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Urothelial carcinomas of the upper urinary tract – how does UK practice compare with European guidelines: is there a difference?

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Abstract

Upper urinary tract urothelial carcinomas (UUT-UCs) are relatively rare tumours that present a challenge to urologists, both in terms of diagnosis and treatment. The diagnostic pathway is often complex and the surgical options continue to generate controversy. The outcomes of treatment are mixed, with invasive tumours having a particularly poor prognosis. In this article we compare UK practice with the most recent European Association of Urology (EAU) guidelines for the management of UUT-UCs.

Keywords

Upper urinary tract urothelial carcinoma, urological cancer guideline

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Introduction

Upper urinary tract urothelial carcinomas (UUT-UCs) are malignant lesions that arise from the lining of the proximal urinary tract from the renal pelvis to the distal ureter. Non-urothelial cancers are rare <5%. The incidence of UUT-UC is slowly rising but it remains a rare tumour when compared with bladder cancers, which are 10 times more common.[1,2] It is twice as common in men compared with women and its peak incidence is in patients aged 70–90 years.

We will compare and contrast current UK practice with the 2015 European Association of Urology (EAU) guidelines on Urothelial Carcinomas of the Upper Urinary Tract.[3] The UK currently does not have recognised national guidelines relating to the investigation and management of UUT-UCs.

The EAU guidelines suggest that 60% of upper tract tumours are invasive at diagnosis compared with 15–25% of bladder tumours.[4,5] We disagree with this and whilst we recognise that upper tract tumours are more frequently invasive when compared with bladder cancers, the proportion of upper tract tumours that are invasive is around 40%. This compares with bladder cancer where approximately 30% are invasive at diagnosis.[6]

The most common presentation of UUT-UC is visible or non-visible haematuria. Patients can also present with loin pain often associated with clots passing down the ureter, 'clot colic'. In addition, upper tract UC can be asymptomatic when detected, and in 17% of cases is associated with a synchronous bladder tumour.[7]

Recurrence in the bladder occurs in 24–47% of UUT-UC patients[8–10] compared with 2–6% recurrence in the contralateral upper tract.[11,12]

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Diagnosis

Computed tomography intravenous urography (CT-IVU) has the highest diagnostic accuracy in the diagnosis of UC of the upper tract.[13] Although recognising that CT-IVU is the preferred imaging modality, the EAU guidelines reflect on the role for magnetic resonance urography (MRU) in the diagnosis of UC especially when radiation or iodinated contrast media are contraindicated.[14] In the UK, diagnostic MRU is rarely used due to limited availability and difficulty in the interpretation of imaging.

Positive urine cytology is highly suggestive of UC of the upper tracts in the presence of normal cystoscopy. Though it is recognised that it has a high specificity and low sensitivity with a high false negative rate in low grade tumours.[4,15,16] Cystoscopy is essential in excluding concomitant bladder tumours.

The EAU guidelines recommend diagnostic retrograde ureteropyelography as an option in the diagnostic pathway for suspected UUT-UC.[3] In the UK it is common practice to assess the upper urinary tract with CT-IVU, which will in the majority of cases provide greater information than retrograde studies alone. In the UK, if there is diagnostic uncertainty after appropriate imaging then the preferred option is to proceed to retrograde studies in combination with diagnostic ureteroscopy to allow visualisation of any upper tract abnormality and to facilitate biopsy and histological confirmation of disease. We would suggest that in the UK retrograde ureteropyelograpy in isolation does not play any significant role in the diagnosis of UUT-UC.

Management

Nephro-ureterectomy (NU) with excision of a cuff of bladder tissue is the gold standard for treatment of non-metastatic UC of the upper urinary tract in the UK.

Current EAU guidelines promote open NU for 'high risk' UUT-UC and state that invasive or large tumours (T3/T4) are contraindications to laparoscopic NU.

UK practice differs with the majority of tumours being managed by laparoscopic NU. The latest British Association of Urological Surgeons (BAUS) Section of Oncology audit for 2014 confirmed that 85% of the total of 1075 patients where data was submitted underwent laparoscopic NU in the UK.[17]

EAU guidelines also place a prominent emphasis on nephron-sparing approaches such as segmental resection and percutaneous access in the management of UC of the upper tract.[3] There is no level 1 evidence to support this approach and in the UK anecdotal evidence would suggest that neither approach is performed with any regularity. Realistically, endoscopic management in the UK is considered to be a palliative treatment in the majority of cases.

There appears to be controversy surrounding the role for lymph node dissection (LND). Anatomical templates for LND are yet to be clearly defined, and whilst the EAU guidelines recommend lymphadenectomy for invasive UUT-UC (level 4 evidence), there is a lack of consensus in the UK and as a result it is not routinely performed. This is the product of both a lack of supporting evidence for the benefit of LND and the very significant difficulties in assessing risk classification, which results from the difficulties in accurately assessing the grade and stage of tumours prior to surgery.

It is recognised that approximately 40% of patients will develop a bladder tumour following NU. The EAU guidelines and UK practice do align on the best approach to reduce bladder recurrence and recommend, a single dose of mitomycin C following catheter removal. A practice supported by the UK's One Dose Mitomycin C (ODMIT-C) study that confirmed an absolute reduction in risk of bladder recurrence of 11% and a relative reduction in risk of 40%.[18]

Multimodal therapy

UUT-UCs are obviously urothelial tumours and it should follow that they should be sensitive to platinum-based chemotherapy. The current EAU guidelines discuss neoadjuvant chemotherapy as optional in UUT-UC. The evidence to support this statement is very limited. Neoadjuvant chemotherapy with cisplatin appears attractive due to fact that the global renal function is preserved prior to NU. Given the significant issues with pre-operative staging, there remains significant concerns about over-treating low stage disease. To date there is no high-quality evidence to support the use of platinum-based chemotherapy in the neoadjuvant setting. In the UK it is not considered standard practice to offer patients neoadjuvant chemotherapy prior to NU, even if there are high risk features identified on the pre-operative staging.

