Endourology for Upper Tract Lesions.

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Abstract: *Nephroureterectomy with excision of cuff of bladder is the standard treatment of upper tract transitional cell carcinoma. Role of endoscopic treatment, either percutaneous or ureteroscopic, has been established in imperative indications like solitary kidney, bilateral tumors and deranged renal functions. Elective indications of endoscopic treatment include tumor size <1.5cm, low grade tumors with normal contralateral kidney. The most important pact which affects the success and prognosis following endoscopic treatment is careful selection of patients andregular ureteroscopic surveillance following surgery. Various studies have compared nephroureterectomy with endoscopic treatment in low grade tumors and concluded that both cancer related and overall survival is same in both the approaches. Adjuvant therapy with mitomycin, thiotepa and BCG has been described. However no study has shown statistical improvement regarding survival and recurrence rates following adjuvant therapy. Patients with low grade, small sized tumors have equal outcomes with endoscopic treatment as compared to expirative surgery with the advantages of minimal morbidity and preservation of renal parenchyma following endoscopic management. For the standardization of endoscopic treatment for patients with normal contralateral kidney, large randomized trials with long follow up results are needed.*

INTRODUCTION

Upper urinary tract lesions are defined as any abnormal growth arising from the lining of upper urinary tract i.e. from the calyces to distal ureter. Upper tract lesions may be benign like inverted papillomas or von Brunn's nests which may be associated with synchronous or metachronous upper tract urothelial carcinoma and these require close follow up. Malignant lesions are usually transitional cell carcinoma (TCC) which accounts for 90% of upper tract tumors. They may be sessile or papillary, unifocal or multifocal. Other malignant lesions are squamous cell carcinoma, adenocarcinoma, and sarcomas.

TCC accounts for 5% of all urothelial tumors and 5–10% of all renal tumours[1,2]. The standard treatment of upper tract TCC is radical nephroureterectomy and excision of cuff of bladder, despite the loss of renal unit and associated morbidity. While laparoscopy has reduced the perioperative morbidity with similar oncological outcomes, the procedure is still radical and does not spare the kidney. Advances in endourology allow us to reach every part of the urinary tract with minimal morbidity, leading to improved diagnosis and renal-sparing surgery. The ultimate aim of endoscopic management is cancer control whilst preserving renal function and the integrity of the urinary tract.

INDICATIONS AND RATIONALE

The histological appearance and clinical behaviour of upper tract urothelial cancers are identical to bladder tumors. Superficial papillary tumors rarely progress despite a high recurrence rate. Endoscopic resection or ablation of tumor can be done in superficial (Ta, T1) low grade (grade 1, 2) tumors. In ≥T2 or high grade (grade3) lesions, nephroureterectomy is the treatment of choice[3, 4]. Conservative therapies were initially reserved for imperative indications like patients with solitary functioning kidney, bilateral disease and renal insufficiency. Indications now also include patients with solitary, small sized low grade lesions with normal contralateral kidneys[3]. Patients with significant co morbid illness which precludes open radical or nephron sparing surgery are also candidates for endoscopic treatment[4]. Various studies have found that cystectomies are not necessary for many superficial bladder tumor, nephroureterectomies are also not necessary in selected low grade tumor patients as low grade tumors are associated with lower stage and have lesser chances of recurrences and metastasis as compared to high grade lesions[5].

Tumor size is also as important as grade for the selection of patients. Size less than 1.5 cm is associated with less recurrences and progression as compared to size more than 1.5 cm[1,6]. Before planning endoscopic treatment; patients should be counselled about aggressive and regular surveillance protocols.

Diagnosis

Hematuria, either gross or microscopic is the most common presentation in 56-98% of the patients followed by flank pain in 30%of cases[7]. Previous bladder cancer has been recorded in 15–84% of patients with upper tract tumours[5]. Diagnostic evaluation includes urine examination, urine cytology, cystoscopy, excretory urography or CT urography, and direct endoscopic evaluation with tissue sampling.

CT urography for detecting upper tract lesion has the sensitivity of 100%, specificity of 60% and negative predictive value of 100%. Differentiating the depth of invasion remains impossible with transaxial imaging[8]. Direct endoscopic visualisation with or without biopsy is indicated in those patients in whom diagnosis is not confirmed after conventional radiology or the patient is planned for endoscopic treatment. With small sized semirigid and flexible ureteroscopes, the entire collecting system can be visualised. The lesion can be biopsied with a biopsy forceps or brush. El hakim et al[9] found that visual assessment alone was inaccurate in 30% of the cases, so biopsies remain essential for accurate grading of upper tract TCC. One study showed multi-biopsy ureteroscopic approach to diagnose urothelial carcinoma in 89% of cases predicted exact histopathological grade in 78%[10]. The histological grade from diagnostic biopsy can be used to predict the pathological stage and can be used for prognostication and choosing the modality of treatment[11, 17]. Therefore, for the best estimation of tumor stage, combination of radiology, visual appearance of tumor and tumor grade are required. Endoscopic treatment is not irreversible like radical surgery and can be repeated if required or can be converted to radical surgery if there is progression of lesion. Diagnostic ureteroscopy has no clinically apparent adverse effect on long term or disease specific survival of these patients who subsequently undergo radical nephroureterctomy[12].

