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ENDO-ONCOLOGY: THE FUTURE IS HERE

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INTRODUCTION

Within the past decade there has been a steady movement towards minimally invasive surgery in the treatment of urologic malignancies. Endoscopic resection of upper tract transitional cell carcinoma (TCC) pioneered this field. Subsequently, laparoscopic approaches to all urologic cancers have been developed and validated. More recently, energy based ablation techniques (cryoablation, radiofrequency ablation, HIFU) have emerged and have undergone several clinical trials in prostate cancer and renal cell carcinoma (RCC). In this manuscript we present an overview of the most recent advancements in minimally invasive modalities for the treatment of upper tract TCC, RCC, prostate cancer, adrenal tumors and germ cell testicular cancer. The merge between endourology and urologic oncology has become reality.

UPPER TRACT TRANSITIONAL CELL CARCINOMA

Endoscopic Treatment

Endoscopic (percutaneous or ureteroscopic) treatment of upper tract TCC was initially advocated in patients with solitary kidney or chronic renal failure. Encouraging results from early clinical series paved the way for elective endoscopic treatment of superficial low-risk upper tract TCC in patients with normal contralateral renal units[1,2]. This approach resulted in an 81% renal salvage rate and a 100% 5-year disease specific survival[2]. Adherence to strict indication criteria is of utmost importance and these include small, low-grade, completely visible and resectable lesions. Unresectable tumors are best treated by nephroureterectomy.

General contraindications to endourologic treatment of upper tract TCC include high-grade lesions, and tumors that appear to be invasive on radiographic imaging or direct endoscopic inspection. Grade or stage progression at recurrence after initial endoscopic treatment indicates an aggressive disease, and is a relative contraindication for further conservative therapy.

Patients with grade-1 disease have an excellent prognosis, while the prognosis of those with grade 3 is guarded. Grade-1 disease has a reported recurrence rate of 16% on average (5-33%)[3-6]. Despite recurrences, death from low-grade urothelial carcinoma is rare. The prognosis of grade-2 disease is also good. The recurrence rate is on average 22% (6-33%)[3-7]. However, no matter how grade-3 urothelial carcinoma of the upper urinary tract is managed, the prognosis is poor. We recently updated our series of endoscopically treated upper tract TCC. Ninety patients were treated with primary endoscopic intent (ureteroscopic and/or percutaneous approach) at our institution, between April 1985 and May 2003. Seventy-two patients (75 renal units) were closely followed thereafter and 18 patients underwent definitive surgical extirpative treatment shortly after initial resection. Using multivariate analysis, tumor grade and tumor focality were the only predictors of survival. Tumor focality correlated with disease progression[8]. In the authors' opinion, endoscopic resection should not be offered for high-grade and multifocal upper tract TCC, except as an alternative in elderly patients with a solitary kidney, who would fare quite poorly on hemodialysis.

Surveillance should be tailored to the recurrence pattern of upper tract tumors. Although long-term recurrences have been reported, most recurrences occur in the first three years following initial therapy[9]. Ureteroscopy is the best modality to detect recurrences[10]. The authors recommend that ureteroscopy be performed every six months, that the contralateral kidney be imaged at least annually with either retrograde or excretory pyelography, and that an abdominal CT scan be done yearly. These

patients should undergo routine bladder surveillance as well.

The indications for adjuvant therapy (BCG, Mitomycin C) in upper tract urothelial cancer have evolved over the years. Grade-2 tumors, multifocal disease, T1 tumors, carcinoma in situ, and bilateral disease used to constitute the main indications for adjuvant *percutaneous* Bacillus Calmette-Guerin (BCG) at the authors' institution. In the recent update of our series we identified 44 patients who had received adjuvant BCG after endoscopic resection and 29 who had not (controls). In this retrospective cohort BCG increased overall survival in low-grade tumors, unifocal tumors, and elective surgical indications. Furthermore, the recurrence rate was decreased in unifocal tumors receiving BCG compared to controls[11]. In view of these findings, adjuvant BCG indications need to be reconsidered, and a prospective multi-center trial is warranted.

In conclusion, endourologic techniques are ideal for managing non-invasive, resectable tumors that are well or moderately differentiated. These modalities are particularly suited to patients with renal compromise, as well as to patients with normally functioning kidneys and favorable tumor characteristics.

