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# Inverted papilloma of paranasal sinuses

Georg EGGERS[1], Joachim MÜHLING[1], Stefan HASSFELD[2]

[1]*Department of Oral and Cranio-Maxillofacial Surgery, Heidelberg University Hospital (Head: Prof. Dr. Dr. Joachim Mühling), Heidelberg, Germany;* [2]*Department of Oral and Cranio-Maxillofacial Surgery, Klinikum Dortmund (Head: Prof. Dr. Dr. Stefan Hassfeld), Germany*

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*SUMMARY.* Introduction: **Inverted papilloma (Schneiderian papilloma) is a primarily benign lesion that occurs in the nasal cavity and paranasal sinuses. Clinical problems include a tendency towards local destruction, recurrence and malignant transformation into squamous cell carcinoma. Hence, complete surgical removal is the therapy of choice and a meticulous follow-up is mandatory.** Study design: **This is a review including a short introduction to the different histological types of nasal papilloma, their pathogenesis and the clinical and histopathological diagnosis. Staging systems, therapeutic approaches, and surgical concepts are discussed.** Result: **The detection and definition of factors that allow a prognosis of recurrence or malignant transformation of inverted papilloma is an active field of research. The results of studies dealing with the definition of prognostic factors, that investigated immunohistochemical methods, virus detection, molecular genetics, and histomorphological studies are discussed including our own results on the prognostic value of histology. A concept for the diagnosis, management, therapy and follow-up of inverted papilloma is proposed.** © **2006 European Association for Cranio-Maxillofacial Surgery**

***Keywords:*** **papilloma; inverted; paranasal sinus**

## HISTORY AND CLASSIFICATION OF NASAL PAPILLOMA

The nomenclature of nasal papilloma is manifold. The first description of this entity by *Ward* (1854) described the macroscopic aspect of a papillomatous neoplasm. The name 'villous carcinoma' for the same entity (*Billroth*, 1855) described the tendency to recur and grow. *Hopmann* (1883) differentiated hard and soft papilloma. He assessed the stroma–epithelium ratio. This, however, proved to be of limited value, since the number of epithelial cell layers varied within the same specimen and made an unambiguous classification impossible. *Ringertz* (1938) recognized the characteristic endophytic growth pattern and coined the term 'inverting papilloma'. Synonyms for the same entity were 'genuine papilloma of the nasal cavity' (*Kramer* and *Som*, 1935), 'inverting papilloma' (*Norris*, 1963), and 'inverted papilloma' (*Fechner* and *Alford*, 1968; *Hyams*, 1971). *Berendes* (1966) noted the tendency towards destructive growth, recurrence, and epithelial metaplasia and named it 'malignant papilloma'. However, this term is misleading since papilloma lacks the essential criteria for malignancy, such as metastasis. In a groundbreaking study, *Hyams* (1971) classified papillomas due to their pattern of growth. Papillomas with endophytic growth were classified as inverted papilloma (IP), papillomas with exophytic growth as fungiform papilloma. The third group were cylindrical cell papilloma. The WHO classification basically followed this classification (*Shanmugaratnam* and *Sobin*, 1991). However, many synonyms are still in current use (*Batsakis*, 1987). In the English-speaking area, it is also called 'inverted Schneiderian papilloma', indicating its origin from the Schneiderian membrane (*Vrabec*, 1994; *Ganzer* et al., 1992). It should be noted, that some authors regard the three types of nasal papilloma as three completely distinct entities (*Michaels*, 1996), while others confirm, that there are hybrid lesions combining features of IP and cylindrical cell papilloma in just one lesion (*Hyams*, 1971; *Kaufman* et al., 2002; *Eggers* et al., 2005).

## DEFINITION OF INVERTED PAPILLOMA

IP of the nose and paranasal sinuses is a primary benign epithelial tumour. Its share of all tumourous lesions of the nose and paranasal sinuses is 0.5–5% (*Batsakis*, 1987; *Lantis* et al., 1968; *Maran* and *Lund*, 1990).

The typical histopathological feature is inversion of the multilayer epithelium into the underlying oedematous stroma. Squamous cell epithelium is frequently found, but there is also transitional cell epithelium, cylinder cell epithelium, or combinations of these. The basement membrane is typically intact. Stroma is well vascularized and infiltrated with lymphocytes and plasma cells (*Hyams*, 1971).