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URETEROSCOPIC TREATMENT

Use of ureteroscopy for upper tract tumors was first described by Goodman. Small diameter rigid and flexible ureteroscopes with greater deflecting abilities along with endoscopic biopsy techniques and devices for tissue ablation has made the endoscopic treatment of upper urinary tract tumours easy. The advantage of ureteroscopy is lower morbidity, ability to perform procedure on outpatient basis and maintenance of a closed system. Non-urothelial surfaces are not exposed to tumor cells, decreasing the incidence of tumor seeding. The limitations of this approach are (a) small sized instruments used (b) smaller field of view (c) smaller working channel (d) size of tumor that may be effectively resected (e) lower pole calyces are difficult
to approach with working instruments (f) patients with prior urinary diversion are difficult for assessment[13].

Technique

Before starting the procedure, there should be pathological and radiological staging to rule out high grade or T2 lesions, which are contraindications for conservative treatment. Rigid /semirigid ureteroscopes are used for distal and midureter lesions but for upper ureter and renal pelvis, flexible scopes are recommended. New generation flexible ureteroscopes smaller than 8 Fr can reach upto most of the parts of pelvicalyceal system. There are various instruments available for the biopsy such as 3 Fr cup biopsy forceps for sessile or flat lesion, a flat-wire basket or 3 Fr snare for papillary lesion, grasper, brush, or aspiration catheter. Brushing of the lesion is recommended along with biopsy, which gives cytological diagnosis despite small biopsy tissue[14]. There are 3 approaches for the ureroscopic management of upper tract lesions. The first approach is used in tumors on a narrow stalk – the tumor is excised with biopsy forceps or with snare, then the base is fulgurated with electrocautery or laser energy. Second, the tumor can be resected with a rigid resectoscope. Depth of the resection should not be muscle deep especially in upper and midureter which lacks the outer longitudinal layer of muscle, leading to perforation. Third, the tumor is first sampled with biopsy forceps followed by ablation with laser or electocautery.

Both Neodymium: YAG or Holmium: YAG lasers can be used [15,22]. Nd: YAG laser has a wavelength of 1064 nm with depth of penetration 5-6mm. The fibre is directed at, and placed near the tumour, activated at 20 to 30w and moved over the surface to coagulate the tissue. With the help of graspers, coagulated tissue is removed to expose further portions of the tumor which can be treated in the same fashion. The Holmium: YAG laser both coagulates and ablates tissue, penetrating to a depth of 0.5 mm with wavelength of 2143nm. This is useful for ureteric lesions as it can ablate and remove an occlusive tumour, opening up the lumen. The two lasers can be used in combination. Initially, Neodymium: YAG laser is used to coagulate the major part of the tumour, and then the coagulated tissue can be removed with the Holmium: YAG laser[16].

Complications of ureteroscopic management of upper tract lesions are the same as for ureteroscopy for benign causes. These are mostly minor including perforation in 1-4% which can be managed by ureteric stenting or percutaneous drainage and ureteric strictures in 4.9–13.6%. Strictures can be managed by stenting, laser ureterotomy, or balloon dilatation[17]. Complications rates have been reduced with smaller endoscopes and refined energy sources .It has been found that stricture following ureterscopy is not always due to technical errors but may be due to recurrence of tumor. Daneshmand et al[18] has shown that 40% of stricture may be due to recurrent malignancy and should always be biopsied. Lim et al[19] suggested that increased renal pelvic pressure may lead to pyelovenous or pyelolymphatic backflow led to possible spread of tumor. However other series show no progression of disease in patients who underwent radical surgery following endoscopic treatment[12].