Laparoscopic Nephroureterectomy

The treatment of upper tract TCC has traditionally been open nephroureterectomy and bladder cuff excision. The morbidity of this operation is not insignificant especially in elderly patients with associated cardiovascular and pulmonary disease. Laparoscopic nephroureterectomy (LNU) can achieve the same oncologic goal while offering all the advantages of minimally invasive surgery. LNU can be performed through a transperitoneal or retroperitoneal approach. There are several alternatives for excising the distal ureter and bladder cuff[12]. The Pluck technique involves the transurethral resection of the ureteral orifice and intramural ureter using a Collins knife. In order to prevent tumor spillage from the upper tract, we recommend performing laparoscopic nephrectomy first and applying a clip on the distal ureter early during dissection. Another approach obviating the need for intraoperative patient repositioning (in lithotomy) has been recently reported[13]. A rigid offset nephroscope is introduced through a 10 mm working port into the bladder and an incision is made around the ureteral orifice using the Collins knife, through the working channel of the nephroscope. Open bladder cuff resection, laparoscopic stapled bladder cuff and ureteral intussusception[14] are all described alternatives. The specimen should be removed intact without morcellation through the hand port incision if hand assisted LNU is performed, or through a lower midline or Pfannenstiel incision.

Four recent clinical series compared LNU with open nephroureterectomy (ONU)[15-18]. There was a total of 108 LNU and 105 ONU in these four series. The mean follow-up (FU) for LNU was 11.1 to 35 months, and for ONU it was 14 to 46 months. All four reports demonstrated a shorter hospital stay for LNU by a mean of 1 to 6 days. The mean blood loss decreased on average from 440-696 ml for ONU to 199-288 ml for LNU. None of the LNU patients had their specimen morcellated. In LNU as compared to ONU there were two and three extravesical local recurrences, as well as five and seven distant metastatic diseases, respectively. There were eight and 14 disease-related deaths, respectively. There were no reported port site recurrences in these four series, despite early reports of tumor seeding into the port sites[19,20].

There are obvious benefits for LNU over ONU, including decreased pulmonary complications, postoperative discomfort, hospital stay, and a shorter convalescence. At medium-term follow-up LNU seems to have similar results to ONU for upper TCC. Although concerns over port site and intraperitoneal seeding have been voiced, these problems have not been reported in recent series. The overall disease-specific survival is comparable to ONU. However, long-term results are required.

RENAL CELL CARCINOMA

Laparoscopic radical nephrectomy has replaced open surgery in many institutions around the world as the primary treatment of localized renal cell carcinoma (RCC). In parallel, nephron-sparing surgery has become well established in the past decade. Currently, 60% of all renal tumors are detected incidentally and are often small ($\leq$ 4 cm), with up to 22% of these being benign[21,22]. Nephron-sparing surgery provides cancer control comparable to radical nephrectomy in selected patients with localized tumors smaller than 4 cm[23,24].

Until recently, the only available nephron-sparing option was open partial nephrectomy. However, within the past five years, various minimally invasive alternatives, including laparoscopic partial nephrectomy, have been the subject of intense basic and clinical investigation. Cryoablation and radiofrequency ablation are the two most studied energy-based techniques in RCC.

Laparoscopic Partial Nephrectomy

Laparoscopic partial nephrectomy (LPN) has not been largely adopted mainly because of the technical difficulty in achieving adequate parenchymal hemostasis and renal hypothermia. LPN was initially reserved for selected patients with small, peripheral, and exophytic tumors[25-28]. With increased experience, indications have been expanded in some centers to include patients with more complex tumors. Open principles of partial nephrectomy should be duplicated. Absolute contraindications for LPN include renal vein thrombus, multifocal or central tumors.

Various techniques of parenchymal hemostasis have been reported including cauterization of the cut surface with argon beam laser and application of fibrin glue. For larger vessels, however, the most effective method remains hemostatic parenchymal sutures. Renal parenchymal tourniquets and cable tie devices have been tested in the porcine kidney, but are clinically unreliable in the human kidney. Other hemostatic aids include prior microwave thermotherapy[29] or radiofrequency coagulation[30] of the tumor followed by laparoscopic partial nephrectomy. Bioadhesives may become an effective method for obtaining renal parenchymal hemostasis in the future.

