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EAU Guidelines on Diagnosis and Treatment of Upper Urinary Tract Transitional Cell Carcinoma

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Abstract

Objectives: On behalf of the European Association of Urology (EAU) guidelines for diagnosis, therapy and follow-up of upper urinary tract transitional cell carcinoma (UUTT) patients were established. Criteria for recommendations are based of level 2 only, as large randomised clinical trials have not been performed in this type of disease.

Method: A systematic literature research using Medline Services was conducted. References were weighted by a panel of experts.

Results: TNM classification 2002 is recommended. Recommendations are developed for diagnosis, radical and conservative treatment and for local chemo-immunotherapy. Prognostic factors are defined. Recommendations for follow-up after different types of treatment are given.

Keywords: Transitional cell carcinoma of the upper urinary tract; Bladder cancer; Guidelines

1. Background

Transitional cell carcinoma of the upper urinary tract is an uncommon disease, accounting for only 5 to 10% of all renal tumours, and 5 to 6% of all urothelial tumours. Ureteral tumours are even more rare than renal pelvis tumours occurring in about 25% of the cases of UUTT [1–3]. Randomised clinical trials, comparing different diagnostic or treatment modalities are not available. Therefore these guidelines can only be based on an extensive literature review and expert opinion rather than on evidence based data.

Therefore most of the statements made here by the members of the EAU Working Party on Superficial Bladder Cancer have a fairly low level of evidence as defined by the US Department of Health and Human Services [4].

The highest level of evidence in this report is 2b: evidence obtained from at least one other type (not randomised) of well-designed experimental study.

The highest level of recommendations provided here is B: based on well-conducted clinical studies, but without randomised clinical trials [4]. A search on the PubMed website has been performed from papers published from 1990 to August 2003 on upper urinary tract tumours.

The incidence of renal pelvic tumours has remained fairly constant in the last 30 years, whereas the incidence

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of ureteral tumours has slightly increased. A moderate improvement in disease specific survival has been observed [5]. Upper urinary tract tumours (UUTT) rarely occur before 40, having the peak incidence in the fifties, sixties and seventies. UUTT are three times more prevalent in men than in women. In families affected with Balkan endemic nephropathy the incidence is 100 to 200 times greater [6].

Many factors have been shown to contribute to the development of UUTT, such as cigarette smoking, abuse of analgesics, occupational factors, cyclophosphamide, coffee consumption, chronic infections and stones [7,8].

Transitional cell tumours are of the upper tract often associated with bladder tumours. Approximately 30 to 75% of UUTT have primary or secondary (developed) bladder tumours [2,3,9]. Transitional cell carcinoma of the bladder is associated with 1 to 4% of UUTT, but this risk could increase up to 20% [10–13].

Multiplicity of urothelial tumours of the ipsilateral upper urinary tract ranges from 27 to 36% but the incidence of bilateral tumours is low, 2 to 8% [1–3,14].

2. Classification

Classification is done according to the UICC TNM classification of malignant tumours 2002 [15].

- T: primary tumour.
  - TX: primary tumour cannot be assessed.
  - T0: no evidence of primary tumour.
  - Ta: noninvasive papillary carcinoma.
  - Tis: carcinoma in situ.
  - T1: tumour invades subepithelial connective tissue.
  - T2: tumour invades muscularis.
  - T3: (renal pelvis) tumour invades beyond muscularis into peripelvic fat or renal parenchyma; (ureter) tumour invades beyond muscularis into periureteric fat.
  - T4: tumour invades adjacent organs or through the kidney into perinephric fat.
- N: regional lymph nodes.
  - NX: regional lymph nodes cannot be assessed.
  - N0: no regional lymph node metastasis.
  - N1: metastasis in a single lymph node 2 cm or less in greatest dimension.
  - N2: metastasis in a single lymph node (more than 2 cm but not more than 5 cm) in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension.
  - N3: metastasis in lymph node more than 5 cm in greatest dimension.
- M: distant metastasis.
  - MX: distant metastasis cannot be assessed.
  - M0: no distant metastasis.
  - M1: distant metastasis.
- G: histopathological grading.
  - GX: grade of differentiation cannot be assessed.
  - G1: well differentiated.
  - G2: moderately differentiated.
  - G3–4: poorly differentiated/undiferentiated.

Pathology of UUTT:

- Transitional cell carcinoma accounts for more than 90%.
- Squamous cell carcinoma 0.7 to 7%.
- Adenocarcinoma less than 1%.
- Inverted papilloma
- Nonurothelial tumours (sarcomas).

3. Diagnosis

The most common presenting symptom of UUTT is gross or microscopic hematuria (75%), flank pain occurs in up to 30% and other symptoms in 10%.

