PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link. http://hdl.handle.net/2066/25072

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

THE PROGNOSTIC VALUE OF A PRIMARY INVERTED PAPILLOMA OF THE URINARY TRACT

J. A. WITJES, M. R. VAN BALKEN AND C. A. VAN DE KAA

From the Department of Urology, University Hospital Nijmegen, Nijmegen, The Netherlands

ABSTRACT

Purpose: Ever since the recognition of the inverted papilloma as a distinct lesion of the urinary tract, there has been discussion about the possible (pre)malignant potential of this rare tumor, with subsequent uncertainty about followup. Hampering the discussion are the low frequency, the unknown etiology, the difficult histopathological diagnosis and the reported association with transitional cell carcinoma. We reviewed the literature and studied our patients, resulting in the largest series reported in the literature to date.

Materials and Methods: We selected 51 patients with an inverted papilloma without a history of or a concordant transitional cell carcinoma of the urinary tract. Histology of all patients was reviewed.

Results: After review, as many as 14 patients appeared to be misdiagnosed (transitional cell carcinoma in 11). In 37 patients, we could confirm the diagnosis of inverted papilloma, with characteristics that were highly comparable to those described in the literature. Only 1 patient had a superficial bladder tumor after 49 months.

Conclusions: Reviewing these data and our own results, we conclude that an inverted papilloma does not seem to be a risk factor for transitional cell carcinoma, although inverted papillomas and transitional cell carcinoma appear to be related to some extent. Therefore, frequent and long-term followup does not seem to be necessary provided that there is no doubt about the difficult histological diagnosis.

KEY WORDS: urinary tract, papilloma

Since the inverted papilloma of the urinary tract was reported as a distinct lesion, there has been discussion about the relation between the inverted papilloma and transitional cell carcinoma of the urinary tract. This question, however, has not been answered for several reasons. First, inverted papillomas are rare, with around 280 cases reported in the literature. Most of these cases have been described in single or small case reports, and only 5 reports have been published with 10 or more patients, 1–5 the largest dealing with 35 patients. A second problem is the difficulty of obtaining a correct histopathological diagnosis, with emphasis on the differential diagnosis with several kinds of cystitis, Brunn's cell nests and transitional cell carcinoma.

Because of these problems, the unknown etiology and recent reports about the association with malignancy, a proper followup policy remains difficult to define. In an attempt to contribute to this problem, we reviewed the literature and compared these results with our own series of 37 patients in whom the diagnosis of inverted papilloma was confirmed after pathological review.

PATIENTS AND METHODS

With the aid of the National Pathological Data Administration, all Dutch patients with the diagnosis of "inverted papilloma of the urinary tract" were selected. The National Pathological Data Administration started in 1979, and patients were selected until 1994, to allow for sufficient followup. For this study, 7 pathology departments were selected in the southeastern part of The Netherlands. Patients with an inverted papilloma of the urinary tract but with a previous or simultaneous transitional cell carcinoma were excluded from this analysis. The medical files of the selected patients were reviewed. Items investigated were symptoms,

cytology, radiological features, localization, macroscopic appearance and size, method of treatment and followup results.

In all patients selected for this study, histological slides (hematoxylin and eosin staining) were reviewed by 1 uropathologist (C. A. vdK.) based on criteria defined by Henderson et al (table 1).⁶ In cases of papillary structures or frequent mitoses, the diagnosis of inverted papilloma was not confirmed. While reviewing the histological slides, the uropathologist was unaware of the followup data.

RESULTS

Diagnosis. From the 7 pathology departments, 73 patients were selected. Sixteen patients appeared to have a concomitant or previous transitional cell carcinoma and were excluded from further analysis. Of the remaining 57 patients, 51 histological slides were available for review. Of these 51 cases originally diagnosed as inverted papilloma of the urinary tract, only 37 proved to be true inverted papillomas (see figure). Misdiagnoses, seen at all 7 pathology departments, were pTaG1-2A transitional cell carcinoma (9), pT1G2A transitional cell carcinoma (2), Brunn's cell nests (2) and polyploid cystitis (1).

Of the 37 patients having a true inverted papilloma of the urinary tract, 6 were women (16.2%), resulting in a male-to-female ratio of 5.2:1. The mean age at presentation was 58.5

Table 1. Diagnostic criteria for inverted papilloma⁶

Inverted configuration
Covering layer of urothelium
Uniformity of the epithelial cells
Absence or rarity of mitoses
Formation of microcysts (crypts)
Presence of squamous metaplasia



Typical inverted papilloma demonstrating inverted, interdigitating growth pattern with uniform cellular pattern without mitoses. Overlying urothelial layer is intact. (H & E, reduced to $\times 150$.)

years (range, 20 to 83 years). In 30 patients (81%), the age was between 50 and 79.