IP occurs predominantly in male patients. Most authors stated a male/female ratio of 3:1 (*Hyams*, 1971; *Beck* et al., 1984; *Nielsen* et al., 1991; *Dolgin* et al., 1992; *Peter* and *Grossenbacher*, 1997;

*Plinkert* et al., 1997). Some authors state a higher rate of male patients (*Maran* and *Lund*, 1990; *Myers* et al., 1981). IP typically occurs between the second and eighth decade of life, with a peak around the age of 50 (*Ridolfi* et al., 1977; *Dolgin* et al., 1992). Cases of sinonasal papilloma in children have been described by *Maran* and *Lund* (1990).

## Aetiology

Little is known about the aetiology of IP. Molecular-genetic investigations have shown that it is a neoplasm arising from a single progenitor cell (*Califano* et al., 2000).

A possible viral aetiology has been the focus of many studies. Papovavirus-DNA was found (*Siivonen* and *Virolainen*, 1989), but the main focus is on Human Papilloma Virus (HPV) which is suspected to be associated with the formation of IP, since HPV-DNA was found in IP. Different patterns of HPV-subtypes were found (*Beck* et al., 1995b), but HPV-DNA could not be found in all samples of IP tissue. On the one hand this might be due to the fact that sometimes old samples were investigated, where the DNA had already been degraded (*Arndt* et al., 1994; *Kashima* et al., 1992). On the other hand there might be other causes for IP (*Syrjänen* 2003). Chronic inflammation has been associated with the genesis of IP (*Vrabec*, 1994) as well as occupational exposure to different smokes, dusts, and aerosols (*Deitmer* and *Wiener*, 1996). *Dictor* and *Johnson* (2000) found an association of IP with non-sinonasal head and neck cancer and hence suspected tobacco as the causative link.

## Clinical presentation

Typically, IP occurs unilaterally. Bilateral growth is only described in approximately 5% of the cases. The most frequent location (80%) is the lateral wall of the nasal cavity in the region of the root of the middle turbinate. Proximity to the nasal septum is much less frequent (*Batsakis*, 1980, 1987; *Majumdar* and *Beck*, 1984; *Myers* et al., 1990; *McCary* et al., 1994; *Lawson* et al., 1995). In the nose and paranasal sinuses, IP occurs only in areas with mucosa of ectodermal origin (*Arndt* et al., 1994).

## Case history and symptoms

Symptoms and case histories of patients suffering from IP are non-specific. Some patients report a history of nasal polyposis with repeated polypectomy or paranasal sinus surgery (*Batsakis*, 1987). However, there is no increased rate of IP in patients with recurrent nasal polyposis (*Garavello* and *Gaini*, 2006). Typical complaints are nasal obstruction, hypoosmia, frontal headache, epistaxis and rhinorrhoea (*Buchwald* et al., 1989; 1995b). Rarely occurring symptoms are tinnitus, sensorineural hearing loss, diplopia or meningitis (*Granet* et al., 1996; *Eisen* et al., 2002; *Lee* et al., 2003). The duration of symptoms is highly variable, between 0 and 72 (*Christensen* and *Smith*, 1986) or even up to 120 months (*Myers* et al., 1981) with an average of 24 months (*Buchwald* et al., 1989). In our cohort of 93 patients (Table 1), it was found that nasal obstruction was the most frequent, (yet non-specific) symptom. It has, however, to be noted that some of the patients with IP or a recurrence of IP were totally asymptomatic. Furthermore, even patients with carcinoma in IP could be completely free of symptoms.

## Diagnostics

Early diagnosis of IP is essential for optimum management. Hence, the clinician should have a low threshold for suspecting the disease (*Lund*, 2000).

### *Clinical Examination*

The best means of examination is nasal endoscopy. The macroscopic appearance has been described as that of a tumour with a mulberry-like uneven surface and a grey-livid colour (*Ganzer* et al., 1992) but other colours can be encountered as well.

### *Imaging*

Typical findings on plain radiographs, tomography, or CT scan are a unilateral opacification of the maxillary or ethmoid sinus and a mass in the nasal fossa. Other findings can be thinning or destruction of the bony lateral nasal wall, as well as decalcification or deformation. Unilateral opacification of the contiguous maxillary sinus is a common finding but there is no specific radiological appearance of IP.