Outcome

The success of endoscopic treatment and prognosis of the disease depends upon grade and stage of the tumors[20-23]. Low grade tumors have very low progression rate as compared to high grade lesions which have a higher progression rate. Ureterosopic treatment act as palliative treatment in high grade lesions and should only be used in imperative indications for conservative treatment[34]. Grasso et al[31] followed 11 patients with low grade tumor which were treated ureteroscopically for 17.3 months. 45% developed low grade recurrences with no progression. They concluded that patients with low grade, papillary and low stage tumors are amenable for endoscopic treatment and high grade patients should be offered standard treatment. Chen et al[32] treated 23 patients with low grade tumors ureteroscopically. At 35 months of follow up, 65% had multiple recurrences, which were treated ureteroscopically. All the patients were alive without disease progression. A review by Bader et al[34] concluded that ureteroscopically guided laser therapy results in recurrence rate ranging from 31-65% and disease free rates of 35- 86% depending upon stage and grade. Upper tract tumors, like bladder tumors have high recurrence rates. These patients require strict surveillance protocols and may require repeated endoscopic resections. The surgeon should have a low threshold for carrying out ablative surgeries[24]. One of the criteria for choosing conservative therapy should be patient compliance and willingness for vigorous follow-up. Mugiya et al[25] followed grade 1 (3 patients) and grade 2 (1 patient) following retrograde laser therapy for 32 months. Each patient received an an average of 5.3 ureteroscopic surveillance procedures and 3.3 recurrences on an average. No patient had disease progression, one with grade 2 died of recurrence after 30 months. They concluded that long term ureteroscopic surveillance is necessary following endoscopic treatment.

PERCUTANEOUS TREATMENT

Percutaneous treatment is used for larger tumors located in the pelvis or proximal ureter. In this approach, because of a larger working channel, better visualisation and use of larger instruments, large tumors in any part of pelvis can be handled . Deep biopsies can be taken and grading and better staging of tumor is possible. Percutaneous approaches can be used in patients with lower pole calyx tumors and patients with urinary diversion where ureteroscopic access is difficult. Established nephrostomy tract can be used for second look nephroscopy and instillation of adjuvant therapy. Disadvantages include the increased morbidity compared with ureteroscopy and the theoretical risk for malignant seeding of the nephrostomy tract because of loss of integrity of urothelium and exposure of nonurothelial surface to tumor cells.

Technique

Percutaneous access is obtained in a desired calyx, distal to the tumor. Tumors in renal pelvis or upper ureter are approached through upper or middle calyx. The tract is dilated and an Amplatz sheath is placed. After establishing the tract, rigid or flexible nephroscopes are used. As described earlier, the tumor can be debulked with cold cup biopsy forceps followed by separate biopsy of the base. Then, the base of

the tumor is ablated with electrocautery or laser energy. Standard monopolar/ bipolar resectoscope can be used for excision of tumor up to its base. 26 At the end of the procedure; a nephrostomy tube is left in place for second look nephroscopy or adjuvant local instillation therapy. A second look nephroscopy is done upto 14 days following first surgey to allow adequate healing. During second look nephroscopy, the tumor resection site is identified and should be biopsied and treated with cautery or laser. Complication rates following this approach are more than ureteroscopy but similar to percutaneous approach for benign renal diseases. The most common complication is bleeding requiring blood transfusion in upto 50 % of case. It may be because of larger tumor requiring deeper resection. 2 Other complications are perforation, ureteropelvic junction obstruction, hemothorax/hydrothorax, renal failure, and malignant seeding of the nephrostomy tract. Seeding of the percutaneous tract is rare although has been reported[27,40]. Precautionary measures suggested to minimize seeding include use of an amplatz sheath to decrease intrarenal pressure <20 cm H2O and immediate irrigation of the collecting system and percutaneous tract with a 5-florouracil solution. There is one report of placing a radioactive iridium wire in the percutaneous tract[28].

Outcome

Outcomes following percutaneous treatment correlate with grade and stage of the tumor. Orihuela et al[29] treated 14 patients percutaneously with follow-up of 5–45 months (mean 19). There was no recurrence in patients with solitary, grade 1 tumors, whereas recurrence occurred in two third of patients with tumor more than 2 cm and patients with grade 2 or 3 tumor. Jabbour et al[30] treated 54 patients percutaneously and found a cancer-specific survival of 100, 94, and 63% for grades I, II, and III, respectively. Jarrett et al 2 demonstrated recurrence rate of 18%, 33% and 50% for grade 1, 2 and 3 lesions respectively. Lee et al[31] compared their patients who underwent nephroureterectomy with those with percutaneous resections and concluded that patients with low grade tumors did well irrespective of modality used and high grade lesions did poorly regardless of treatment modality. Montanari et al[32] did percutaneous resections in 62 patients and gave BCG instillations 6 weekly, if biopsy of base of the tumor was negative in second look nephroscopy. On 71 months follow up. All the patients were tumor free except one patient with bladder relapse. Roupret et al[33] assessed the outcomes following percutaneous treatment with follow up 62 months. 33.3% had a recurrence. The 5 year disease specific and tumor free rates were 79.5% and 68% respectively.