The inverted papillomas were located in the bladder (35) or prostatic urethra (5), with 3 patients having 2 localizations. All lesions were resected transurethrally. Most were macroscopically described as a polyploid lesion with a diameter of 3 to 25 mm. (specified in 27 cases). Very small lesions (0 to 5 mm.) were discovered while evaluating prostatism complaints.

Fourteen patients presented with more than 1 symptom, with hematuria (43.1%) and obstructive complaints (23.5%) as the main symptoms. Cytology results were available for 22 patients; mild atypia was seen in only 4. In 28 patients, an excretory urogram (IVP) was performed. A filling defect was seen in 11 (39.3%), mild dilatation in 1 (3.6%), unrelated changes such as stones in 7 (25%) and a normal IVP in 9 (32.1%).

Followup. Followup, mostly by means of urethrocystoscopy and cytology, was obtained in all cases. Mean followup was 34.3 months (range 0.5 to 128 months). In 1 case, a pTaG1 transitional cell carcinoma was found at the right ureteral orifice 49 months after resection of an inverted papilloma located at the trigone. This patient remained free of recurrences during a subsequent followup period of 96 months. In 2 patients, recurrent inverted papillomas were seen. In 1 patient, the recurrence was found at 3 months at the same location (left orifice), probably because of an incomplete resection. Nevertheless, the same patient showed a second recurrence at 7 months that originated from the right orifice. This patient died after 24 months of an unrelated cause. The second patient had a recurrence after 10 months.

In 1927, Paschkis described 4 cases of adenoma-like polyps in the bladder. Histopathologically, these tumors were identical to the lesion that Potts and Hirst described as an inverted papilloma of the urinary tract in 1963. This tumor, with a histological appearance similar to that of the inverted papilloma of the sinonasal tract, is a rather infrequent tumor: in a series of 1,829 tumors of the urothelial tract, only 2.2% were inverted papillomas. Until now, 277 cases of this rare tumor have been reported in the literature, usually as case reports with 1 or only a few patients. Only 5 series of 10 or more cases have been reported.

Apart from the fact that this tumor is infrequent, the differential diagnosis with transitional cell carcinoma is difficult. Also, the etiology is an unsolved problem. In this large series of patients with histologically confirmed inverted papillomas, several aspects of this distinct lesion have been documented and can be compared with data from the literature

Epidemiology. As in the literature, we found a male predominance. In our series, the male-to-female ratio was 5.2:1 (31 versus 6). In different series, the male-to-female ratio ranges from 3:1² to 7:1⁸. Review of 277 cases reported in the literature reveals a ratio of 5.0:1 (231 versus 46).

An inverted papilloma of the urinary tract is usually found in patients in the 6th or 7th decade of life, 1,9-11,77 but it may occur at any age, and even some cases in children have been reported. 12-14 In 241 of 277 patients reviewed, age at presentation was specified. Mean age at presentation is 60.3 years (range 9 to 94 years), which is comparable to our results (mean 58.5 years, range 20 to 83 years). Also in the literature, the majority of patients (73%, versus 81% in our series) are between 50 and 79 years of age.

Symptoms. Hematuria and obstruction are the main presenting symptoms of patients with inverted papillomas, especially for lesions originating from the trigone, bladder neck and prostatic urethra. In many cases, the obstruction is probably the result of a simultaneous prostate enlargement rather than the inverted papilloma. In 219 of 277 patients reviewed, symptoms (271) were specified. It is of interest that in 21 of 25 patients with pain complaints, the lesion was found in the upper urinary tract. Together with our own results (51 symptoms in 37 patients), the symptoms are presented in table 2.

Radiological aspects. There are no specific radiological characteristics to support the diagnosis of inverted papilloma. Usually, a filling defect or signs of obstruction are seen on contrast films. In other cases, these investigations are normal or show unrelated changes such as concrements. 1,9 Also in our series, the most frequent abnormality on an IVP is a filling defect (39.3%, versus 54.9% in the literature). All but 1 of the patients showing mild dilatation, 17-19 obstruction 17, 19-23 or hydronephrosis 20, 23-28 on contrast film had the inverted papilloma located in the lower half of the ureter or very near the ureteral orifice. Some have reported the diagnosis of the lesion by ultrasound. 14, 29, 30

Endoscopy. As for all bladder tumors, endoscopy is the diagnostic procedure of choice to detect an inverted papil-

Table 2. Presenting symptoms

| | Mo. Current Series (%) | No. Literature (%) | |
|---|---------------------------|--------------------|--|
| | 22 (43.2) | 148 (54.6) | |
| Obstruction/anuria | 12 (23.5) | 55 (20.3) | |
| Infection, penile soreness | 12 (23.5) | 24 (8.9) | |
| Flank pain/low back pain, others such as nocturia, dysuria, urge and incontinence | 4 (7.8) | 25 (9.2) | |
| None | 1 (2.0) | 19 (7.0) | |

loma. The macroscopic aspect can be a gray to white solid or polyploid, generally pedunculated lesion with color.³ A round, compact appearance with a smooth mucosa covering surface and pedicle is characteristic of inverted papillomas.¹⁷ The size varies from a few millimeters to many centimeters, but rarely exceeds 3 cm.¹⁵ Inverted papillomas are predominantly seen in the bladder, especially in the trigone and bladder neck region. Inverted papillomas of the upper urinary tract are rare. Only 1 case has been reported in the penile urethra.³¹