**Table 1** – Frequency of symptoms prior to diagnosis in 93 patients with an inverted papilloma (IP; all values: Percentage of all patients within the respective group)

| Symptom | Primary Diagnosis IP (%) ($n = 68$) | Recurrence of IP (%) ($n = 13$) | Carcinoma in IP (%) ($n = 12$) |
|---|---|---|---|
| Nasal obstruction | 82 | 62 | 75 |
| Rhinorhoea | 19 | 23 | 0 |
| Impaired sense of smell | 18 | 0 | 17 |
| Pain | 12 | 0 | 17 |
| Feeling of pressure | 7 | 15 | 8 |
| Epistaxis | 9 | 0 | 25 |
| Diplopia | 4 | 0 | 8 |
| None | 6 | 23 | 8 |

Angiography is of limited use since it is a relatively avascular tumour. Furthermore, ultrasound and radionuclide scanning have not been found to be useful (*Momose* et al., 1980).

CT-imaging is the modality of choice (*Lund* and *Lloyd*, 1984). However, due to its poor soft tissue contrast, the tumour cannot be differentiated from retained secretion or inflammation in CT. Hence the size of an IP may be exaggerated by CT (*Lund*, 2000). Steroids and antibiotics applied prior to imaging can reduce concomitant inflammatory polyps to avoid overestimation of the disease mass (*Kraft* et al., 2003). Strictly unilateral opacification of paranasal sinuses is a warning sign of the presence of IP (Fig. 1) but since there are no definite diagnostic criteria, the role of imaging is just for preoperative staging of an otherwise confirmed IP (e.g. by means of biopsy).

A tumour of convoluted cerebriform appearance in T2-weighted or enhanced T1-weighted MRIs, located in the maxillary sinus and middle nasal meatus, is suspicious of IP. Central necrosis could be a sign of associated malignancy (*Ojiri* et al., 2000). Furthermore, inflammation or retained secretion can be identified in MRI (*Lund*, 2000). Hence, with MRI the tendency to overestimate the size of IP is less than with CT (*Oikawa* et al., 2003).

*Histology*

The definite diagnosis of IP can only be made by histology. Haematoxylin–eosin staining of a specimen obtained by transnasal biopsy under local anaesthesia is routine. Diagnosis of IP can also be performed using fine needle aspiration (*Bocklage* and *Herzon*, 1994; *Gould* et al., 2004).

*Laboratory*

There is no specific tumour marker for IP. *Yasumatsu* et al. (2002) found elevated serum levels of squamous cell antigen (SCCA1) in 91% of IP cases, decreasing after resection. SCCA1 was overexpressed in IP tissue but not in SCC or normal tissue. However, this data is not yet confirmed in routine clinical practice.

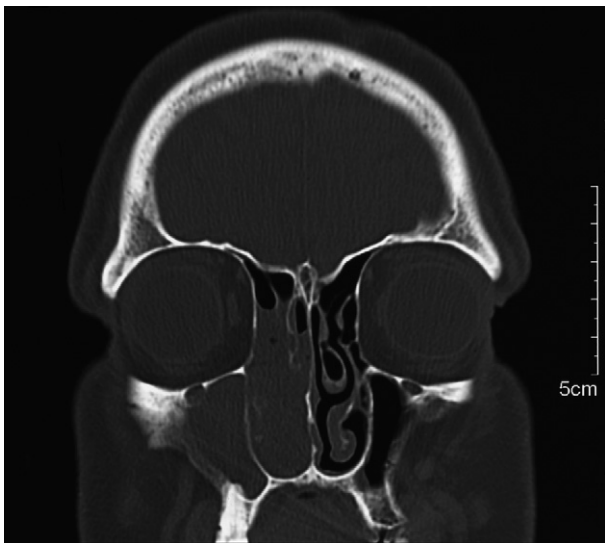


**Fig. 1** – Typical CT findings (coronal image) in a male patient with inverted papilloma: unilateral opacification of the paranasal sinuses on the right caused by the papilloma. It cannot be differentiated from obstructed secretions or nasal polyps.

## Clinical problems in the management of IP

There are three clinical problems that require particular attention in the management of IP: local destruction of bone, a tendency to recur, and associated malignancy (*Lawson* et al., 1989).

*Local bone destruction*

IP will displace neighbouring structures. The pressure of the growing IP causes also erosion of bone. In the event of osteolysis the presence of associated malignancy has to be considered (*Batsakis*, 1980).