Excretory urography: IVP is still the first choice examination in the exploration of hematuria. Often hematuria is the first sign of bladder cancer and therefore an IVP is done before the detection of the bladder cancer by cystoscopy or any other method. A filling defect is present in approximately 50 to 70% of cases. In 10 to 30% of patients, tumours cause obstruction or nonvisualization of the collecting system, this finding is usually associated with invasive tumour.

The detection rate of UUTT by IVP is rather disappointing in patients with bladder tumours [16].

Retrograde urography may be useful in these last cases and in doubtful images with a sensitivity over 75% [17,18].

Ultrasonography is helpful in distinguishing between UUTT and calculus.

CT scan may be useful in diagnosis and in staging and to discriminate renal parenchymal tumours, but it is difficult to accurately diagnose small volume tumours of the renal pelvis and ureter [19,20]. Better than any other imaging technique CT can determine the local extent of the primary tumour, invasion in renal parenchyma, presence of lymph nodes or liver metastasis [19,20]. As such, CT is only advocated when an invasive tumor has to be ruled out. Chest X-ray and bone scan is advocated in invasive disease.

MRI has no advantages over CT.

Cystoscopy: because the high incidence of associated bladder cancer, cystoscopy should always be performed at initial diagnostic workup. Conversely, the number of UUTT detected in the presence of bladder tumours is very low, ranging from 0.3 to 2.3% [17–22].

Cytology: voiding urinary cytology in case of absence of bladder tumours, and/or ureteral catheterisation for collecting urine directly from the involved upper tract for selective cytology are helpful in diagnosis and tumour grading. Urinary cytology testing has a high specificity (over 90%) but low sensitivity (below 50%), as it is related to the tumour grade [18].

Because of the difficulty to obtain an adequate biopsy from UUTT lesions, cytologic examination is very practical. It is the only way to detect carcinoma in situ in the upper urinary tract. Different methods exist to obtain adequate samples. Beside voided urine, one can sample by ureteral catherisation, by washing and brushing [21]. Because of the small published series, it remains doubtful if any of these techniques can be advocated as a standard.

Ureteroscopy and nephroscopy: flexible or rigid ureteroscopy allows to confirm the diagnosis, evaluate the appearance of the tumour and take cup or brush biopsies for grading and staging of tumours with a sensitivity over 80% but with a low specificity of about 60% [18,21].

4. Treatment

4.1. Radical treatment

Nephroureterectomy with bladder cuff removal has been considered and still is the standard treatment for upper urinary tract tumours, because of the high recurrence rate in the remaining distal ureter 16 to 58%, the multicentricity on the same side (15–44%) and the low incidence of bilateral tumours 2 to 5% [1–3,14,17]. Radical surgery decreases the risk of unilateral recurrence and makes follow-up less complicated. Whether nephroureterectomy is performed with one or two incisions is less important but transection of the ureter has to be avoided because of the potential of tumour spill. Different surgical techniques have been described to simplify the distal ureteral resection, stripping [24], transurethral resection of the intramural ureter [25–27] but long term follow-up in terms of recurrence are not available.The laparoscopic approach is being reported more and more often in recent years [28–31].

Survival of upper urinary tract tumours depends mainly on the stage and the grade of the treated tumour and results are excellent in patients with low grade and stage tumours.

4.2. Conservative treatment

For decades, the use of conservative treatment in patients with imperative indications has demonstrated that this approach has survival rates comparable to radical treatment, when performed in selected patients [31,32].

There is much more experience in conservative elective open surgery of ureteral tumours than in renal pelvic tumours. Renal sparing surgery is performed by many urologists in cases of ureteral tumours located in the distal third of the ureter, even for invasive tumours. In the upper tract of the ureter this is advocated less because of the surgical difficulty to bridge the gap between resection planes.

The improvement of endourological techniques and equipment have encouraged the development of conservative approaches in the management of upper urinary tract tumours, such as ureteroscopic and percutaneous approaches [33]. Recent reports have demonstrated the feasibility of these approaches, but the recurrence rate in the ipsilateral unit can be as high as 23 to 54% [34–44]. Despite this high recurrence rate, patients can be treated with a conservative treatment or with radical surgery. Although the progression rate has not been analysed since only a few series with long-term follow-up are available, a cause specific mortality between 11% and 18% has been observed [35–45].

Intraluminal techniques are only advocated in low grade and low stage tumours. This means no malignant cells in the urine at cytological examination, no signs of invasion at CT-scan and filling defect at IVP without complete obstruction.

