

## STATE OF THE ART IN THE DIAGNOSIS AND TREATMENT OF THE UPPER UROTHELIAL CANCER

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**Summary.** Upper urothelial cancer (UUT) is not a common neoplasm. It's a biological potential expressed as a more frequent occurrence in patients with Balkan endemic nephropathy (BEN). Analgesic nephropathy was discussed in this paper too. The most important facts and dilemmas in the evaluation, treatment and follow-up of patients with UUT were analyzed. Diagnosis is still most frequently performed by excretory urography and retrograde pyelography. Additional diagnostic tools like ureteroscopy, CT are helpful and even more sensitive but not always approachable. The therapeutic strategy is based on radical operation. Organ sparing surgery must be carefully evaluated especially in patients from the regions of BEN because of different biological behavior of UUT and less expressed malignancy.

**Key words:** Urothelial cancer, etiology, diagnosis, therapy

### Introduction

Upper urinary tract urothelial cancer (UUT) is not a common clinical entity. About 4% of all kidney neoplasms are UUT. There are three recognized etiological factors connected with the more common occurrence of UUT: industrial solvents and dyes, previously used contrast material (Thorotrast), with the radioactive Thorium as the main constituent, and high frequency in patients from the regions of the Balkan Endemic Nephropathy area (BEN) as well as in patients with the chronic analgesic abuse and a consequent Analgesic nephropathy (1). These neoplasms are commonly associated with bladder neoplasms, and have both synchronous and metachronous bilateralism, frequent recurrence rate, and unexplained appearance of chronic renal failure. So, patients are faced with two important problems: renal failure and permanent evolution of the neoplastic process.

The aim of this paper is to discuss the most important diagnostic and therapeutic possibilities in patients with UUT.

### Etiology

The first and the second mentioned etiological factors are primarily of historical interest now because of the highly sophisticated industrial protection, as well as more refined contrast materials. BEN is a relatively new recognized disease, first diagnosed by Danilovic in 1957 (2). It is defined as a chronic progressive tubulointerstitial disease. Initial pathological conditions in the evolution of BEN are glomerular hyalinosis, discrete tubular atrophy and interstitial fibrosis, leading to extensive

fibrosis and resulting in bilaterally small kidneys. The etiology of BEN has been unclear, until now but it is generally recognized as an environmental disease. There are several important etiological factors (mycotoxins, viruses, organic substances dissolved in the water). Besides these, there are more than two dozen different hypotheses, regarding the evolution of BEN, but all of them are characterized by an lack of real proofs to confirm real etiology of the disease. It is assumed that patomorphological lesions in BEN and UUT are produced by the same influence, and are distinctly different from carcinogenesis that results in UUT appearance outside the regions of BEN (2,3). There is no difference in histological appearance and classification between UUT from the regions and outside the regions of BEN. Biological differences are, quite to the contrary, prominent. UUT from BEN areas have slower growth, they are less malignant, and after progression up to the grade 3 and invade muscular layer. Neoplasms outside BEN can invade the wall even as grade 2 neoplasms. There is the evidence from certain biological markers, that apoptosis (programmed cell death) is more frequent in BEN associated UUT that results in decreased malignancy. It is supposed that possible causative factor that promotes tumor growth also expresses tumor toxicity. Average survival rate of patients BEN associated UUT is around 8 years, compared to 3 years in patients from non-endemic areas. Average tumor grade was also statistically different (2,3) from endemic compared to 2,8 and non-endemic areas. During the period from 1969-1988 incidence of UUT was 57 to 62 times greater in regions of BEN compared to non-endemic areas. During the next decade incidence of BEN is constantly decreasing, and UUT appear less frequently in BEN areas (11 time more

frequent in endemic areas) up to the present time. Occurrence of both BEN and UUT shifted to the older age compared to the previous results (fifth and sixth decade compared to third and fourth decade previously). Familiar clustering is confirmed, and that supported the hypothesis of genetic susceptibility and environmental contributing factors that influence on the evolution of the disease (2, 4, 5).

Analgesic nephropathy is also a similar disease with a more frequent occurrence of UUT in long lasting analgesic abusers. In the recent decade there is especially increased incidence of bladder neoplasms among the analgesic abusers compared to non abusers (5,8 times) (5).

## Diagnosis

The clinical diagnosis is based mainly on relevant clinical symptoms and signs as well as on the appropriate use of radiological techniques. The most important clinical symptom-total painless hematuria is present in 70-90% of patients with a significant difference in intensity. Symptoms of renal colic are coming from the passing of the blood clots through the urinary system. Flank tumor caused by hydronephrosis is present in 10-20% of patients and, in a small number of them, from the extensive neoplasm. Extensive neoplasm is followed by the symptoms of general cachexia and abundant weight loss, secondary anemia etc (1).

