Upper Tract Urothelial Carcinoma (UTUC)

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Dr Richard Haddad has been in clinical practice since 2012. After urology and general surgery training in Sydney, he undertook a robotic uro-oncology fellowship at Montreal General and The Jewish Hospital of Montreal (McGill Univ.) Canada. Dr Haddad advocates a multi-disciplinary and evidence based approach to decision making. His other interest is complex open pelvic, retroperitoneal and renal surgery, which he performs for advanced urologic malignancies. Dr Haddad consults at the San, Norwest Private Hospital and RPAH Medical Centre.

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Upper Tract Urothelial Carcinoma (UTUC) accounts for 5-10% of all urothelial carcinomas. UTUC is 2-4 times more likely to be invasive at presentation. Exposure to industrial chemicals including hydrocarbons/aromatic amines within fumes and dyes, as well as smoking, are the risk factors for the development of UTUC. At risk occupations include; petroleum, rubber, textile dyes, hairdressing, laundromats and aeronautical petrols. The carcinogens are excreted within the urine and create a "field-defect change" that can cause malignancy anywhere along the upper urinary tract (renal pelvis, calyces, ureter) or more commonly within the bladder/lower tract. Bladder cancer is by far the more common clinical presentation. UTUC is rare, however is more likely to be metastatic at initial presentation than primary bladder cancer. Therefore, in general, the management of UTUC should be more aggressive from the outset, as delays in staging and definitive surgery could result in rapidly progressive metastatic disease (i.e. within weeks to months). The management of

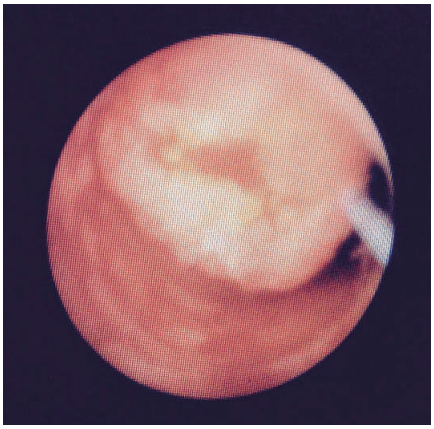

Figure 1: Ureteroscopic confirmation of tumour.

non-invasive bladder cancer by comparison tends to allow a more protracted course of staging and repeat endoscopic surveillance +/- intravesical therapies, depending on the initial stage and grade. The other point to remember is that a subset of patients have genetic syndromes where UTUC is a manifestation of a broader inherited familial syndrome including other malignancies (uterus, colon) and a geneticist should be involved to counsel the extended family.

The cornerstone of UTUC management is radical nephroureterectomy (rNU). Other options depending on stage, grade, and comorbidity include; (i) segmental ureterectomy with reconstruction (renal-preserving) and (ii) less effective laser endoscopic therapy (ET) with subsequent endoscopic surveillance/ureteric washings. A US national cancer database study of 43,036

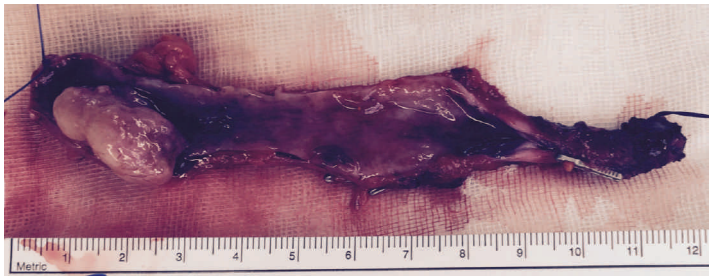

Figure 2: Operative specimen, right distal ureterectomy / ureteric urothelial carcinoma.

patients with UTUC, confirmed that gold standard rNU is associated with superior overall survival outcomes, when compared with ET. One major disadvantage of ET is that the true stage and grade of the UTUC cannot be established because ureteric biopsies, via ureteroscopy, are inaccurate. Therefore the risk is the tumour is under-treated with laser ablation alone. By comparison, a definitive segmental ureterectomy with reconstruction allows formal tissue pathology of the complete specimen and therefore a complete understanding of tumour aggressiveness.