In all 277 patients reviewed (285 inverted papillomas), localization was specified. As expected, most of the lesions were found in the bladder neck and trigone. This percentage is even higher in a subset of the 5 largest series (105) and also in our own series (40 in 37 patients) (table 3). It is possible that less frequent localizations, such as those in the upper urinary tract, are reported more often in case reports. This is illustrated by the fact that all case reports written in 1986 and 1987 (8 articles reporting 12 cases^{25, 28, 32–36, 74}) describe lesions of the upper urinary tract.

Cytology. Because an inverted papilloma is covered by a normal and intact mucosal layer, the cytological morphology falls within the range of normal or degenerate transitional epithelium, as can be seen in patients with stones and a variety of inflammatory conditions. In the literature, cytology is specified in only 22 of 277 cases; of these cases, showed mild atypia. One patient had malignant cells, but he appeared to have a concomitant transitional cell carcinoma. In our series, 4 patients with mild atypia were seen. In conclusion, cytology does not seem helpful for diagnosis.

Treatment. Simple transurethral resection of the tumor and/or electrocoagulation is generally accepted as the treatment of choice. 1,5,6,9,32,38 However, because of initial diagnostic problems, many patients are treated with open (radical) surgery. Treatment is specified in 173 of 277 patients reviewed. Transurethral resection (58.4%), open local resection (18.5%) and (hemi-)nephroureterectomy (17.9%) are the most frequent procedures. Most of the open local excisions have been performed for lesions of the upper urinary tract (27 of 32). In our series, all patients were treated with transurethral resection.

Histopathology. The typical appearance of an inverted papilloma is that of a polyploid lesion covered by a flattened but otherwise normal-looking layer of transitional cell epithelium.3 Beneath this surface, there are numerous communicating and interdigitating epithelial strands lying within a characteristic loose connective tissue stroma. Although slight atypia can be seen, the tumor cells have a monomorphic and often basaloid appearance, with a tendency toward pallisading at the periphery of the strands and spindling in the center of the epithelial strands. Mitotic figures are rare or absent.1,41 Central in the epithelial strands, cyst (or communicating crypt^{39,40}) formation may occur, resulting in an adenomatous appearance of the tumor. 15 This cyst may contain periodic acid, Schiff positive material and occasionally crystals.1,11 Henderson et al6 defined 6 criteria for the diagnosis of inverted papilloma (table 1). However, it can still be difficult to differentiate this lesion from low grade transitional cell car inoma, cystitis cystica, cystitis glandularis and

Table 3. Localization of inverted papilloma

| Localization | No. Current Series (%) | % All Cases | % Large Series |
|---------------------|---------------------------|-------------|----------------|
| Upper urinary tract | 0 — | 26.8 | 2.9 |
| Bladder: | | | |
| Neck | 16 (40.0) | 26.0 | 30.5 |
| Trigone | 11 (27.5) | 16.5 | 21.0 |
| Lateral wall | 5 (12.5) | 6.0 | 16.2 |
| Elsewhere | 3 (7.5) | 20.5 | 25.8 |
| Prostatic urethra | 5 (12.5) | 4.2 | 3.6 |

Brunn's cell nests. Although a transitional cell carcinoma may have an intact basement membrane, it shows bulbous masses of proliferating epithelium, frequent mitotic figures, a high degree of nuclear atypia and pleomorphia and more rarely cyst formation. In inverted papillomas, on the other hand, central cores of delicate vascular stroma in the epithelial strands or exophytic papillary components are absent. In Inverted papillomas, on the diagnosis were also seen in our series at all 7 participating pathology departments. After histology review, 14 of 51 diagnoses had to be changed. The 2 pT1 grade 2 transitional cell carcinomas are most striking in this respect.

Some attempts have been made to define a histopathological classification. Although these classifications are followed by some authors, and none of them is widely used.

Etiology. In their first description of this lesion, Potts and Hirst⁷ suggested that an inverted papilloma is a neoplastic transformation of basal cells of subcervical Albarran's or subtrigonal Home's glands. Because inverted papillomas were later found outside the bladder, this idea seemed very unlikely. Instead, Trites43 stated that this lesion was an inverting variant of the urothelial papilloma, a belief adopted by some others. 1,21,44,45 A high frequency in the trigone and bladder neck and localization of the inverted papilloma in the pelvis and ureter may be explained by the mesodermal origin of the urothelium of these areas, whereas the remainder of the bladder epithelium is derived from endoderm. 1,46 In contrast to this view, Cummings⁴⁷ and Matz et al⁴⁰ postulated that this lesion was not neoplastic, but rather a kind of hyperplastic reaction, especially of Brunn's cell nests, to chronic inflammation or irritative agents. This could explain the predominance at areas of greatest irritative potential, the rare multicentricity and the very low recurrence rate of the inverted papilloma. In recent years, this theory has been supported by others.^{6,37,48} The development of the tumor can be caused by chronic inflammation^{5,49} and by carcinogenic agents as well, as was proved in rats by Kunze and Schauer.80 Today, most authors believe that the inverted papilloma of the urinary tract is a true neoplasm, although precise tissue of origin and causative agents or processes are still not known.