Laboratory is unspecific and is characterized by the presence of leucocyturia and erythrocyturia (1). Urinary cytology was hoped to be relevant for the diagnosis and follow up of patients but there is lack of positive clinical usable experience. It is not enough sensitive or specific. Clinical utility of the cytology is decreased because of inadequate urine sampling (insufficient number of cells, great dilution of the urine in the bladder etc). The sensitivity of urinary cytology is, according to the best results, around 60% for high-grade neoplasms and about 20% for low grade and low stage neoplasms (1, 6, 7). New markers like BTA test are not still evaluated sufficiently for the clinical use.

Radiology is the mainstay of clinical diagnosis. Appropriate radiological diagnosis means determination of the morphology of the neoplasms as well as clinical staging. Ultrasound is of a limited value for the neoplasms only in renal pelvis (1). Excretory urography (retrograde pyelography) is still the most frequently used in the routine clinical praxis. Important radiological sign "filling defect" can be produced by the benign morphology (clots, papilloma) or by the neoplasm (1). Papillary neoplasms are characterized by the lack of signs of local infiltration (tortuosity, rigidity etc). Infiltrating neoplasms evolve like an "iceberg" passing through the calyceal wall thickness that is recognized as a rigidity, tortuosity etc. on the "X ray" film. It must be kept in mind that there is no way to see "carcinoma in situ" i.e. intraepithelial neoplasm by imaging techniques. Significant clinical problem is to make difference between

nonopaque calculi and papillary tumor (possible on ultrasound- stones make an acoustic shadow) and make a difference between ureteral tumor and the stone. Filling defect from the neoplasm is never so smooth, dilatation is both proximal and distal (in stones proximal) and filling defect is like "goblet" if neoplastic. Deep infiltration can be best noticed on CT and MRI. Metastatic lymphatic spread is visible on CT or MRI only as a lymph node enlargement (1). CT has an overall sensitivity of 57% and specificity of 87% in making a difference between deep infiltrating and superficial UUT (statistics on 29 patients). Sensitivity and specificity of CT are not the same for superficial and deep infiltrating neoplasms with the better results in characterizing deep infiltrating and extravisceral tumor spread (8). There is no reliability on CT in distinguishing between pT<sub>a</sub> and pT<sub>2</sub> neoplasms. Sensitivity and specificity of CT for parenchymal invasion are 100% and perirenal fat 70% respectively, and specificity 82-97% (statistics performed on 51 cases). The main reason for low sensitivity of CT, are suboptimal CT scans, wide "blind" space between the scans and very thick scans. Keeping in mind that CT is the method that is not precise by itself, some additional criteria seem to be helpful in tumor characterizing. In the series of 31 patients proximal hydronephrosis was contributing criterion for the overstaging of the neoplasm. Size of the neoplasm 3cm or less, is an indirect sign of non-infiltrating neoplasm (8-11).

Ureteroscopy performed retrogradely, and pyeloscopy are recently evaluated methods that give a possibility of direct vision, evaluation and biopsy of the ureter and renal pelvis. Sensitivity and specificity of ureteroscopy are 79% and 83% respectively. If a biopsy is available, sensitivity and specificity are further increased by the detection of neoplasms in cases with urographically unrecognized filling defects (82% and 92% respectively) (series of 40 patients). There is also a chance (although little) of tumor seeding through the trace of the ureteroscope (1, 7). Ureteroscopy (antegrade and retrograde) is even more sensitive than urography, and used in cases with positive urinary cytology, absent of filling defect and unilateral gross hematuria without the filling defect.

No one of the methods has an absolute detection ability, but surgeon must be sure in the treatment plan, before the surgery because of the lack of "palpable feeling" conclusions and further information on the operating table (or they are very limited).

## Treatment and follow-up

The common oncological principle of "wide resection" is expressed in UUT in extrafascial nephrourethrectomy and excision of the bladder cuff. The operation can be performed classically, or like a laparoscopic surgery. Laparoscopy is more time consuming but equally effective entailing a shorter recovery period. Hospital stay is shorter, and faster is return to normal activities (12). Metastatic extravisceral tumor spread is mainly

lymphogenic, so it is generally accepted that lymphadenectomy is hardly curative in patients with UUT. There is a lack of evidence for any survival benefit in patients after the resection of the metastatic lymph nodes. It may be helpful only in patients with minimal metastatic disease (13).

