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Guidelines

European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma: 2015 Update

Morgan Rouprêt^{a,*}, Marko Babjuk^b, Eva Compérat^c, Richard Zigeuner^d, Richard J. Sylvester^e, Maximilian Burger^f, Nigel C. Cowan^g, Andreas Böhle^h, Bas W.G. Van Rhijnⁱ, Eero Kaasinen^j, Joan Palou^k, Shahrokh F. Shariat^l

^a Department of Urology, Hospital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, University Pierre et Marie Curie, Institut Universitaire de Cancérologie, Paris, France; ^b Department of Urology, Hospital Motol and 2nd Faculty of Medicine, Charles University, Prague, Czech Republic; ^c Department of Pathology, Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, University Pierre et Marie Curie, Institut Universitaire de Cancérologie, Paris, France; ^d Department of Urology, Medizinische Universität Graz, Graz, Austria; ^e EAU Guidelines Office Board, European Association of Urology, The Netherlands; ^f Department of Urology, Caritas St. Josef Medical Centre, University of Regensburg, Regensburg, Germany; ^g Department of Radiology, Queen Alexandra Hospital, Portsmouth, UK; ^h Helios Agnes Karll Krankenhaus, Schwartau, Germany; ⁱ Department of Urology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; ^j Department of Surgery, Hyvinkää Hospital, Hyvinkää, Finland; ^k Department of Urology, Universitat Autònoma de Barcelona-Fundació Puigvert, Barcelona, Spain; ^l Department of Urology, Comprehensive Cancer Centre, Medical University of Vienna, Vienna General Hospital, Vienna, Austria; Department of Urology, Weill Medical College of Cornell University, New York, NY, USA; Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA

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Abstract

Context: The European Association of Urology (EAU) guidelines panel on upper urinary tract urothelial cell 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 a brief 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 these keywords: *urinary tract cancer; urothelial carcinomas; upper urinary tract, carcinoma; renal pelvis; ureter; bladder cancer; chemotherapy; nephroureterectomy; adjuvant treatment; instillation; neoadjuvant treatment; recurrence; risk factors; and survival*. References were weighted by a panel of experts.

Evidence synthesis: Due 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 interest in UTUC. The 2009 TNM classification is recommended. Recommendations are given for diagnosis and risk stratification as well as radical and conservative treatment, and prognostic factors are discussed. A single postoperative dose of intravesical mitomycin after nephroureterectomy reduces the risk of bladder tumour recurrence. Recommendations are also provided for patient follow-up after different therapeutic strategies.

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.

* Corresponding author. Hospital Pitié-Salpêtrière, Academic Department of Urology, 83 Bd de l'Hôpital, 75013 Paris, France. Tel. +33 1 44 17 71 39.
E-mail address: morgan.roupret@aphp.fr (M. Rouprêt).

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Patient summary: Urothelial carcinoma of the upper urinary tract is rare, but because 60% of these tumours are invasive at diagnosis, an appropriate diagnosis is most important. A number of known risk factors exist.

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1. Introduction

The previous European Association of Urology (EAU) guidelines on upper urinary tract urothelial cell carcinoma (UTUC) were published in 2013 [1]. The EAU guidelines panel has prepared updated guidelines to provide evidence-based information on the management of these tumours in clinical practice.

2. Methodology

2.1. Data identification

A Medline search was performed using combinations of the following terms: urinary tract cancer; urothelial carcinomas, upper urinary tract, urothelial carcinoma, renal pelvis, ureter, chemotherapy, nephroureterectomy, adjuvant treatment, neoadjuvant treatment, recurrence, risk factors, nomogram, and survival. The publications identified were mainly retrospective including some large multicentre studies. Due 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. Epidemiology, aetiology, and pathology

3.1. Epidemiology

Urothelial carcinomas (UCs) are the fourth most common tumours [1]. They can be located in the lower urinary tract (bladder and urethra) or the upper (pyelocaliceal cavities and ureter). Bladder tumours account for 90–95% of UCs and are the most common urinary tract malignancy [3]. However, UTUCs are uncommon and account for only 5–10% of UCs [1,4], with an estimated annual incidence in Western countries of almost 2 cases per 100 000 inhabitants. Pyelocaliceal tumours are approximately twice as common as ureteral tumours. In 17% of cases, concurrent bladder cancer (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 (HNPCC) [10], and these patients can be screened during an interview (Fig. 1) [11]. Patients should undergo DNA sequencing to identify hereditary cancers misclassified as sporadic [10,12].

3.2. 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.

UTUC is secondary to an amino tumour of the bladder. The average duration of exposure before the development of UTUC is approximately 7 yr, with a latency of almost 20 yr following termination of exposure. The odds ratio of developing UC after exposure to aromatic amines is 8.3 [1,13]. UTUCs caused by phenacetin consumption almost disappeared after the product was banned in the 1970s [13].

Several studies have demonstrated the carcinogenic potential of aristolochic acid contained in *Aristolochia fangchi* and *Aristolochia clematis*. The aristolochic acid derivative d-aristolactam causes 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 on the decline, roles have been proposed for aristolochic acid and the consumption of Chinese herbs in the pathophysiology and induction of this nephropathy, respectively.

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 [1,13].

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 or molecular disruption pathways with bladder UC. Only two UTUC-specific polymorphisms have been reported [1,15].

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