Malignant potential. The problem of benign or malignant potential has important clinical consequences. In favor of a benign character of an inverted papilloma are the histological appearance, rare recurrences and multiplicity and lack of invasion and metastasis. However, in recent years several authors reported multiple and recurrent lesions, the presence of a concomitant transitional cell carcinoma or malignant transformation of the inverted papilloma itself. This raised the question of whether the idea of the inverted papilloma as a benign tumor should not be reevaluated.

Multiple tumors were reported in 15 of 277 patients (5.4%) reviewed. In 9 patients, 2 lesions were found; 1,5,11,35,50-52 in 3 patients, 3 lesions; 53-55 in 1 patient, 4 lesions; 10 in 1 patient, a total of 7 lesions in 1 ureter, 35 and in 1 recent case, the number of tumors was not specified. 56 If we review only the larger series to eliminate the bias of over publications of multiple cases, the percentage of multiplicity is 3.6% (4 in 110 patients). 1-5 In our series, 3 patients had 2 tumors (8.1%). These percentages are much lower than those in primary superficial transitional cell carcinoma and do not suggest malignant potential.

Confirmation of malignant potential of the inverted papilloma cannot be found in the number of recurrences, which has been estimated to be between less than 1% and about 7%.29 Of 199 patients for whom followup was presented in the literature, 10 (5.0%) were reported to have had probable recurrent lesions (only larger series 6.1%) after a followup of 9 to 120 months (table 4).1,3,5,50,56-58 In 2 patients, recurrence appeared twice,3,50 and in 4 patients,1,2 no histological confirmation of the recurrent papilloma was obtained. We

Table 4. Followup data

| | All Cases | Large Series | Current Series |
|--|------------|--------------|----------------|
| Total No. | 199 | 98 | 37 |
| No. alive and well (%) | 166 (83.5) | 85 (86.7) | 31 (83.8) |
| No. recurrence of inverted papilloma (%) | 10 (5.0) | 6 (6.1) | 2 (5.4) |
| No. transitional cell Ca afterward* (%) | 10 (5.0) | 3 (3.1) | 1 (2.7) |
| Unrelated death (%) | 13(6.5) | 4 (4.1) | 3 (8.1) |
| Followup range (yrs.) | 0-17 | 0-14 | 0-13 |

* In 8 of 10 patients (2 of 3 in large series), there was a previous transitional cell carcinoma. In our series, patients had only primary inverted papillomas.

found 2 patients with recurrent inverted papillomas (5.4%). Again, these percentages are much lower than in transitional cell carcinoma (60 to 70%).

A simultaneous transitional cell carcinoma elsewhere in the urinary tract is reported in 25 of the patients (11.1%) with inverted papillomas (15, or 13.6% in larger series). Of interest are the 16 cases with malignant transformation of (9) or a transitional cell carcinoma in (7) the inverted papilloma. All of these transitional cell carcinomas were well or moderately differentiated and not reported to recur, with the exception of 1 case in which a recurrent G2 transitional cell carcinoma of the bladder was found. In our original group of 73 patients, 16 (22%) appeared to have concomitant previous transitional cell carcinoma.

Concordance with or a history of transitional cell carcinoma in patients with an inverted papilloma of the urinary tract at least suggests that both kinds of tumors may share some causative factors. Investigation by Kunze and Schauer⁸⁰ with carcinogens in rats supports this idea.

Only recently, Urakami et al⁸¹ investigated p53 and proliferating cell nuclear antigen immunoreactivity as well as intense Feulgen staining in inverted papillomas and concluded that these lesions might have high proliferative activity and that inverted papillomas with a high immunoreactivity for p53 may be susceptible to malignant transformation. Similar findings were reported by Kunimi et al. 82 Deoxyribonucleic acid (DNA) analysis of 8 patients revealed diploid histograms in all except 1, but the inverted papillomas had a relatively higher proliferative activity (average percentage of Sphase in normal DNA was 4.87 versus 9.78% in tumor DNA histograms). One patient showed an aneuploid DNA pattern (index 1.26) and subsequently had a bladder carcinoma. Valero Puerto et al⁸³ determined the proliferative activity using Ki-67 antigen expression in 12 patients with inverted papillomas. They also concluded that a higher proliferative activity was generally associated with poorer outcome.