*Recurrence*

The frequency of recurrence after surgical removal is reported as 28–74% (*Alford* and *Winship*, 1963; *Norris*, 1963; *Hyams*, 1971; *Snyder* and *Perzin*, 1972; *Batsakis*, 1987; *Ganzer* et al., 1992). The observation that IP tends to recur after incomplete surgical removal supports investigations suggesting that IP is a true neoplasm arising from a single progenitor cell and that recurrence represents growth of the residual clone (*Califano* et al., 2000).

Some authors assume that HPV subtyping enables a prognosis of the probability of recurrence. *Beck* et al. (1995a) found that patients with proof of HPV types 6 or 11 have a lower rate of recurrence than patients with HPV types 16 or 18.

*Associated malignancy*

Carcinoma occurs with IP (synchronous carcinoma) or at a later time (metachronous carcinoma). The majority of cases in the literature are synchronous carcinomas (*Myers* et al. 1990; *Dolgin* et al., 1992; *Lawson* et al., 1995). However, *Christensen* and *Smith* (1986) found equal numbers of synchronous and metachronous carcinomas.

Cases of verrucous carcinoma (*Orvidas* et al., 1999) or adenocarcinoma (*Buchwald* et al., 2001) have also been reported, but the associated malignancy is predominantly squamous cell carcinoma (SCC). Sinonasal SCC associated with IP has an incidence of approx. 0.38 cases/million persons/year (*Buchwald* et al., 2001). The frequency of carcinoma in patients with IP is reported to be 1–53% (*Hyams*, 1971; *Calcaterra* et al., 1980; *Lawson* et al., 1989; *Myers* et al., 1990; *Dolgin* et al., 1992; *Lesperance* and *Esclamado*, 1995; *Lawson* et al., 1995; *Peter* and *Grossenbacher*, 1997). This considerable variation results from different follow-up periods and cohort sizes (*Arndt* et al., 1994). There are many reports of a change from primarily benign IP to carcinoma in situ and to invasive carcinoma (*Marcial-Rojas* and *De Leon*, 1963; *Mabery* et al., 1965). Patients with carcinoma in IP are older than those IP patients without carcinoma (*Myers* et al., 1981; *Christensen*

and *Smith*, 1986; *Lesperance* and *Esclamado*, 1995) and predominantly male (*Lesperance* and *Esclamado*, 1995; *Buchwald* et al., 1995b).

The cause of development of a carcinoma in the IP has not yet been identified. Cytokeratin 5 and cytokeratin 13 have been found to be elevated in IP compared with normal epithelium (*Plinkert* et al., 1997). While molecular genetic investigations show that IP is a neoplasm arising from a single progenitor cell, IP is not necessarily premalignant. Squamous cell dysplasia, the precursor of SCC, exhibits specific genetic alterations in the first stages, before development of morphological features. In contrast, IP does not accumulate key genetic alterations of head and neck squamous cell carcinoma (loss of heterozygosity on chromosomes 3p, 9p, 11q, 13q, 17p; *Califano* et al., 2000). Key genetic alterations are present in squamous epithelial dysplasia, even in the earliest stages of tumour progression (*Califano* et al., 1996).

Mutation of the p53 tumour suppressor gene was named as a risk factor for malignant transformation (*Caruana* et al., 1997) and elevated levels of epithelial growth factor receptor (EGFR) and TGF-alpha were found in precancerous IP-lesions (*Katori* et al., 2005).

Some authors assume an influence of HPV subtyping. Transcripts of HPV DNA were found in malignant IP (*McKay* et al., 2005). *Beck* et al. (1995b) found that patients with HPV types 6 or 11 have a lower rate of associated malignancy than patients with HPV types 16 or 18. However, other authors did not find a correlation between development of malignancy in IP and proof of HPV (*Buchwald* et al., 1995a; *Kraft* et al., 2001).

## Therapy

*Surgery*

Complete surgical removal is the first option for the treatment of IP and is superior to radiation or chemotherapy (*Ganzer* et al., 1992; *Lund*, 2000). Removal should be complete to avoid recurrence (*Thorp* et al., 2001). The extent of the disease should be determined preoperatively by CT-imaging (*Myers* et al., 1990) or MRI for proper planning.