4.3. Local chemo- or immunotherapy

While the role of chemo- and BCG instillations has been clearly established in the prevention of recurrence for superficial bladder cancer (SBC) and the treatment of Tis, this has not been clearly demonstrated in UUTT. The number of reports on its use is increasing, indicating its feasibility, acceptable toxicity and possible efficacy [46–50]. It seems logical to use the same topical application as advocated in the treatment of SBC [51]. It may be a method to cure Tis of the UUTT [52–54]. Local BCG has been applied through nephrostomy, ureteral catheters and by vesical urethral reflux through dubbel J catheters. High pressure in the renal pelvis and extravasation after BCG application

must be avoided. It is advocated to use ureteral catheters not larger than 5 French to allow drainage along the catheter to the bladder and to control drainage beforehand using contrast dye [55,56]. However a small catheter makes injection of BCG difficult. The contact with the urothelium must be sufficiently long so that an injection period over 1 to 2 hours has to be assured by a continuous pump system avoiding high pressure in the collecting system.

4.4. Radiation therapy and systemic chemotherapy

The role of radiotherapy is poorly defined, but may have some benefit in local control in the case of high grade or high stage lesions, but without improving survival [57,58].

Chemotherapeutic regimes are the same as those used for bladder cancer and are indicated in case of systemic disease. Their role as adjuvant treatment in locally advanced or N+ tumours must be proved by prospective, randomised trials, which will be extremely difficult regarding the low prevalence of UUTT.

5. Prognostic parameters

Many authors have looked retrospectively to their series of patients to determine prognostic factors for the course of the disease. Most of these studies are hampered by the small number of reported cases which reduces the chance to detect the factors which are statistically significant.

5.1. Tumour stage

The largest studies since 1990 reviewed 252 [2] and 198 [1] patients respectively. Tumour stage was shown to be a predictor of disease specific survival in a multivariate analysis. Actuarial 5 years disease free survival rates by tumour stage were 100% for Ta, 91.7% for T1 and 72.6% for T2 and 40.5% for T3 tumours. The median survival for T4 was only 6 months. Significant prognostic factors for recurrence in a univariate analysis were tumour grade and stage but these are strongly correlated with each other. Other, smaller studies have confirmed this [2,14,59,60].

5.2. Radical nephro-ureterectomy

Several studies compared radical nephro-ureterectomy to a conservative approach [2,14,61,62,63]. A better outcome was found after radical surgery than after organ sparing treatment. The recurrence rate was 40% versus 70% and survival was significantly better after radical treatment. Therefore organ sparing therapy should be used cautiously and mainly in low stage and grade cases. However this technique was not compared in prospective randomised trials in which patient characteristics were balanced between treatment groups. Several studies also contain older data.

5.3. Age, sex and tumour localisation

Some investigators found age [2], sex [63,64] and localisation of the UUTT in the renal pelvis [65] as an important negative prognostic factor. This however could not be confirmed by others.

5.4. Multifocal localisation

A previous history of superficial bladder cancer was found by some investigators [65] to be associated with a high recurrence rate.

Others found multifocality of upper urinary tract cancer [66–70] or bladder tumour [71,72] an independent factor which influences intravesical recurrence. This has been confirmed by others [73].

6. Risk factors of metachronous UUTT after bladder cancer

The probability of a tumor appearing in the upper urothelial tract after a primary tumour of the bladder varies in the literature between 0.2 to 3 up to 11% [74,75]. These differences can be explained by selection of the patients and the duration of follow-up [13]. From 9 reports, including a total of 2580 patients the number of UUTT after bladder cancer in general was less than 0.5 per year [75].

In a study of 1529 patients [78] with primary superficial bladder tumors, the overall incidence of UUTT was 2.6%. Patients with low risk SBC developed UUTT in 0.6%, the intermediate risk patients in 1.8% and the high risk patients in 4.1%. The most important risk factor for UUTT is multiplicity of the bladder tumour.

This is completely different in SBC at high risk for progression. The percentage of patients in whom UUTT is detected increases to 25% [12,76] and this occurred even after 10 years. Nearly all of these tumours are invasive and therefore the advice was to follow these patients lifelong.

The number of UUTT after invasive bladder cancer with cystectomy is low: 4% [12]. The incidence for development of UUTT is significantly higher (11%) when cystectomy has been done for SBC [79]. The bladder tumors which subsequently developed UUTT, were high grade in 84% and multifocal in more than 80% of the cases. Panurothelial invasion

occurs up to 30% if grade 3 tumors are involved [77].

Vesico-ureteral reflux: Two reports observed a high frequency of UUTT after bladder tumours in the presence of vesico-ureteral reflux [80,81]. However, another investigator could not detect such an association [82]. The higher incidence noticed by the first could be due to the selection of patients. As such the value of this observation remains uncertain.