In muscle invasive bladder cancer there is an established benefit of pelvic lymph node dissection, particularly when the lymph node count is high. In UTUC there is a lesser proven theoretical benefit of retroperitoneal lymph node dissection (RPLND) at the time of rNU. A 2019 systematic review published in European Urology, analysed 6 studies, and concluded that in high-stage disease of the renal pelvis (greater or equal to T2), an anatomic template based RPLND improves cancer specific survival, 3-5yr CSS, 67-82%(LND) v 40-45%(no LND), and reduces the risk of local recurrence. Additionally, RPLND improves staging and aids decision making regarding adjuvant systemic therapy. This benefit is not as clearly demonstrated for ureteral tumours. Overall, concomitant RPLND is rarely performed (<27% of the time). Amongst the patients who do receive concomitant RPLND, these patients are also much more likely to receive adjuvant chemotherapy or immunotherapy. Peri-operative outcomes did not appear to be worse when RLPND was performed. Options for the surgical approach are either open or minimally invasive, although open surgery is the safer established technique for concomitant RPLND.

The hot topics in 2019 are the important role of immune checkpoint inhibitors (ICI) including clinical trials, through MDT - (multi-disciplinary team) and medical oncologists, and the role of adjuvant chemotherapy (gemcitabine, cisplatin). Although CT scan staging is the initial imaging tool, FDG-PET scanning is helpful in clarifying the relevance of sub-centimeter retroperitoneal lymph nodes seen on initial CT, that may represent early metastatic disease, and if confirmed at PET, can have significant implications in changing the overall management. Suspicious nodes can be biopsied prior to final decision making. Immune checkpoint inhibitors can be used in metastatic urothelial carcinoma, after prior platinum-based chemotherapy. These include, pembrolizumab, atezolizumab, and nivolumab. They target the programmed cell death axis (PD-1, PD-L1). Toxicity management

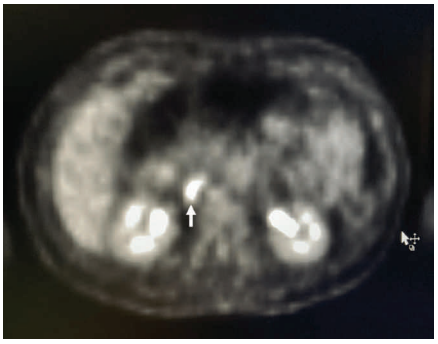

Figure 3: FDG-PET shows metastatic (biopsy confirmed) retrocaval lymph node 10 x 5 mm, in right renal UTUC.

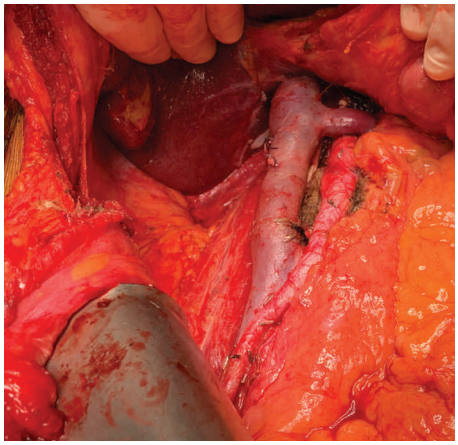

Figure 4: Open right radical nephroureterectomy with template retroperitoneal lymph node dissection.

and dosing are beyond the surgical realm and are the domain of the medical oncologist. Pembrolizumab has shown an overall survival benefit (10 v. 7 months), after prior platinum based chemotherapy.

These patients require close surgical and oncologic follow up with multi-disciplinary management.

References available on request.