A variety of surgical techniques has been developed. Radical transfacial approaches like lateral rhinotomy, minimally invasive transnasal endoscopic techniques, and anything in between including midface degloving procedures are in use for the treatment of IP. The aim of surgery must always be the eradication of the disease at the first attempt (*Han* et al., 2001). The recurrence rate increases markedly if there was inadequate removal in the first place (*McCary* et al., 1994). Another important goal of surgery is to have an anatomically clear situation postoperatively allowing the site to be properly monitered at follow-up (*Delank* et al., 2000).

Lateral rhinotomy has been regarded as the traditional standard surgical approach to control IP and to avoid recurrence (*Myers* et al., 1981). It gives a good overview and wide access to the surgical field and can also be performed bilaterally (*Hosal* and *Freeman*, 1996). However, side-effects of this procedure may be epiphora, chronic dacryocystitis, transient diplopia, Eustachian tube dysfunction and facial scarring (*Tomenzoli* et al., 2004). Lateral rhinotomy was found to be associated with fewer recurrences and a better probability of cure than other approaches (*Weissler* et al., 1986).

Alternative techniques have been sought to avoid the facial scarring. The midface degloving procedure (*Casson* et al., 1974) as an alternative access has been further modified depending on the extent of disease (*Fliss* et al., 2000; *Jeon* et al., 2003). Midfacial degloving gives a good intraoperative view and wide access to bilateral IP (*Buchwald* et al., 1995b). Some authors recommend Denker's approach for good access without a facial skin incision (*Sanderson* and *Knegt*, 1999). However, less aggressive non-endoscopic access to the sinuses such as Caldwell–Luc's approach have been associated with high recurrence rates (*Krouse*, 2001).

The most recent developments in surgery are minimally invasive transnasal endoscopic techniques (*Winter* et al., 2000; *Wormald* et al., 2003). *Waitz* and *Wigand* (1992) first reported a series of patients in whom the recurrence rate was not worse when compared with open access (17% vs. 19%). Other reports on similar results of endoscopic surgery followed (*Buchwald* et al., 1989; *McCary* et al., 1994; *Han* et al., 2001).

The technical advantage of endoscopy can be a multi-angled magnified view making differentiation of diseased and normal mucosa easier (*Tomenzoli* et al., 2004). However, in the case of frontal sinus involvement, a combined approach is necessary even though endoscopic techniques are improving (*Chandra* et al., 2004). The piecemeal approach, inherent with endoscopic surgery, could be acceptable because what is most important is to identify and widely remove the site of attachment (*Han* et al., 2001; *Kraft* et al., 2003). Recently, the use of navigation systems for endoscopic removal of IP has been reported (*Von Buchwald* and *Larsen*, 2005) but recurrences were still reported.

The question as to whether endoscopic treatment is as safe as open surgical access, is ongoing in the (scientific) literature. In endoscopically accessible locations, recurrence rates for endoscopic vs. open surgery were similar (*Klimek* et al., 2000). However, other studies reported higher recurrence rates of IP (*Phillips* et al., 1990), particularly in cases of peripheral extension, especially into the maxillary sinus (*Zumegen* et al., 2000).

A possible reason for these differences could be different patient selection criteria. In a retrospective review, *Krouse* (2001) found low recurrence rates with endoscopic surgery, but conceded the probability of a bias in patient selection by the surgeon. Since endoscopic resectability depends on location and extent of the tumour, the external approaches are commonly used to avoid incomplete resection and recurrence in patients in whom the disease extended

towards the periphery of the paranasal sinuses or beyond. In cases of malignancy, en-bloc resection is the method of choice (*Krouse*, 2001). Other contra-indications for endoscopic surgery are extensive erosion of the skull base, extensive involvement of the frontal sinus, or scarring (*Tomenzoli* et al., 2004).

As a consequence of these difficulties and differences it appears necessary to develop a reproducible staging of the patients in order to allow proper comparison of the different treatment options. A number of staging systems for diseases of the nose and paranasal sinuses have already been suggested.