Another indication of (pre)malignant behavior could be occurrence of transitional cell carcinoma in the followup of an inverted papilloma. This was reported in 10 patients for whom this was specified (199 of 277 reviewed, table 4). However, 8 of these 10 patients (larger series 2 of 3) already had a history of transitional cell carcinoma. The 2 other patients had G3 tumors after 5 and 8 years.4,24 In our study, in which only patients (mean age 58.5 years, mean followup 34.3 months) with no previous or concordant transitional cell carcinoma were selected, 1 patient (2.7%) had a pTaG1 bladder tumor 49 months after transurethral resection of an inverted papilloma. This percentage is much higher than the risk in the general Dutch population, where a 60-year-old man has a 0.36% chance of bladder cancer within 3 years.84 However, in our series, only 1 patient had a bladder tumor, which makes statistical comparison impossible. Moreover, there is some diagnostic bias, because patients with a history of an inverted papilloma are examined with cystoscopy, whereas the general population is not.

In conclusion, the histological appearance, rare multiplicity, very low recurrence rate and absence of progression support a benign character of the inverted papilloma. Our

data confirm this. On the other hand, inverted papillomas and transitional cell carcinoma are related to some extent, as can be seen in patients in whom the inverted papilloma was preceded, accompanied (11 to 14%) or followed (3 to 5%) by a transitional cell carcinoma, or in whom there was malignant transformation of or transitional cell carcinoma in the inverted papilloma. Moreover, several studies suggest a higher proliferative activity of inverted papillomas compared with normal urothelium.

CONCLUSIONS

The inverted papilloma of the urinary tract is a rare lesion. Most information comes from case reports, whereas few large series have been published. Comparison of characteristics of the inverted papilloma found by reviewing the literature on one side and our own results on the other side reveals no major differences. The lesion is particularly diagnosed in white men between the ages of 50 and 80 complaining of hematuria or outflow obstruction. Contrast film shows a filling defect, mild obstruction or nothing. Cytology and macroscopic appearance are nonspecific. The inverted papilloma, which is located mostly in the bladder neck or trigone, is treated by transurethral resection and finally diagnosed by the pathologist for its characteristic features.

Recently, transitional cell carcinoma in or malignant transformation of inverted papillomas has been described, raising questions about the malignant potential of this lesion. This question remains unsolved because the etiology is unknown and the incidence is very low. Another problem is the difficult histopathological differential diagnosis, especially with several kinds of cystitis, Brunn's cell nests and low grade transitional cell carcinoma. Misdiagnoses occur frequently, as was also seen in our series (14 of 51).

Because of the histological appearance, rare multiplicity, very low recurrence rate and absence of progression, the inverted papilloma itself does not seem to be a (pre)malignant lesion, in spite of the fact that some recent data suggest a higher proliferative activity of inverted papillomas compared with normal urothelium. On the other hand, there is a limited but clear relation with transitional cell carcinoma, possibly because of a common cause, although in 8 of 10 patients in whom a transitional cell carcinoma developed after an inverted papilloma this could have been the result of a previous or concordant transitional cell carcinoma. In our study, for which only patients with no previous or concordant transitional cell carcinoma were selected, 1 patient (2.7%) had a pTaG1 bladder tumor 49 months after transurethral resection of an inverted papilloma.

We conclude that an inverted papilloma does not seem to be a risk factor for transitional cell carcinoma, although inverted papillomas and transitional cell carcinoma appear to be related to some extent. Therefore, we do not advocate frequent and long-term followup provided that there is no doubt about the difficult histological diagnosis.

REFERENCES

- 1. Cameron, K. M. and Lupton, C. H.: Inverted papilloma of the lower urinary tract. Brit. J. Urol., 48: 567, 1976.
- 2. Goertchen, R., Seidenschnur, A. and Stosiek, P.: Die klinische Pathologie invertierter Papillome der Harnblase: eine komplexe morphologische und katamnestische Studie. Pathologe, 15: 279, 1994.
- 3. Aubert, J., Dore, B. and Touchard, G.: Inverted papilloma of the bladder: a report of 10 cases. Eur. Urol., 10: 24, 1984.
- 4. Mattelaer, J., Leonard, A., Goddeeris, P., D'Hoedt, M. and Van Kerrebroeck, P.: Inverted papilloma of bladder: clinical significance. Urology, 32: 192, 1988.
- 5. de Meester, L. J., Farrow, G. M. and Utz, D. C.: Inverted papilloma of the urinary bladder. Cancer, 36: 505, 1975.

