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European Association of Urology



Guidelines

European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2017 Update

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Abstract

Context: The European Association of Urology (EAU) Guidelines Panel on Upper Urinary Tract Urothelial Carcinoma (UTUC) has prepared updated guidelines to aid clinicians in the current evidence-based management of UTUC and to incorporate recommendations into clinical practice.

Objective: To provide an overview of the EAU guidelines on UTUC as an aid to clinicians.

Evidence acquisition: The recommendations provided in the current guidelines are based on a thorough review of available UTUC guidelines and articles identified following a systematic search of Medline. Data on urothelial malignancies and UTUC were searched using the following keywords: urinary tract cancer; urothelial carcinomas; upper urinary tract, carcinoma; renal pelvis; ureter; bladder cancer; chemotherapy; ureteroscopy; nephroureterectomy; adjuvant treatment; instillation; recurrence; risk factors; and survival. References were weighted by a panel of experts.

Evidence synthesis: Owing to the rarity of UTUC, there are insufficient data to provide strong recommendations (ie, grade A). However, the results of recent multicentre studies are now available, and there is a growing number of retrospective articles in UTUC. The 2017 tumour, node, metastasis (TNM) classification is recommended. Recommendations are given for diagnosis and risk stratification, as well as for radical and conservative treatment; prognostic factors are also discussed. A single postoperative dose of intravesical mitomycin after radical nephroureterectomy reduces the risk of bladder tumour recurrence. Kidney-sparing management should be offered as a primary treatment option to patients with low-risk tumours and two functional kidneys.

Conclusions: These guidelines contain information on the management of individual patients according to a current standardised approach. Urologists should take into account the specific clinical characteristics of each patient when determining the optimal treatment regimen, based on the proposed risk stratification of these tumours.

Patient summary: Urothelial carcinoma of the upper urinary tract is rare, but because 60% of these tumours are invasive at diagnosis; appropriate diagnosis and management is most important. We present recommendations based on current evidence for optimal management.

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1. Introduction

The previous European Association of Urology (EAU) guidelines on upper urinary tract carcinoma (UTUC) were published in 2015 [1]. The EAU Guidelines Panel has prepared updated guidelines to provide evidence-based information on the management to guide and facilitate clinical decision-making.

2. Evidence acquisition

2.1. Methodology

2.1.1. Data identification

A Medline search was performed using combinations of the following terms: urinary tract cancer; urothelial carcinomas (UCs); upper urinary tract, carcinoma; renal pelvis; ureter; bladder cancer (BCa); chemotherapy; ureteroscopy; nephroureterectomy; adjuvant treatment; instillation; recurrence; risk factors; and survival. The publications identified were mainly retrospective including some large multicentre studies. Owing to the scarcity of randomised data, articles were selected based on the following criteria: evolution of concepts, intermediate- and long-term clinical outcomes, study quality, and relevance. Older studies were only included if they were historically relevant. To facilitate evaluation of the quality of information provided, levels of evidence (LEs) and grades of recommendation were included according to the general principles of evidence-based medicine [2].

3. Evidence synthesis

3.1. Epidemiology, aetiology, and pathology

3.1.1. Epidemiology

Urothelial carcinomas are the fourth most common tumours [1]. They can be located in the lower (bladder and urethra) or the upper (pyelocaliceal cavities and ureter) urinary tract. Bladder tumours account for 90–95% of UCs and are the most common urinary tract malignancy [3]. UTUCs are uncommon and account for only 5–10% of UCs [1,4] with an estimated annual incidence in Western countries of almost two cases per 100 000 inhabitants. Pyelocaliceal tumours are approximately twice as common as ureteral tumours. In 17% of cases, concurrent BCa is present [5]. Recurrence in the bladder occurs in 22–47% of UTUC patients [1,6] compared with 2–6% in the contralateral upper tract [1,7].

Overall, 60% of UTUCs are invasive at diagnosis compared with 15–25% of bladder tumours [1,8]. UTUCs have a peak incidence in individuals aged 70–90 yr and are three times more common in men [1,9].

Familial/hereditary UTUCs are linked to hereditary nonpolyposis colorectal carcinoma [10], and these patients can be screened during a short interview (Fig. 1) [11]. Patients identified at high risk for HNPCC syndrome should undergo DNA sequencing for patient and family counselling [10,12].

3.1.2. Risk factors

Many environmental factors contribute to the development of UTUC [1,13]. Tobacco exposure increases the relative risk from 2.5 to 7 [1,13].

Historically, UTUC “amino tumours” were related to occupational exposure to carcinogenic aromatic amines including benzidine and β -naphthalene, both of which have been banned since the 1960s in most industrialised countries.

The average duration of exposure needed to develop UTUC is 7 yr, with a latency of up to 20 yr following termination of exposure.

Several studies have demonstrated the carcinogenic potential of aristolochic acid contained in *Aristolochia fangchi* and *clematis* plants. The aristolochic acid-derivative d-aristolactam is associated with a specific mutation in the *p53* gene at codon 139 that occurs mainly in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy who present with UTUC [1,13,14]. Although the incidence of Balkan endemic nephropathy is also declining, aristolochic acid plays a key role in the pathophysiology of this nephropathy.

There is a high incidence of UTUC in Taiwan, especially on the southwest coast, which represents 20–25% of UCs in the region [1,13]. There is a possible association between UTUC, blackfoot disease, and arsenic exposure in drinking water in this population [1] as well as aristolochic acid in Chinese herbs [13].

Differences in the ability to counteract carcinogens may contribute to host susceptibility to UTUC. Some genetic polymorphisms are associated with an increased risk of cancer or faster disease progression that introduces variability in the interindividual susceptibility to the risk factors previously mentioned. UTUC may share some risk factors and molecular pathways with bladder UC. So far, two UTUC-specific polymorphisms have been reported [1,15].

3.1.3. Histology and classification

3.1.3.1. *Histological types.* UTUC with pure nonurothelial histology is rare [1], but variants are present in approximately 25% of cases [16,17]. These variants correspond to high-grade tumours with worse prognosis compared with pure UC. Squamous cell carcinoma of the upper urinary tract represents <10% of pyelocaliceal tumours and is even rarer within the ureter. Squamous cell carcinoma of the urinary tract is assumed to be associated with chronic inflammatory diseases and infections arising from urolithiasis [1]. Other variants include: micropapillary and sarcomatoid carcinomas, and lymphoepithelioma. Collecting duct carcinoma can have similar characteristics to UTUC due to its common embryological origin [1]. They are, however, considered as kidney cancers and not UTUC.

3.2. Staging and classification systems

3.2.1. Classification

The classification and morphology of UTUC and bladder carcinoma are similar [1]. It is possible to distinguish between noninvasive papillary tumours (papillary urothelial

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