*Staging*

There is a variety of systems for staging inflammatory sinus disease (*Friedman* et al., 1990; *Kennedy*, 1992; *Lund* and *MacKay*, 1993) and also for staging of carcinoma of the paranasal sinuses (*Carinci* et al., 1966; *Greene* et al., 2002). Systems have also been developed for staging IP (*Skolnik* et al., 1966; *Schneider*, 1976). These systems propose four stages, with the disease confined to the nose as T1, disease outside the nose or paranasal sinuses as T4. Based on the involvement of paranasal sinuses, intermediate levels are staged as T2 or T3. The more advanced the disease, the higher the stage. However, for the assessment of resectability of the disease, the difficulties encountered during the operation should also be considered (*Krouse*, 2000). IP that arise from the lateral or inferior maxillary sinus are more difficult to remove endoscopically and are more likely to recur than IP, which is sessile on medial parts of the maxillary sinus (*Stankiewicz* and *Girgis*, 1993). Hence *Waitz* and *Wigand* (1992) recommended the external approach for those IP growing from peripheral regions of the sinuses.

This important difference in location was not considered by most of the existing staging systems. Hence, another staging system for IP was introduced considering the specific difficulties of endoscopic surgery of IP (Table 2; *Krouse*, 2000). The intention was to allow an assessment of outcome following different approaches. Standardized grouping of IP is necessary to allow valid studies or meta-analysis (*Han* et al., 2001). To date, there are no prospective long-term studies with sufficiently large cohorts of equivalently staged patients. Hence, the definite role of therapeutic endoscopy has yet to be determined. Today, there is no single right or wrong method, but a range from which to choose in the individual case. The optimum surgical approach is determined by the extent of disease. Other factors in the choice of surgery are the surgical expertise, particularly in endoscopic IP surgery (*Lane* and *Bolger*, 2006), previous treatment, and individual patient factors (*Lund*, 2000).

*Radiotherapy*

There are no comparative data for radiotherapy and surgery for the treatment of IP. Few reports have been published with only small cohorts of patients who underwent radiotherapy for the treatment of IP. Furthermore, in most of these cases, IP was associated with a malignancy, was inoperable or was a recurrence (*Mendenhall* et al., 1985; *Weissler* et al., 1986; *Guedea* et al., 1991; *Hug* et al., 1993; *Gomez* et al. 2000). Also, some of the cases had been treated with a combination of surgery and radiotherapy. Some authors recommended radiotherapy as an adjunct to surgical therapy in cases with associated malignancy or when complete resection was impossible (*Lawson* et al., 1995; *Dolgin* et al., 1992).

*Chemotherapy*

Reports about chemotherapy for IP are rare and always related to cases with associated malignancy (*Podd* et al., 1994). Not a single publication was found on chemotherapy for IP without malignancy.

## Postoperative management

The tendency to recur and the associated malignancy warrant meticulous follow-up of patients with IP. A good field of view of the affected region is essential (*Dolgin* et al., 1992). This should be considered during surgery (*Delank* et al., 2000). Long-term follow-up is necessary as recurrence may occur even after several years (*Winter* et al., 2000; *Eggers* et al., 2005).

The diagnosis of recurrence is based on endoscopy, CT imaging and biopsies (*Lenders* et al., 1994). Some authors recommend follow-up CT scans after surgery (*Lesperance* and *Esclamado*, 1995). MR imaging has also been suggested as a follow-up technique to discriminate recurrent tumour from postoperative change and to identify optimum sites for control biopsy (*Lai* et al., 1999; *Petit* et al., 2000).

Whilst recurrence of IP is not necessarily associated with any symptom (*Eggers* et al., 2005), it would be advantageous for further progress of a patient to identify prognostic factors.

## Prognostic factors

A variety of prognostic factors have been suggested for IP.

**Table 2** – Characterisitcs of the staging system for inverted papilloma (IP) as suggested by *Krouse* (2000)

| | |
|---|---|
| T1 | IP confined to nasal cavity. No malignancy |
| T2 | IP limited to ethmoid sinus and to medial and superior parts of the maxillary sinus. No malignancy |
| T3 | IP extends into frontal or sphenoid sinuses or involves inferior or lateral parts of maxillary sinus. No malignancy |
| T4 | IP associated with malignancy – or IP spreads outside the nose and paranasal sinuses with or without malignancy |

*Tumour size*
*Lawson* et al. (1995) reported that the only prognostic factor for recurrence was the size of the tumour. However, it remains unclear whether he observed real recurrence or incomplete removal of the lesion.

