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Inverted papilloma: a twenty years retrospective study from one institution

Invertni papilom: retrospektivna dvadesetogodišnja studija u jednoj ustanovi

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Summary -

We have been treating endoscopically different kinds of inverted papilloma including malignant inverted
papilloma since 1995. This is a retrospective study which demonstrates our experience in the treatment of
inverted papilloma. Inverted papilloma is defined as a benign, locally aggressive tumor with malignant
transformation and frequent recurrence. The aim of the study is to investigate whether the malignancy starts
developing at the beginning of disease or later, and whether we can consider deviated septum as a etiologic
factor of inverted papilloma. We also wanted to show endoscopic endonasal surgery as a method of choice in
the treatment of inverted papilloma. Data in the period from 1998 to 2017 were analyzed retrospectively. Out
of a total number of 62 patients, three (4.8%) were diagnosed with inverted papilloma with squamous cell
carcinoma in some part of the lesion and 59 (95.2%) were diagnosed like inverted papilloma. The patients
diagnosed with inverted papilloma and with squamous cell carcinoma were significantly older than the
patients diagnosed with IP (Mann-Whitney U test, p = 0.006). The most common localization of primary
tumor was the maxillary sinus. The dominant symptom in patients with inverted papilloma was epistaxis in
more than half of our patients, followed by nasal obstruction in more than one third of our patients. We
compared our results with the results from literature. Our results show a low percentage of malignant
transformation only in three cases (4.8%). The obtained result corresponds to previous studies, with values
below the average obtained in other studies. Finally, the endoscopic endonasal approach is the contemporary
gold standard in the treatment of inverted papilloma.

Key words: inverted papilloma, malignant transformation, endoscopic endonasal approach

Sažetak

Od 1995. godine endoskopskim pristupom liječimo različite oblike invertnog papiloma, uključujući i zloćudni invertni papilom. Ovom retrospektivnom studijom pokazali smo naša iskustva u liječenju invertne bolesti. Invertni papilom definira se kao benigni, lokalno agresivni tumor sklon malignoj transformaciji i čestim recidivima. Cilj studije bio je istražiti razvija li se zloćudni tumor odmah na početku, ili do maligne transformacije dolazi kasnije, te ima li devijacija septuma utjecaj na razvoj invertnog papiloma. Također smo željeli prikazati endoskopski endonazalni pristup kao metodu izbora u liječenju invertnog papiloma. Podaci u razdoblju od 1998. do 2017. godine analizirani su retrospektivno. Od ukupnoga broja bolesnika 62, kod njih troje (4,8%), postavljena je dijagnoza invertnog papiloma s karcinomom pločastih stanica u dijelu invertnog papiloma, a dok je kod njih 59 (95,2%) postavljena dijagnoza invertnog papiloma. Bolesnici s dijagnozom invertnog papiloma s karcinomom pločastih stanica bili su značajno stariji od bolesnika s dijagnozom

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invertnog papiloma (Mann-Whitney U test, p = 0,006). Maksilarni sinus najčešće je sijelo primarnoga tumora. Epistaksa predstavlja dominantni simptom invertnog papiloma u više od polovine bolesnika, a slijedi ju nosna opstrukcija, zapažena kod više od trećine bolesnika. Usporedili smo naše rezultate s rezultatima iz literature. Naši rezultati pokazuju nizak postotak maligne transformacije u samo tri bolesnika, odnosno u 4,8% slučajeva. Dobiveni rezultat odgovara ranijim istraživanjima, s time što dobivene vrijednosti spadaju u niže od prosjeka dobivenih u drugim istraživanjima. U našem istraživanju potvrdili smo kako je endoskopski endonazalni pristup metoda izbora u liječenju invertnog papiloma.

