Three out of 79 cases did not have information regarding recurrence. [b]First row shows mean age of the sample with its standard deviation.