INTRACAVITATORY THERAPY

To decrease the recurrence, adjuvant topical immunotherapy or chemotherapy has been suggested following endoscopic treatment for upper tract lesions Instillation therapy can be given in several ways like through nephrostomy tube following percutaneous treatment, retrograde instillation into ureteral catheters or by reflux through an indwelling stent. Nephrostomy tube position should be checked before starting therapy. Instillation should always be done under low pressure and in the absence of infection. Most commonly used agents are BCG, mitomycin and thiotepa[29]. Adjuvant BCG should be started 2-4 weeks following surgery in the absence of infection and hematuria. It allows adequate healing of the urothelium and avoids BCG sepsis. However no study has shown statistical improvement in survival or recurrence rates following adjuvant therapy. Most common complication of BCG therapy is sepsis. It can be avoided by using a low pressure system delivery system.

SURVEILLANCE

The most important prerequisite before planning endoscopic treatment is patient compliance for follow–up. The high chances of recurrence and progression of disease require strict endoscopic follow up. 18 Urine cytology and retrograde pyelography alone are insufficient for detecting upper tract recurrences. Endoscopic follow up is essential in these patients. The sensitivity of ureteroscopy (93%) is higher than that of intraoperative pyelography (72%) or bladder cytology (50%)[34]. Office ureteroscopic surveillance can be done with minimal patient discomfort, complications and an accuracy similar to ureteroscopy in the operating room[35]. Narrow band imaging flexible ureteroscopes can be used for follow up to improve the tumor detection rate by 22.7% compared with white light ureteroscopy[36]. As such, there is no fixed protocol but patients require follow up ureteroscopies at 3 and 6 months, then 6 monthly for a year and then annually for life time[1]. Low grade recurrences require re-resection but high grade or advanced lesions require nephroureterectomy.

UPPER TRACT TCC FOLLOWING RADICAL CYSTECTOMY

The incidence of upper tract transitional cell carcinomas (TCC) following radical cystectomy is 3-6%. The incidence increases if the bladder tumor is multifocal, near the ureteric orifices and associated with carcinoma in situ[37]. The ideal treatment of these recurrences is still nephroureterctomy. Advancements in endourology have made endoscopic treatment of these recurrences possible if these are low grade, small size and non invasive. A retrograde approach is difficult because of the abnormal ureteral access. In patients with a neobldder, the ureter can be assessed with rigid or flexible ureteroscoscopes and the conduit can be approached with flexible scope. Loopogram or cystograms can be done under fluoroscopy to delineate the afferent limb and ureteral anastomosis. Systemic indigo carmine can be given to delineate the ureteral orifices. Once the ureter is cannulated, an access sheath can be placed to prevent trauma. Advantages are low morbidity, day care procedure and maintainance of closed system. Percutaneous approach has advantages of easy access, better staging, and availability of a nephrostomy tract for adjuvant treatment.

NEPHROURETERECTOMY OR ENDOSCOPIC TREATMENT

Various studies have compared nephroureterectomy with the endoscopic treatment and concluded that cancer related and overall survival is similar in both approaches in low grade cancers with frequent re-treatments in endoscopic approach. High grade cancers should be treated with nephroureterectomy unless there are indications for nephron sparing surgery[31]. Lucas et al[39] compared endoscopic treatment with nephroureterectomy in low grade patients and concluded that disease specific survival at 5 years is 86.2% vs. 87.4% respectively. Therefore a conservative approach in selected patients provides comparable outcomes to expirative surgery in low grade diseases. Another study showed 5-year diseasespecific survival rate after nephroureterectomy, ureteroscopy, and percutaneous endoscopy was 84%, 80.7%, and 80%, respectively (P= 0.89) in low grade tumors and the corresponding 5-year tumor-free survival rates were 75.3%, 71.5%, and 72% (P = 0.78). (40) Pak et al[41] calculated the cost effectiveness of conservative treatment. They concluded that a patient with a solitary kidney with recurrences at each followup for 5 years v nephroureterectomy and dialysis for the

same period, an estimated $252,272 U.S. dollars would be saved in conservative treatment.

CONCLUSIONS

The most important requirement for the success of endoscopic surgery is careful patient selection. Imperative indications for endourological resections are solitary kidney, bilateral synchronous disease, renal insufficiency or significant comorbidity precluding nephroureterectomy. With the advancement in technology, the elective indications are expanding. Patients with low grade, small sized tumors have equal outcomes following endoscopic treatment as compared to expirative surgery with the advantages of minimal morbidity and preservation of renal parenchyma following endoscopic management. For the standardisation of endoscopic treatment for patients with normal contralateral kidney, large randomised trials with long follow up results are needed. Upper tract TCC has high rates of recurrence rate requiring frequent re-treatments. It is necessary that these patients should be motivated and must be compliant as lifelong follow up is necessary. Role of adjuvant immunechemotherapy is still not established.

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