Given the relatively low survival rates for muscle invasive UUT-UC post-NU there appears to be a move towards offering adjuvant chemotherapy. The 5-year survival figures are shown in Table 1.[19] Studies by Hellenthal *et al.* and Vassilakopoulou *et al*. suggest that adjuvant chemotherapy can achieve a recurrence-free rate of <50%.[20,21] A systematic review and meta-analysis by Leow *et al.* does suggest an overall benefit for cisplatin-based adjuvant chemotherapy, but does acknowledge that the evidence base to make a definitive conclusion is weak.[22] Outside the UK this practice is common and the EAU guidelines are contradictory as they appear to suggest benefit whilst counselling caution

Current evidence does not support the routine use of adjuvant chemotherapy in patients who have undergone NU for muscle-invasive UUT-UC, and in the UK the standard of care remains observation with the offer of palliative chemotherapy if recurrence is identified radiologically.

Clinicians in the UK are addressing this question through a randomised controlled multicentre trial

Table 1. Disease-specific 5-year survival rates by tumour stage.[17]

Stage	Disease-specific 5-year survival rates by tumour stage (%)
pTa / CIS	100
pT1	91.7
pT2	72.6
pT3	40.5
pT4	<5.0

CIS, clinically isolated syndrome.

Table 2. A comparison of the major differences between the EAU guidance and UK practice.

EAU	UK practice
Low risk UUT-TCC should be offered kidney sparing surgery	In the presence of a normal contralateral kidney NU remains the current standard of care for the majority cases of UUT-UC
Invasive or large tumours are a contraindication to laparoscopic NU	Laparoscopic NU is the most common surgical option for UUT-UC and significant numbers of patients will have invasive disease
Lymphadenectomy is recommended for invasive UUT-UC	Lymph node dissection is not performed routinely
Neoadjuvant chemotherapy is optional	Neoadjuvant chemotherapy is not offered
Annual CT-IVU for all stages of disease	Annual CT for high risk tumours only (pT1 and above)
Routine use of urine cytology in follow up	Urine cytology is not offered as routine follow up

CT: computed tomography; CT-IVU: computed tomography intravenous urography; NU: nephro-ureterectomy; UUT-TCC: upper urinary tract – transitional cell carcinoma.

comparing adjuvant platinum-based chemotherapy with observation (deferred treatment) in patients with muscle-invasive UUT-UC.[23] The POUT (Peri-Operative chemotherapy *versus* surveillance in Upper tract urothelial cancer Trial) is ongoing and recruiting well, given the fact that invasive UUT-UC represents a relatively rare cancer. Unfortunately, no centres from mainland Europe have joined the collaboration, which would have helped answer this key question.

Metastatic disease

The EAU guidelines for patients with advanced or metastatic urothelial carcinoma are brief, amounting to half a page of the 26-page document. The brevity of the recommendations reflects the paucity of clinical evidence in this condition.

NU is not recommended unless to palliate local symptoms particularly haematuria which reflects UK practice. In contrast to the guidelines, UK radiation oncologists would also consider palliative radiotherapy in this setting to avoid the risks and potential complications of surgery when the site of bleeding is known.

The general approach to palliative chemotherapy for advanced UUT-UC is to use platinum-based chemotherapy. The safe delivery of treatment is dependent upon performance status, renal function and comorbidities. The EAU guidelines state that there is currently insufficient data to make specific clinical recommendations in this area. Whilst true in the UK, the systemic management is identical to that offered in metastatic bladder cancer. This unified approach is reflected in recent and proposed clinical trials (PLUTO and ATLANTIS) which are investigating exciting new treatments and permit UUT-UC as well as bladder cancer patients.

Unfortunately, the prognosis for patients with advanced or metastatic UUT-UC is poor with a 5-year specific survival of <50% for pT2/pT3 and <10% for pT4 disease.[24,25]

Follow up

The EAU guidelines recommend an extravagant follow-up regime for low risk disease. This is based on level 4 evidence and includes annual CT-IVU for 5 years. In addition, they emphasise the role for urine cytology in low grade disease. In the UK the standard follow up for low risk disease is not defined but annual cystoscopy would appear reasonable. In the absence of haematuria, it remains debatable as to when or indeed if upper tract imaging should be performed. An issue that remains relevant given the fact that many of these patients will have impaired renal function rendering a CT-IVU potentially harmful in terms of the risks of contrast-induced acute kidney injury.

Conclusion

EAU guidelines on the management of UC of the upper tract are based on fairly low level evidence. There are quite a few areas where UK practice and EAU guidelines appear to differ (see Table 2). These differences almost certainly reflect the lack of available level 1 evidence on which to base practice. This is the direct result of the relative rarity of UUT-UC, and in particular the low numbers of patients with invasive UUT-UC. There is also very limited data available on UK practice regarding the management of UC of the upper tract in terms of both diagnosis and treatment.

There is a very real need for high-quality data to inform our management of patients with UUT-UC. In respect to invasive tumours, the ongoing POUT study should answer the question as to whether adjuvant chemotherapy confers a survival benefit. It will also provide valuable insights into how UK urologists manage patients with invasive UUT-UC.

Conflicting interests

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