Before the discussion about the place of "organ sparing" surgery there are several absolute indications for it: solitary kidney (anatomically, functionally), renal failure, or bilaterally damaged kidneys. Local resection of the neoplasm was first reported by Albarran in 1903. It was later confirmed that patients with locally resected tumors have respectable survival rate, almost like patients with radical operation (14). Local resection (polar resection, ureteral resection plus anastomosis or ureterocystoneostomy etc.) is useful only in less invasive neoplasms (pT1; G1-2), or in cases where the indication is absolute (1). However it is difficult to have a preoperative exact evaluation of the tumor stage. It is very reasonable to obtain biopsy in possible candidates, because there is a significant concordance between tumor grade and tumor stage. Less invasive treatment is also possible by endoscopy with the acceptable risk immanent to the method, like seeding over the operating channel or iatrogenic trauma. The recurrence rate after conservative surgery mainly depends on case history, tumor size, tumor grade and multiplicity (15). If the patients are extremely well selected, rate of local recurrences is 33% (statistics on 23 patients) up to 70% (statistics on 47 patients). Local resections performed by endoscopy (fluguration, laser excision etc) are equally successful like opened method but with the shorter hospital stay (15, 16, 17). Patients with the previous history of bladder neoplasms are at substantially greater risk to get UUT.

Additional treatments can be obtained using bilateral DJ stents or percutaneous perfusion of the upper urothelium with Bacillus Calmette-Guerinne. These procedures are performed in cases with histologically proved "in situ" neoplasms, but there are conflicting results regarding the real utility of this procedure (18, 19).

"Disease free" survival according to the multivariate analysis performed over the common important parameters showed that only age, tumor stage and type of surgery were relevant for the survival rate. Statistics of Hall et al. performed on 252 patients showed that local recurrence of the disease is most frequent during the first 12 months (27%) and follow up over thirty years showed that five year disease-free survival is the best for pTa or "pT-in situ" neoplasms (up to 100%), and not more than 6 months for pT4 neoplasms (20).

Follow up of UUT is a substantial part of the treatment because of its recurrences and bilateralism. In cases with a conservative surgery performed, there are more demands for a competent follow up. There are several possibilities: urinary cytology, retrograde pyelography, excretory urography and urteropyeloscopy. The least sensitive and specific are urinalysis (37,5% and 85% respectively) and cytology with the sensitivity 50%-71% and specificity 51%-100% (series of 285 patients). Retrograde pyelography has a sensitivity of 71% specificity 84,7% and ureteropyeloscopy is the most sensitive (93,4%) and little less specific (65,2%) (both statistics on 23 patients) (21). Ureteroscopy is recommended as the best method for surveillance of UUT. Retrograde pyelography also looks like a good compromise between simplicity and reliability. There is a general agreement that urinary cytology must not be the central method for follow-up (21). Every patient with UUT is under risk for recurrence but there are special groups like patients with the previous history of UUT and patients with the previous bladder tumors. In these cases annual contrast imaging is advisable (24). Excretory urography is especially important for the postoperative follow up of these patients (22-26).

Some other data suggests that there is a chance of about 2,7% for the UUT to evolve after primary bladder tumor, and only specific risk factor is tumor multiplicity that further supports theory about panurothelium origin of the urothelial neoplasms (19).

Metastatic UUT neoplasms are out of the focus of surgical interest. Almost all of patients with metastases will die in 5-15 months from the time of diagnosis. The most important fact for determination of the survival, are patients performance status, serum alkaline phosphates and absence of the lung metastases. Chemotherapy improves survival significantly but the quality of life is questionable (5,1 months compared to 15, 3 months) (27).

## Conclusion

BEN still remains the most important etiological factor connected with the increased occurrence of UUT. UUT are the usually diagnosed with excretory urography and retrograde pyelography. Additional diagnostic methods are useful in special cases. Classical therapy is based on the radical surgery (extrafascial nephrectomy and ureterectomy). New diagnostic opportunities allow frequent use of conservative and endoscopic surgery in selected cases of non-invasive neoplasms. It is especially important because of synchronous and metachronous bilateralism, but request very competent, time and financially consuming follow-up.

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## SAVREMENI PRISTUP DIJAGNOZI I LEČENJU TUMORA GORNJEG UROTELIJUMA

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*Kratak sadržaj. Tumori gornjeg urotelijuma nisu česte neoplazme. Analizirana je njihova češća pojava u regionima Balkanske endemske nefropatije (BEN) i kod bolesnika sa Analgezičkom nefropatijom. Najznačajnije činjenice i dileme u proceni, lečenju i praćenju bolesnika sa tumorima gornjeg urotelijuma su diskutovane. Dijagnoza se najčešće postavlja intravenskom urografijom i retrogradnom pijelografijom. Dopunske metode kao uretroskopija i CT su nekada i osetljivije ali nisu uvek dostupne. Strategija lečenja tumora gornjeg urotelijuma je bazirana na radikalnoj operaciji. Konzervirajuća operacija mora se pažljivo razmotriti posebno kod bolesnika iz regiona BEN zato što tumori imaju drugačije biološko ponašanje i manje izražen maligni potencijal.*

*Ključne reči: Tumor urotelijuma, etiologija, dijagnoza, terapija*