Ključne riječi: invertni papilom, maligna transformacija, endoskopski endonazalni pristup

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Introduction

Inverted papillomas (IP) are benign sinonasal tumors that originate from the Schneiderian membrane formed from layers of squamous type cells, transitional and ciliated columnar epithelium. It covers about 0.5-4% of all primary tumors in the nose and paranasal sinuses and is one of the most common benign lesions of the described anatomical region with male-to-female ratio 3.4:1 and the peak onsets in the 4th-7th decade of life. 2,3

There are three main characteristic features. One of the most important characteristics of the IP is the ability to spread to surrounding tissues and the destruction of the osseous areas of the nasal cavity and sinuses, spreading over the facial skeleton and the anterior cranial fossa, a high propensity for recurrence and the possibility of malignant alteration.⁴ Chronic inflammation, nicotinism, allergy or occupational exposures are some of the factors having the role in respiratory mucosa remodeling into IP. Some studies described the possibility of HPV as a possible factor in the development of IP. The percentage of positive HPV among IP ranged between 38 and 63%, but further research is needed.^{5,6}

Recent study⁷ confirmed the incidence of malignancy in their work 5.1% with other literature, which suggests that the incidence of malignancy among patients with IP varies widely and ranges from 2-27%. ^{8,9} Most histological interpretations confirmed squamous cell carcinoma (SCC) although mucoepidermoid carcinomas, small cell carcinomas, adenocarcinomas were associated with IP. ¹⁰ The association of inverted papilloma with the development of SCC according to available data in literature is between 10 and 20%. ⁸

With respect to the ability of local destruction, the tendency of recurrence and malignant transformation, a large number of surgeons recommend an open surgical approach as the therapy of choice in advanced cases. ¹¹ In order to facilitate the recovery of patients after surgery and a better quality of life, more surgeons are deciding for the endoscopic approach because endoscopic techniques have shown excision control

rates comparable to the traditional open methods - external frontoethmoidectomy and lateral rhinotomy. 12

The aim of the study was to retrospectively analyze 62 patients and their treatment experiences. During the research, it was observed that there was a deviation of septum on the same side where IP and / or IP with SCC occurred. We also wanted to investigate if the patient's age is a predictive factor in the development of IP with SCC. Lastly to show Endoscopic Endonasal Surgery as a method of choice in the treatment of IP.

Patients and methods

This retrospective study involved 62 participants who were diagnosed IP or carcinoma associated with IP in the nasal cavity and paranasal sinuses in the Otorhinolaryngology and Head and Neck Surgery Clinic in Osijek during 20 years from the begining of the research 1998. The study included 45 males and 17 females. The median age of all patients was 59 years (interquartile range of 50.25 to 68 years). In three cases we noticed a malignant transformation; in two males and one female. The follow up period was 15 years. The criteria for inclusion in the study were age 18 or older, and subjects with histologically confirmed diagnosis of IP or carcinoma associated with IP in the nasal cavity and paranasal sinuses. The criteria for exclusion from the study was the absence at follow-up treatments. A detailed history of the disease and an endoscopic examination were taken from all the patients. Prior to the endoscopic endonasal surgery which was performed by two surgeons, all the patients had a CT scan performed. Endoscopic endonasal surgery was performed in the general endotracheal anesthesia. All participants were introduced to the study purpose and protocol and signed informed consent approval to the examination procedure. The study protocol was approved by the Ethical Committee of Osijek University Hospital Centre and the Ethics Committee of the Faculty of Medicine in Osijek, and it was conducted with the Nuremberg Code and the latest revision of the Helsinki Declaration.

Statistical analysis

Categorical data were represented by absolute and relative frequencies. Numerical data were described by the median and the limits of the interquartile range (IQR). The differences of categorical variables were tested by Fisher's Exact. All P values are two - sided. A p-value of less than 0.05 was considered statistically significant. The statistical analysis was performed using the MedCalc Statistical Software version 19.4.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020), and SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

In the last 20 years, we have treated 62 patient with inverted papilloma. Each patient was preoperatively examined – necessary CT scan and underwent endoscopic endonasal surgery performed by two surgeons. The follow-up period for each patient was 15 years. Data in the period from 1998 to 2017 were analyzed retrospectively. Out of the total number of patients, 59 (95.2%) were diagnosed with IP and 3 (4.8%) in a

certain part of the IP, and the diagnosis of SCC was confirmed.

Patients diagnosed IP with SCC were significantly older than patients diagnosed with only IP (Mann-Whitney U test, p = 0.006). There is no significant difference in the diagnosis of IP with SCC and IP with respect to gender (Fisher's exact test, p > 0.99) (Table 1.).