Gill et al. reported on the first 50 patients who underwent LPN without renal hypothermia.[31] Warm ischemia time was 23 minutes, the mean operative time was 3 hours, and the mean hospital stay was 2.2 days. On pathology, renal cell carcinoma was confirmed in 68% of the patients, all with a negative surgical margin. The intraoperative complication rate was 5%. There were 9% postoperative and 15% late complications. Janetschek et al. recently reported on 15 patients treated with LPN. Cold ischemia was achieved by continuous perfusion of Ringers lactate at 4°C through the clamped renal artery. The mean operative time was 185 minutes, ischemia time was 40 minutes, and the estimated blood loss was 160 ml. Pathology revealed formal RCC in 13 patients and angiomyolipoma in two. The resection margins were negative in 14 patients and there were no significant postoperative complications[32].

Cryoablation

Cryoablation of renal tumors has the longest follow-up among energy-based ablation techniques. Studies on animals have shown that tissue destruction is complete and may be reliably reproduced[33,34]. Long-term results from clinical trials are soon going to be available. Cryoablation may be performed using the open, laparoscopic or percutaneous approach, with ultrasound or magnetic resonance image (MRI) monitoring.

Cryotherapy involves a direct cellular injury and an indirect effect from microvascular impairment. Direct damage results in cellular dehydration due to the osmotic imbalance created by the iceball. Indirect damage may be the dominant killing mechanism during cryosurgery[35]. The renal collecting system does not seem to be affected even when exposed to very low temperatures[36,37].

The goal of cryotherapy is to decrease the target temperature below the temperature that correlates with complete tissue necrosis, which is highly dependent upon the cell type. Chosy et al.[38] found that renal tissue needed exposure to or below -19.4°C. Clinical protocols have erred on the side of caution and generally freeze to -40°C.

Currently two procedural endpoints are possible. A temperature of -40°C or ultrasound can be used to verify the extension of the iceball 1 cm beyond the margin of the tumor[39]. Although cell death is certain in the central area of liquefaction necrosis, the tumor margin is the area of concern. Some studies have shown no difference in renal tissue ablation when comparing single versus double-freeze or active versus passive thaw[40,41].

Rukstalis et al. reported on 29 patients with localized renal tumors treated with an open approach[42]. A double-freeze sequence was performed. The median preoperative lesion size was 2.2 cm, with 22 solid renal masses and 7 complex renal lesions. At a median follow-up of 16 months all patients but one, who

had a biopsy-proven local recurrence, demonstrated radiographic regression to only a residual scar or a small non-enhancing cyst. Using the laparoscopic approach, Gill et al. treated 32 patients with a mean tumor size of 2.3 cm. Twenty-three patients underwent a 3 to 6-month follow-up CT-guided biopsy which was negative in all cases. No evidence of local recurrence was found during a mean follow-up of 16.2 months[43]. Shingleton et al. reported on 65 patients with percutaneous cryotherapy. At an average follow-up of 18 months all 60 surviving patients had no radiographic evidence of disease, although nine out of 65 (14%) required repeat treatment[44].

No set algorithm exists for post-procedure monitoring, but patients need close follow-up for 12-18 months to ensure complete regression or stabilization of the lesion, and yearly thereafter. The intermediate results look promising, and long-term follow-ups will soon be available to assess the durability of renal cryotherapy.

Radiofrequency Ablation

Radiofrequency ablation (RFA) of renal tumors requires placement of an interstitial needle electrode into the tumor via a percutaneous, laparoscopic or open approach. Alternating current is delivered to the tissue causing ionic agitation in the cells with the electrical impedance of the tissue producing local heating. As tissue temperatures increase to between 60°C and 100°C, there is an instantaneous induction of irreversible cellular damage referred to as coagulation necrosis[45]. RFA also produces vascular thrombosis within the treatment zone causing an ischemic lesion.

A barrier to successful RFA is the 'heat sink' effect during treatment of well-vascularized tumors or those located near large blood vessels (i.e. hilar tumors). Another limitation is the increased tissue resistance and decreased conduction of the electrical current away from the needle tines. Saline-enhanced RFA is a strategy designed to amplify the ablative area and involves the infusion of normal or hypertonic saline into the target tissue via a cannulated radiofrequency probe. The saline solution facilitates the conduction of energy and improves thermal transmission. Another limitation is that there are no direct radiographic means to monitor RF treatment, as opposed to ultrasound for cryosurgery.