*Virus*
The importance of human papilloma virus (HPV) and its subtypes is not clear yet. High- and low-risk-associated HPV types are known for other disorders. This was also claimed for IP, with HPV 6 and 11 as low-risk- and HPV 16 and 18 as high-risk-types (*Arndt* et al., 1994), while other authors reject HPV screening as not being useful as a prognostic parameter (*Kraft* et al., 2001). Furthermore, the overall detection rate of HPV in IP varies considerably, between 24% (*Kashima* et al., 1992) and 63% (*Beck* et al. 1995a). In a meta-analysis, *Syrjänen* (2003) found HPV 6 and 11 in 33.3% of all benign sinonasal papillomas, whereas 21.7% of all sinonasal carcinomas contained HPV 16 and 18. This author concluded that sinonasal SCC could be seen as an emerging HPV lesion, but still conceded the possibility, that the aetiology of sinonasal papillomas and carcinomas is heterogeneous.

### Histopathological criteria

*Epithelium*
Various studies have been performed in order to derive prognostic factors from the histopathological examination of IP tissue. *Kaufman* et al. (2002) found an increased rate of recurrence and malignancy for papilloma with cylindrical cell epithelium. This finding could not be confirmed by own investigations (*Eggers* et al., 2005). *Luhn* and *Hörmann* (1987) grouped IP into a 'solitary nodal IP' with a nodular smooth surface, a 'multilocular nodular IP' with verrucous flat growth, and a 'myxoid IP', forming masses in the nasal cavity. The first two groups were found on the nasal septum, while the latter was found on the lateral wall of the nasal cavity and in the paranasal sinuses. Only this last subtype showed malignant transformation in that study. However, cases of multilocular nodular IP and solitary nodal IP with a malignant transformation have also been reported (*Eggers* et al., 2005).

*Buchwald* et al. (1989) classified IP according to their epithelium: squamous cell epithelium, metaplastic epithelium and glandular epithelium, as well as combinations of these. There was no coherence between clinical course (recurrence, malignant transformation) and histological classification (type of epithelium, frequency of mitosis). *Batsakis* and *Suarez* (2001) suggested that 'obvious keratosis' might be an 'ominous sign' but they conceded that there was no strong predictive factor from histology. Subtyping into hard and soft papilloma due to the ratio of stroma:epithelium (*Kramer* and *Som*, 1935) did not show any correlation with the prognosis (*Eggers* et al., 2005), nor did a classification relating to infiltration or eosinophilia.

*Cellular changes*
*Snyder* and *Perzin* (1972) related cellular atypia to an increased incidence of recurrence of IP. An increased rate of mitoses or dyskaryoses in IP was the only parameter associated with an increased rate of malignant transformation in the study by *Eggers* et al. (2005). However, *Lawson* et al. (1995) found no coherence between cellular atypia and recurrence. In essence, there is no reliable parameter for the prognosis of recurrence or malignant transformation of a diagnosed IP yet.

This does not have any negative consequences for patients with synchronous SCC, because malignant transformation has already occurred and will be diagnosed by routine histopathology examination. In all other cases these parameters might help to identify a group with a high risk for metachronous SCC that needs particular attention in follow-up.

## CONCLUSION

Inverted papilloma (IP) is a true neoplasm having a possible association with HPV infection, but the aetiology is not yet fully understood. The disease has no typical symptoms, no typical history or radiological findings. Key features are the local destruction of bone, the tendency to recur, and the association with malignancy.

It is important to consider the possibility of IP in patients with unclear nasal symptoms that last longer than one month. Furthermore, in case of a unilateral opacification of the sinonasal system in CT-imaging, a biopsy should be performed, if no firm alternative diagnosis can be reached.

Definite diagnosis is possible only by histological examination. This warrants the routine examination of all tissues surgically removed from the nose!

IP should be removed completely at the first operation. Minimally invasive endoscopic surgery has been introduced successfully for the management of IP, but there is a lack of data to assess the outcome of this method in comparison with conventional open surgery.

Long-term follow-up is necessary. Older male patients at the time of first diagnosis, patients with increased mitoses or atypia of nuclei in histological examination, and patients having undergone the resection of a large papilloma seem to be at higher risk and need particular attention. However, no reliable factors for the prognosis is known as of today. Hence, meticulous follow-up is mandatory.

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**Priv.-Doz. Dr. med. Dr. med. dent. Georg EGGERS**
Department of Oral and Cranio-Maxillofacial Surgery
Im Neuenheimer Feld 400 69120
Heidelberg, Germany

Tel.: +49 6221 56 73 32
Fax: +49 6221 56 42 22
E-mail: georg.eggers@med.uni-heidelberg.de

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