The maxillary sinus was confirmed by both imaging radiological methods and operative findings as the most common primary site in 45.76% in patient with IP and 66.67% in patients with IP with SCC. In the second place, the most common primary site of IP was ethmoid, while frontal recess, sphenoid, nasal septum and inferior turbinate were present in only one case of IP out of the total number of patients. Table 2 demonstrates the origin site of the primary lesion.

Patients complained of epistaxis as the first symptom that would indicate the development of IP and IP with SCC. Nasal obstruction was the second most common cause observed during the disease development. Other symptoms included cheek pain. The least common are epiphora and decreased vision (Table 3).

Table 1 Diagnosis according to gender *Tablica 1. Dijagnoza prema spolu*

		Participants (%) according to gender <i>Učesnici (%) prema spolu</i>		Total	D *
		Male <i>Muško</i>	Female <i>Žensko</i>	Sveukupno	Ρ"
Diagnosis	IP with SCC	2 (4)	1 (6)	3 (5)	
Dijagnoza	IP	43 (96)	16 (94)	59 (95)	> 0.05
Total/Sveukupno		45 (100)	17(100)	62 (100)	_

^{*} Fisher's exact test, p > 0.99, Fisherov točni test p > 0.99

Table 2 Localization of primary tumor *Tablica 2. Lokalizacija primarnog tumora*

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Origin site		IΡ
Mjesto		with/sa
postanka	IP	SCC
Maxillary	27 (45,76%)	2
Ethmoid	18 (30,51%)	
Lateral nasal	6 (10,17%)	
Papiracea	4 (6,78%)	
Frontal recess	1 (1,69%)	1
Sphenoid	1 (1,69%)	
Nasal septum	1 (1,69%)	
Inferior	1 (1,69%)	

Table 3 Dominant symptom in patients with IP and SCC *Tablica 3. Dominantni symptom kod pacijenata s IP I SCC*

Dominant symptom Dominantni simptom	IP	IP with/sa SCC
Epistaxis	32 (54,24%)	2 (96.55%)
Nasal obstruction	22 (37,23%)	1 (3.45%)
Cheek pain/ <i>Bolovi</i> obraza	3 (5,08%)	
Epiphora	1 (1,69%)	
Decreased vision/Smanjeni vid	1 (1,69%)	

Table 4. The presence of deviated septum with respect to diagnosis IP and IP with SCC
Tablica 4. Prisutnost devijacije septuma u odnosu na dijagnozu IP te IP s SCC

		Number (%) of patients according to diagnosis Broj (%) pacijenta prema dijagnozi IP IP with SCC		Total Sveukupno	P*
Deviated septum	Yes/Da	53 (90)	2 (67)	55 (89)	
Devijacija septuma	No/Ne	6 (10)	1 (33)	7 (11)	< 0.05
Total		59 (100)	3 (100)	62 (100)	-

^{*} Fisher's exact test, p < 0.30, Fisherov točni test p > 0.30

Of the total number of 62 patients, 55 (88.7%) had a deviated septum on the same side where IP and IP with SCC were localized. A comparison of patients with IP and IP with SCC showed that there was a significantly higher number of patients with septal deformity in the group of patients with IP and SCC. This data cannot be interpreted due to the small number of patients with IPP and SCC included in this study. (Table 4).

The open method external frontoethmoidectomy was required only in one patient for there was an extension of the IP to the frontal sinus area and bone destruction. We did not notice a discrepancy between the CT findings and the intraoperative bone destruction findings in the last 13 years of study. During a twenty-year study period in three patients, reoperation was required due to the recurrence of IP by endoscopic approach because there was no need for an open technique. During the follow-up period, there was no occurrence of SCC after IP removal. We have no data on patients who died due to tumor recurrence.



Picture 1 Squamous cell carcinoma in 74-year-old woman Slika 1. Karcinom pločastih stanica kod žene 74

godina starosti



Picture 2 Nasal septum deviation on the same side of the localization of inverted papilloma Slika 2. Devijacija nazalnog septum na istoj strani lokalizacije obrnutog papiloma

Discussion

We have been treating patients with endoscopically different kinds of inverted papilloma, including and malignant inverted papilloma since 1995. This is a retrospective study which demonstrates our experience in the treatment of inverted papilloma.