Radiofrequency ablation has recently entered phase-II clinical trials for the treatment of small renal tumors. Four recent clinical studies using percutaneous RF reported outcomes with post-procedure CT or MRI enhancement as the primary measure of treatment failure. Unfortunately, the absence of contrast enhancement is not an accurate predictor of tumor viability. However, there is as of yet no other reliable postoperative imaging to identify failures. Gervais et al.[46] treated nine renal tumors with a mean diameter of 3.3 cm. Tumors showing residual enhancement underwent additional RF procedures. A total of 24 treatments were performed in 14 sessions. At 10.3 months mean follow-up, 2 of 3 central tumors measuring 4.4 and 5.0 cm showed residual enhancement at the periphery. DeBaere[47] reported on five tumors of biopsy-proven renal cell carcinoma, all less than 4 cm. A total of six RF treatments were required. All tumors did not enhance on subsequent CT scans with a mean follow-up of 9 months. Pavlovich et al.[48] reported on 24 tumors, all less than 3 cm, in von Hippel-Lindau or hereditary papillary RCC. At least two treatments per tumor were performed. Follow-up was short at two months, and 5 of 24 tumors (22%) showed residual enhancement at the periphery. Of note, five tumors failed to achieve adequate treatment temperature. Lewin et al.[49] reported on 10 tumors with a volume range from 1 to 17 ml. MRI revealed no evidence of enhancement at a mean of 18.5 months follow-up.

When histology was used as a measure of outcome, several studies showed incomplete tumor ablation. Both hematoxylin and eosin stain (H&E) and nicotinamide adenine dinucleotide (NADH) diaphorase staining should be part of the histological assessment of RF ablated tumors because there are 'viable-appearing' cells on H&E in *acutely* ablated lesions[45]. Rendon et al.[50] evaluated tumors at nephrectomy immediately, and one week following percutaneous RF ablation. The mean tumor size was 2.4 cm. Four of five tumors in the immediate nephrectomy group, and three of six in the delayed nephrectomy group showed residual viable tumor in about 5% of the tumor volume at the peripheral margin using H&E alone. Matlaga et al.[51] used RF ablation to treat renal tumors immediately before partial or radical nephrectomy. Based on both H&E and NADH staining, two of the 10 tumors were incompletely ablated. Michaels et al.[52] treated 20 small tumors with an open surgical approach followed immediately by partial

nephrectomy. The five most recent tumors were stained with H&E and NADH. Four of the tumors were incompletely ablated according to NADH stain.

Complete tumor cell death has not been consistently achieved with RF ablation of RCC. Based on findings of viable tumor cells only at the periphery of treated tumors, it seems reasonable to believe that a better intraoperative monitoring would decrease or eliminate positive margins. Until long-term efficacy is well documented, RF treatment should be limited to small (< 3cm) and exophytic renal tumors in the setting of clinical trials.

All minimally invasive nephron-sparing procedures must aim at excising or effectively ablating renal tumors as they would have been excised during open partial nephrectomy. Complete tumor cell death and adequate margins are premises for success. Although exciting, these new developments should await long-term follow-up data before widespread application.

PROSTATE CANCER

The current treatments for early prostate cancer have significant acute and delayed morbidities that affect negatively the quality of life. In view of the high incidence of early disease and the indolent course in many patients, there appears to be a need for new treatment strategies.

Laparoscopic Radical Prostatectomy

In the late 1990s, Guilloneau et al. described a technique for laparoscopic radical prostatectomy (LRP), an approach that has the potential to offer lower morbidity than open procedures[53]. They recently reported on 1,000 consecutive patients with clinically localized prostate cancer that underwent LRP. The positive surgical margin rate was 6.9%, 18.6%, 30% and 34% for pathological stage pT2a, pT2b, pT3a and pT3b, respectively. The overall actuarial biochemical progression-free survival rate was 90.5% at three years. Preservation of the neurovascular bundles was possible in selected patients and did not increase the rate of surgical margins or biochemical recurrence[54]. Other approaches to LRP have also been described with equally favorable oncologic results and low morbidity rates[55,56]. Accordingly, LRP is at least equivalent to published series of open radical prostatectomy in terms of local disease control and biochemical progression-free survival. Continence and potency rates compare to open series. LRP is feasible and reduces the perioperative blood loss, but has a steep learning curve. Controversy remains whether LRP offers significant advantages in postoperative analgesic requirements, hospital stay and recovery period. Prospective randomized trials comparing LRP and open retropubic prostatectomy are underway, and results should clarify theses issues.