- 6. Henderson, D. W., Allen, P. W. and Bourne, A. J.: Inverted urinary papilloma: report of five cases and review of the literature. Virchows Arch. A. Path. Anat. Hist., **366**: 177, 1975.
- 7. Potts, I. F. and Hirst, E.: Inverted papilloma of the bladder. J. Urol., 90: 175, 1963.
- 8. Grainger, R., Gilias, P. W. and Grossman, H. B.: Urothelial carcinoma occurring within an inverted papilloma of the ureter. J. Urol., 143: 802, 1990.
- 9. Caro, D. J. and Tessler, A.: Inverted papilloma of the bladder: a distinct urological lesion. Cancer, 42: 708, 1978.
- 10. Kyriakos, M. and Royce, R. K.: Multiple simultaneous inverted papillomas of the upper urinary tract: a case report with a review of ureteral and renal pelvic inverted papillomas. Cancer, 63: 368, 1989.
- 11. Lazarevic, B. and Garret, R.: Inverted papilloma and papillary transitional cell carcinoma of urinary bladder: report of four cases of inverted papilloma, one showing papillary malignant transformation and review of the literature. Cancer, 42: 1904, 1978.
- 12. Francis, R. R.: Inverted papilloma in a 14-year-old male. Brit. J. Urol., 51: 327, 1979.
- 13. Lorentzen, M. and Rohr, N.: Urinary bladder tumours in children: case report of inverted papilloma. Scand. J. Urol. Nephrol., 13: 323, 1979.
- 14. Tamsen, A., Casas, V., Patil, U. B. and Elbadawi, A.: Inverted papilloma of the urinary bladder in a boy. J. Ped. Surg., 28: 1601, 1993.
- 15. Berkhoff, W. B., Jöbsis, A. C., Bruijnes, E. and Dabhoiwala, N. F.: The inverted urothelial papilloma. Urol. Int., 40: 93, 1985.
- 16. Gläser, M., Hagemann, U., Smitz, W., Dettman, H., Jr. and Göckel, B.: Das invertierte Papillom des Urothels. Urol. Ausg. A, 22: 382, 1983.
- 17. Aubert, J., Dore, B., Villemonteix, P. and Touchard, G.: Inverted papilloma of upper urinary tract: four case reports. Eur. Urol., 15: 150, 1988.
- 18. Embon, O. M., Saghi, N. and Bechar, L.: Inverted papilloma of ureter. Eur. Urol., 10: 139, 1984.
- 19. Stower, M. J., MacIver, A. G., Gingell, J. C. and Clarke, E.: Inverted papilloma of the ureter with malignant change. Brit. J. Urol., 65: 13, 1990.
- 20. Ajrawat, H. S., Skogg, D. P., Asirwatham, J. E. and Gonder, M. J.: Lobulated inverted papilloma of ureter. Urology, 20: 290, 1982.
- 21. Geisler, C. H., Mori, K. and Leiter, E.: Lobulated inverted papilloma of the ureter. J. Urol., 123: 270, 1980.
- 22. Selli, C., Dini, S., Fiorelli, C., Nicita, G. and Turini, D.: Chronic inflammation of the ureter with urothelial ingrowth simulating inverted papilloma. Brit. J. Urol., **53**: 80, 1981.
- 23. Silverstein, S. V. and Carlton, C. E., Jr.: Inverted papilloma of ureter. Urology, 17: 160, 1981.
- 24. Lausten, G., Anagnostaki, L. and Thomsen, O. F.: Inverted papilloma of the upper urinary tract. Eur. Urol., 10: 67, 1984.
- 25. Mulkens, T. H., Vereycken, H. A., Van Nueten, J. C., Govaerts, G. C., De Schepper, A. M., Van Camp, K. O. and Van Marck, E. A.: Bilateral ureteral inverted papillomas in association with bladder carcinoma: a case report and review of the literature. Urol. Radiol., 12: 154, 1990.
- 26. Naito, S., Minoda, M. and Hirata, H.: Inverted papilloma of ureter. Urology, 22: 290, 1983.
- 27. Risio, M., Coverlizza, S., Lasaponara, F., Vercesi, E. and Giaccone, G.: Inverted urothelial papilloma: a lesion with malignant potential. Eur. Urol., 14: 333, 1988.
- 28. Villani, U., Leoni, S. and Casolari, E.: Inverted papilloma of the ureter: two cases of conservative therapy. Eur. Urol., 13: 125, 1987.
- 29. Govaerts, J., Beelaerts, W. and Van Camp, K.: Inverted papilloma of the bladder: a report of two typical cases, including sonographic figures. Acta Urol. Belg., 51: 504, 1983.
- 30. Summers, D. E., Rushin, J. M., Frazier, H. A. and Cotelingam, J. D.: Inverted papilloma of the urinary bladder with granular eosinophilic cells. An unusual neuroendocrine variant. Arch. Path. Lab. Med., 115: 802, 1991.
- 31. Heaton, N. D., Kadow, C. and Yates Bell, A. J.: Inverted papilloma of the penile urethra. Brit. J. Urol., 66: 661, 1990.
- 32. Abulafi, A., Leese, T. and Osborn, D. E.: Inverted papilloma of the ureter. Brit. J. Urol., 59: 480, 1987.