Only a few studies have recorded the characteristics and survival rates of IP-related carcinomas. ¹³ SCC is considered to be the most common malignant tumor arising from IP. ¹⁴ SCC in IP occurs synchronously, localized in the same initial place or synchronously, arising on the same site where the IP had already been operated. ¹⁵ Symptoms like epistaxis, rhinorrhea, nasal obstruction, and anosmia are directly associated with IP and/or SCC-related IP incidence. However, unfortunately, these symptoms are not specific to allow the diagnosis of IP or SCC-related IP. During an investigation, we have noticed that the most common localization of primary tumor was the maxillary sinus.

The dominant symptom in patients with inverted papilloma was epistaxis in more than half of our patients, followed by a nasal obstruction in more than one-third of our patients. In support of the poor prognosis of the SCC, data are showing that 5 and 10 year survival reaches 39.6% and 31.8%.16 The same authors found that the prognosis is worse when the diagnosis is made in elderly age. The tumor shows low differentiation, an advanced stage, and infiltrates the cranial base or orbital cavity. Some authors reported MRI as a helpful diagnostic tool in recognizing IP malignant transformation. Inverted papilloma in the MRI should be indicated by a convoluted cerebriform pattern, a bandlike region of hyperintense and hypointense signals on T2 weighted images¹⁷ Focal loss of the cerebriform pattern is an indicator for simultaneous IP with malignant alteration^{13,18} Fujima et al. proposed that tumor blood flow measurement values can be used to differentiate SCC and IP.¹⁹

In our study, all three SCC cases associated with IP appeared as a primary case, not as a recurrence of IP in elderly patients. According to these results, older age could be a predictive factor in cancer development, primarily in contrast to recurrent IP. Reccurrence is a predictive factor of malignant alteration. In order to confirm this thesis, further research and follow-up on a larger sample are needed.

We noticed in the 55 (88.7%) of a total of 62 patients, the nasal septum deviated on the same side where IP and IP with SCC were localized. Such a high percentage of coincidence of septal deviation and IP ipsilaterally can be explained by the generally high percentage of septum deviation in the general population, about 80%. ^{20,21} A comparison of patients with IP and IP with SCC showed a significantly higher number of patients with a septal deformity in the group of patients with IP and SCC. This data cannot be interpreted due to the small number of patients with IP and SCC included in this study. Septum deviation plays an essential role in nasal congestion and increased nasal airway resistance thickening of the maxillary sinus mucosa, and it is associated with increased prevalence of chronic inflammation. 21-23 Danese et al. demonstrated that anatomical deformity source of obstruction would lead to the accumulation and retention of secretions as predispositions for inflammation.²⁵ Also, it has been noted that septum deviation increases the nose's airflow velocity with consequent mucosal dryness and impaired mucociliary clearance. 25 So far, the association between a deviated septum and IP formation has not been described in the literature. We noticed that a deviated septum could cause chronic inflammation, which is one factor in the development of IP. From the obtained result, it is

difficult to claim that septum deformities cause IP, but further research is needed. Patients with IP should be operated on, although it is not always entirely confident whether it will be an open or endoscopic approach.^{26,27} The type of approach that will be chosen depends primarily on the size of the tumor, its localization, spreading to surrounding areas, and the surgeon's experience. Endoscopic endonasal resection is the gold standard in the treatment for sinonasal IP. This approach is described with good outcomes for treating benign and selected malignant tumors with an intracranial extension.²⁸ Therefore, this study's main limitations are the small number of patients, primarily IP with SCC, and insufficient data on patients who were not available to us like CT images to confirm the radiologist written findings in the first seven-year study.

Conclusion

The endoscopic endonasal approach is a surgical treatment of choice with good outcomes for treating both other benign and selected malignant tumors. Elderly age plays a role in the early malignant transformation of IP. Continuous health professionals' education and early diagnosis with an early surgical treatment guarantee a minor percentage of SCC.

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