



Paradigm Shift in the Management of Upper Tract Urothelial Cancer

Upper tract urothelial carcinoma (UTUC) is rare, constitute only 5–10% of urothelial cancer. Annual incidence 2 / 100,000 population in Western countries. Due to lack of RCT and large series, management of UTUC follows Bladder cancer.^{1,2} But there are some biological similarities and dissimilarities between UTUC and Bladder Cancer. As we know urinary bladder developed from endoderm-derived epithelium, the urogenital sinus, whereas ureter developed from mesoderm-derived epithelium. As risk factors Lynch Syndrome, aristolochic acid in aristolochic plant found more common to upper tract urothelial cancer (UTUC) on the other hand tobacco smoking, arsenic in drinking water, are considered as risk factors for both upper and lower tract urothelial cancer.^{3,4} Genetically FGFR3, HRAS, and KMT2D mutation are more common in upper UTUC in comparison to bladder cancer. But TP53, RB1, ERBB2, and KDM6A mutation higher in Bladder cancer than UTUC.⁵ Seeing the difference in development, risk factor, genetic factors it is logical to think that these two diseases may not be a spectrum of same disease. UTUC may be incidental, or symptom related. Micro or Macroscopic hematuria is the most common symptom. But flank pain may be present in quarter of patients. 15 to 25% cases UTUC found are to be invasive at initial diagnosis. Urine cytology, Barbatose cytology, urinary markers may be helpful in the diagnosis, but Imaging like CT urography gives almost 96% sensitivity and 99% specificity of diagnosis.^{6,7} However, uretero-rensoscopy (URS) and biopsy can determine the grade in 90% of the cases.⁸ Use of newer optical Imaging techniques like narrow band imaging, SPIES, photodynamic diagnosis, optical coherence tomography etc in ureteroscopy improves vision quality.⁶ Standard Treatment for upper tract TCC has been Radical Nephroureterectomy (RNU). However perioperative complication of RNU sometimes can go up to 40%. One third of then found to have Clavien III

or greater. It has also been observed that more than fifty percentage of patient undergoing RNU might have pre-existing CKD with an estimated GFR below 60cc/min and nearly eighty percent of patient can develop CKD post operatively.⁹ We know that risk stratification of different malignant tumor sometime led to less radical treatment in low-risk disease in comparison to high-risk disease. Unifocal disease, tumour size < 2 cm, negative for high grade cytology, low grade for URS biopsy, no invasive aspect on CT stratified as low risk disease by EU guideline panel, on the other hand Multifocal disease, tumour size e- 2 cm, high-grade cytology, high-grade on URS biopsy, local invasion on CT, hydronephrosis, previous radical cystectomy for high grade bladder cancer and variant histology stratified as high-risk disease. RNU for low-risk disease now considered to be overtreatment. This is where kidney sparing approaches coming up as options over the last decade. It has been observed that segmental resection provides almost equal oncological outcome. Distal ureterectomy with ureteroneocystostomy is preferred option. But segmental resection of the proximal two-thirds of ureter has higher failure rates. Total ureterectomy with an ileal-ureteral substitution and partial Nephrectomy can also be done in selected cases. Surgical resection provides adequate pathological specimens for staging and grading with Lymphadenectomy.¹⁰ Other options kidney sparing approach for includes endoscopic ablation.¹¹ Which can be approached retrogradely by semirigid ureteroscope for ureteric and flexible ureteroscopy for pelvicalyceal tumour.¹¹ Percutaneous access can also be done to reach caliceal system that are inaccessible or difficult to manage by flexible URS, like lower pole but has got risk of tumour seeding. Adjuvant treatment with topical instillation of topical agents like mitomycin or BCG has been tried, but the meta-analysis shows no difference in the recurrence rates. Another kidney sparing approach is chemoablation by a novel agent mitomycin hydrogel introduced by Oympus (UGN-101). Recently got FDA approval, is a reverse thermal gel, which remains liquid in room

temperature but solidifies in the body temperature and remain in contact with tumor for longer time. Phase III OLYMPUS study on low-Grade UTUC, shows promising result.¹² It is to be mentioned these KSS approaches are currently recommended for uses in low-risk diseases. For High-risk non-metastatic UTUC, open radical nephroureterectomy is still the gold standard. Laparoscopic RNU is safe only in experienced hands when adhering to strict oncological principles.¹³ Retroperitoneal metastatic dissemination and tract seedlings has been reported with laparoscopic approach and invasive or large tumours are contraindications for laparoscopic approach, where outcome is worse compared to an open approach. Complete bladder cuff excision is preferable to reduce the risk of tumor recurrence in this area and in the bladder. Several techniques have been considered to simplify distal ureter resection, including the pluck technique, stripping, transurethral resection of the intramural ureter, intussusception. None of these techniques has shown to be equal to complete bladder cuff excision. It has been found that a single dose of intravesical chemotherapy after RNU or ureteroscopy (diagnostic or therapeutic) of non-metastatic UTUC lower the rate of intravesical recurrence.¹⁴ Use of neoadjuvant chemotherapy and adjuvant chemotherapy has been shown promising result with some advantages with neoadjuvant therapy where, treatment is given prior loss of renal tissue and pathological down staging. Lower recurrence, OS and CSS benefit compared to RNU alone.¹⁵ Adjuvant immunotherapy with also shows improved disease-free survival compared to placebo. In conclusion it has been observed that, although many aspects of the current management strategies of UTUC have been extrapolated of data from bladder cancer, growing evidence suggest that UTUC may be a distinct disease entity. Conservative kidney-sparing techniques can be reserved for low-risk disease, whereas extirpative radical surgery remains the standard of care for high-risk patients. The benefit of lymph node dissection at the time of nephroureterectomy and the role of perioperative systemic therapy are still being investigated. Outcomes of UTUC patients have not improved over the past decade and continued research is needed to optimize the management of UTUC.

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