- 33. Corkill, M., Srigley, J., Graham, R. and Herschorn, S.: Inverted papilloma: an uncommon benign cause of a ureteral filling defect. Urol. Rad., 9: 164, 1987.
- 34. Kimura, G., Tsuboi, N., Nakajima, H., Yoshida, K., Masugi, Y. and Akimoto, M.: Inverted papilloma of the ureter with malignant transformation: a case report and review of literature. The importance of the recognition of the inverted papillary tumor of the ureter. Urol. Int., 42: 30, 1987.
- 35. Moss, J. G. and Gunn, A. A.: Inverted papilloma of the ureter lying within an ileal carcinoid. Brit. J. Urol., 60: 272, 1987.
- 36. Taylor, F. M. and Arroyo, J. G.: Inverted papilloma of the renal pelvis: cytologic features of ureteral washings. Acta Cytol., 30: 166, 1986.
- 37. Watters, G., Grant, A., Wiley, S., Kneale, K. and Mitterdorfer, A.: Inverted papilloma of the upper urinary tract. Brit. J. Urol., 55: 176, 1983.
- 38. Whitesel, J. A.: Inverted papilloma of the urinary tract: malignant potential. J. Urol., 127: 539, 1982.
- 39. Iwata, H., Yokoyama, M., Morita, M., Bekku, T., Ochi, K. and Takeuchi, M.: Inverted papilloma of urinary bladder: scanning and transmission electron microscopic observation. Urology, 19: 322, 1982.
- 40. Matz, L. R., Wishart, V. A. and Goodman, M. A.: Inverted urothelial papilloma. Pathology, 6: 37, 1974.
- 41. Romanelli, R.: Inverted urothelial papilloma: report of five cases and review of the literature. Pathologica, 78: 89, 1986.
- 42. Pardijs, W. H., de Ruiter, H. J. and Jacobs, A. S.: The inverted papilloma. Neth. J. Surg., 34: 130, 1982.
- 43. Trites, A. E. W.: Inverted urothelial papilloma: report of two cases. J. Urol., 101: 216, 1969.
- 44. Jacobellis, U., Resta, L. and Ruotolo, G.: Inverted papilloma of the ureter. Eur. Urol., 9: 370, 1983.
- 45. Kostakopoulos, A., Delakas, D., Legaki, S. and Sofras, F.: Inverted papilloma of the ureter. Acta Urol. Belg., **56:** 471, 1988. 46. Phillips, D. E. and Blenkinsopp, W. K.: Inverted papilloma and
- 46. Phillips, D. E. and Blenkinsopp, W. K.: Inverted papilloma and papillary transitional cell carcinoma of bladder. Brit. J. Urol., 61: 162, 1988.
- 47. Cummings, R.: Inverted papilloma of the bladder. J. Path., 112: 225, 1974.
- 48. Kim, Y. H. and Reiner, L.: Brunnian adenoma (inverted papilloma) of the urinary bladder: report of a case. Hum. Path., 9: 229, 1978.
- 49. Pienkos, E. J., Iglesias, F. and Jablokow, V.: Inverted papilloma of bladder. Urology, 2: 178, 1973.
- 50. Palvio, D. H.: Inverted papillomas of the urinary tract: a case of multiple, recurring papillomas of the renal pelvis, ureter and bladder associated with malignant change. Scand. J. Urol. Nephrol., 19: 299, 1985.
- 51. Salm, R.: Neoplasia of the bladder and cystitis cystica. Brit. J. Urol., 39: 67, 1967.
- 52. Schulze, S., Holm Nielsen, A. and Ravn, V.: Inverted papilloma of upper urinary tract. Urology, 27: 58, 1986.
- 53. Anderstrom, C., Johansson, S. and Pettersson, S.: Inverted papilloma of the urinary tract. J. Urol., 127: 1132, 1982.
- 54. Bar-Moshe, O., De Roy, G. and Vandendris, M.: Les papillomes inversés urothéliaux. J. d'Urol., 89: 35, 1983.
- 55. Page, C. M., Nelson, J. H. and Drago, J. R.: Multifocal, synchronous inverted papillomas involving the ureter. J. Urol., 145: 357, 1991.
- 56. Rozanski, T. A.: Inverted papilloma: an unusual recurrent, multiple and multifocal lesion. J. Urol., 155: 1391, 1996.
- 57. Schultz, R. E. and Boyle, D. E.: Inverted papilloma of renal pelvis associated with contralateral ureteral malignancy and bladder recurrence. J. Urol., 139: 111, 1988.
- 58. Renfer, L. G., Kelley, J. and Belville, W. D.: Inverted papilloma of the urinary tract: histogenesis, recurrence and associated malignancy. J. Urol., 140: 832, 1988.
- 59. Bassi, P., Piazza, R., Milani, C., Aragona, F., Oliva, G. and Dalla Palma, P.: Inverted papilloma of the renal pelvis. Urol. Int., 46: 73, 1991.
- 60. di Cello, V., Brischi, G., Durval, A. and Mincione, G. P.: Inverted papilloma of the ureteropelvic junction. J. Urol., 123: 110, 1980.
- 61. Dirschmid, K., Breitfellner, G. and Kiesler, J.: Das invertierte Papillom des Urothels. Urol. Ausg. A, 15: 180, 1976.
- 62. Dörr, R. A., Helsdingen, P. R. and Bakker, P. M.: Het inverted papilloma van urinewegen. Ned. Tijdschr. Geneeskd., 123: 5, 1979.