Based on these data one can make the following recommendations on the follow-up of UUTT in patients with bladder cancer.

- Investigation of the UUTT in SBC at low risk for recurrence is of very limited use.
- Follow-up of the UUTT is mandatory in any grade 3 bladder tumor, and in the case of Cis of the bladder.

7. Follow-Up

7.1. Rationale and principles

Follow-up of UUTT after surgical treatment is recommended to detect local recurrence (in all cases) and distant metastases (in case of invasive tumours).

If radical nephroureterectomy has been performed, local recurrence is very rare, and the risk of distant metastases is directly related to the grade and the stage of the treated tumour . The bladder should be observed in all cases because of the high risk of developing metachronous bladder tumours [69], which is about 30%.

If conservative treatment has been performed, ipsilateral UUT needs a careful follow-up because of the high risk of recurrences. Despite the notable improvements in endourological technology, follow-up of patients treated with conservative therapy is difficult and minimally invasive procedures are frequently needed [18,23,29].

Stage and grade of the recurrences are usually the same as the primary tumour: 90% present the same grade and 79% the same stage [2,62]. However, during follow-up 25% will progress to a higher stage.

About 50% of recurrences occur during the first 2 years, but may continue to appear many years later thereafter [44].

7.2. Follow-up procedures

Intravenous urogram is performed in the case of conservative treatment after 3 months to detect early recurrence. Then yearly to check late complications and recurrences.

Urinary voiding cytology is an excellent method to detect high risk tumours and might be done in all cases after 3 months. Thereafter the frequency will depend on the type of surgery and the risk of recurrence in bladder and upper urinary tract. Selective upper tract cytology must be performed in the case of conservative treatment at the time of endoscopy and it is advised in cases of carcinoma in situ of the upper urinary tract and in high risk tumours.

Cystoscopy is performed because of the high incidence of associated bladder tumour and its frequency should be related to risk factors such as the initial presence of bladder tumours and tumour stage and grade.

Retrograde pyelography is indicated in case of suspicious lesions on intravenous urogram, positive cytology, and if ureteroscopy is not available or not possible.

Ureteroscopy is recommended in all conservative treated patients, at 3 months, particularly in patients at high risk for recurrence (high grade and TIS) and its frequency thereafter will depend on the risk of recurrence according to the stage and grade of the tumour.

CT scan is the best imaging technique to detect metastases in the follow-up of invasive tumours [78,83,84].

Table 1
Recommended diagnostic methods

Diagnostic method	Strongly recommended	Recommended
IVP	In all cases	
Cystoscopy + cytology	In all cases	
Ureteroscopy ± biopsy ± cytology		In case of diagnostic doubt or potential conservative therapy
Retrograde or antegrade pyelography ± cytology	Non-functional kidney	In case of ureteroscopic failure
CT scan or MRI + chest X-ray		In case of invasive tumour
Bone scan		In symptomatic patients or increased alk phosphatases

Table 2
Recommended therapy

Therapy approach	Strongly recommended	Recommended
Radical nephroureterectomy	Symptoms of invasive tumour	Decision according to the case, co-morbidity
Conservative partial ureterectomy	Solitary functioning kidney or bilateral. Low stage (non-invasive tumour)	1. Single, <3 cm, G1–2, negative cytology, non-infiltrating radiological signs for intraluminal tumour 2. Secondary upper tract tumours 3. Ureter tumour in distal third
BCG (percutaneous, retrograde) or chemotherapy	Tis	
Percutaneous resection of renal pelvis tumour or partial nephrectomy		Decision according to case and experience of the urologist

8. Conclusion and summary

Recommendations can be made only based on level B evidence (well conducted, but not randomised clinical trials). See Tables 1 and 2.

8.1. Follow-up schedule in case of nephroureterectomy

1. ≥T2 tumours → cystoscopy at 3 months, then once a year → 5 years → chest X-ray and CT-scan every 6 months → 2 years and yearly thereafter.
2. Ta–1 tumours → cystoscopy at 3 months → once a year thereafter → chest X-ray + CT scan and bone scan → when symptomatic.

8.2. Follow-up schedule in case of a conservative approach

1. At 1–3 months → IVP + urinary cytology repeated after 6 months and then once a year → 5 years.
2. Cystoscopy + ureteroscopy + urinary cytology and upper tract cytology at 3 months and 12 months, then once a year thereafter → 5 years (alternating with IVP in between these controls).
3. Carcinoma in situ → cystoscopy+ ureteroscopy + bladder and upper tract cytology every 3 months → 2 years, then every 6 months → 5 years.
4. Chest X-ray, CT scan and bone scan in symptomatic patients.

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