- 63. Fromowitz, F. B., Steinbook, M. L., Lautin, E. M., Friedman, A. C., Kahan, N., Bennett, M. J. and Koss, L. G.: Inverted papilloma of the ureter. J. Urol., 126: 113, 1981.
- 64. Garritano, A., Vecchioli Scaldazza, C. and Morosetti, C.: Inverted papilloma of the ureter. Eur. Urol., 14: 249, 1988.
- 65. Perrin, P., Dutrieux, N. and Durand, L.: Inverted papilloma of the ureter. Brit. J. Urol., 56: 223, 1984.
- 66. Spevack, L., Herschorn, S. and Srigley, J.: Inverted papilloma of the upper urinary tract. J. Urol., 153: 1202, 1995.
- 67. Stanfield, B. L., Grimes, M. M. and Kay, S.: Primary carcinoid tumor of the bladder arising beneath an inverted papilloma. Arch. Path. Lab. Med., 118: 666, 1994.
- 68. Stein, B. S., Rosen, S. and Kendall, A. R.: The association of inverted papilloma and transitional cell carcinoma of the urothelium. J. Urol., 131: 751, 1984.
- 69. Théôret, G., Paquin, F., Schick, E. and Martel, A.: Inverted papilloma of urinary tract. Urology, 16: 149, 1980.
- 70. Uyama, T., Nakamura, S. and Moriwaki, S.: Inverted papilloma of bladder. Two cases with questionable malignancy squamous metaplasia. Urology, 16: 152, 1980.
- 71. Uyama, T. and Moriwaki, S.: Inverted papilloma with malignant change of renal pelvis. Urology, 17: 200, 1981.
- 72. Vicini, D., Ravasi, S. and Castello, A.: II papilloma invertito dell'urotelio: contributi di 4 casi. Urologia, 123: 753, 1979.
- 73. Yamaguchi, K., Kitagawa, N., Zama, S., Yanagi, S., Ito, H., Matsuzaki, O. and Nagao, K.: Inverted papilloma of renal pevis associated with transitional cell carcinoma of the bladder. Urol. Int., 43: 302, 1988.
- 74. Paschkis, R.: Über Adenome der Harnblase. Z. Urol. Chir., 21: 315, 1927.
- 75. Hyams, V. J.: Papillomas of the nasal cavity and paranasal

•

- sinuses: a clinicopathological study of 315 cases. Ann. Otol. Rhinol. Laryngol., 80: 192, 1971.
- 76. Oberman, H. A.: Papillomas of the nose and paranasal sinuses. Amer. J. Clin. Path., 42: 245, 1964.
- 77. Kunze, E., Schauer, A. and Schmitt, M.: Histology and histogenesis of two different types of inverted urothelial papillomas. Cancer, 51: 348, 1983.
- 78. Highman, W. J.: Urinary cytology in inverted papilloma of the lower urinary tract. Acta Cytol., 22: 335, 1978.
- 79. Grignon, D. J. and Sakr, W.: Inflammatory and other conditions that can mimic carcinoma in the urinary bladder. Path. Ann., 30: 95, 1995.
- 80. Kunze, E. and Schauer, A.: Morphology, classification and histogenesis of N-butyl-N-(4-hydroxybutyl)-nitrosamine-induced carcinomas in the urinary bladder of rats. Z. Krebsforsch., 88: 273, 1977.
- 81. Urakami, S., Igawa, M., Shirakawa, H., Shiina, H. and Ishibe, T.: Biological characteristics of inverted papilloma of the urinary bladder. Brit. J. Urol., 77: 55, 1996.
- 82. Kunimi, K., Uchibayashi, T., Hasegawa, T., Lee, S. W. and Ohkawa, M.: Nuclear deoxyribonucleic acid content in inverted papilloma of the urothelium. Eur. Urol., 26: 149, 1994.
- 83. Valero Puerto, J. A., Redondo Martinez, E., Jiemenez Gonzalez, C., Gomez Medina, M. L. and Martinez de la Riva, S. I.: Inverted transitional-cell papilloma: the expression of the Ki-67 nuclear antigen as a prognostic factor. Arch. Esp. Urol., 48: 887, 1995.
- 84. Visser, O., Coebergh, J. W. W. and Schouten, L. J.: Incidence of Cancer in The Netherlands 1993. Utrecht: SIG Health Care Information, 1996.