Cryoablation

Cryosurgery offers several advantages over radical surgery. It has low general surgical morbidity, can be performed on an outpatient basis, and blood transfusions are not needed. Prostate cryotherapy aims at achieving a temperature of -40°C throughout the entire prostate. The technique has evolved during the past decade and the results of a retrospective multicenter analysis of cancer-related outcome have recently been published[57]. The 5-year biochemical-free survival rate was 76% for low-risk patients, which was comparable to the results for similar patients undergoing brachytherapy or conformal radiation at the same institutions. Results in the medium- and high-risk groups were also comparable. Potential complications of cryosurgery can include rectal fistula, urethral sloughing, urinary incontinence and impotence. In the aforementioned series, the incidence of rectal complications was lower than for radiotherapy but potency rates were lower. Nerve-sparing cryosurgery has recently been described and may increase the popularity of cryosurgery.

High-Intensity Focused Ultrasound

Beerlage and colleagues reported in a phase-II trial on high-intensity focused ultrasound (HIFU) treatment in patients with localized prostate cancer prior to radical prostatectomy and as monotherapy for patients for whom radical prostatectomy was not an option[58]. Complete necrosis was seen in the treated region in all 14 cases treated prior to prostatectomy. However, tissue destruction was not complete on the dorsal border. For patients receiving HIFU as monotherapy in whom the entire prostate was treated, a nega-

tive biopsy result and PSA <4 ng/ml was obtained in 60% of patients. The short-term results of a large phase-II/III European prospective multicenter trial were recently published. 402 patients with localized prostate cancer unfit for radical prostatectomy were treated with HIFU. The mean serum PSA concentration was 10.9 ± 8.7 ng/ml. The Gleason scores were 2 to 4 in 13.2% of the patients, 5 to 7 in 77.5%, and 8 to 10 in 9.3%. The patients received a mean of 1.4 HIFU sessions. The mean follow-up duration was 407 days. 87.2% of cT1-2 patients achieved a negative biopsy postoperatively[59].

These new minimally invasive techniques aim at destroying the malignant prostatic tissue while minimizing complications and patient morbidity. However, they are still investigational at present and before their role in localized prostate cancer can be defined it will be necessary to conduct larger studies with longer follow-up as well as comparative studies against traditional therapeutic options. Their role as salvage therapy also warrants investigation.

ADRENAL CANCERS

Laparoscopic Adrenalectomy

Laparoscopic adrenalectomy has replaced open surgery for the treatment of most surgical adrenal pathologies. Pheochromocytomas, once considered a contraindication for laparoscopic surgery, can now be excised safely and effectively[60].

Primary adrenal carcinoma is a rare tumor occurring in children and adults, and has a poor prognosis despite aggressive multimodality treatment approach[61]. Most malignancies of the adrenal are metastases from other primaries. If the metastasis is solitary, surgical excision confers a survival benefit with a 5-year survival rate approaching 45% for metastatic non-small cell lung cancer, and a 62% disease- free survival at a 26-month follow-up for metastatic renal cell carcinoma[62]. Our technique of laparoscopic adrenalectomy was previously described[60].

Laparoscopic adrenalectomy for primary adrenal carcinoma is still controversial because 90% of adrenal carcinomas are larger than 6 cm[63], potentially infiltrate locally, and are not encapsulated which increases the risk of spillage and subsequent recurrence. Size and recurrence do not seem to be the limiting factors, and several authors reported successful laparoscopic adrenalectomy for tumors > 6 cm with an acceptable operative time and low conversion rate and recurrence[60]. However, most experienced surgeons agree that invasive tumors with surrounding tissue infiltration or adrenal vein thrombus are formal contraindications to laparoscopic adrenalectomy.

TESTICULAR CANCER

Laparoscopic Retroperitoneal Lymph Node Dissection

In the early 1990s, the laparoscopic approach to retroperitoneal lymph node dissection (RPLND) was introduced as an alternative to open surgery in order to reduce the morbidity, which is too high for a diagnostic procedure. Janetschek et al. reported on the first large series of laparoscopic RPLND with a significant follow-up demonstrating similar cancer control in patients with clinical stage-I testis cancer compared to traditional open surgery[64]. Seventy-three patients underwent a modified unilateral template dissection. The conversion rate was 2.7%. In the last 44 patients there was no major postoperative complication. The mean hospital stay was 3.3 days. Ejaculation was preserved in all patients. Twenty-six percent of the patients had pathologic stage II. There was one contralateral retroperitoneal recurrence at a mean follow-up of 43.3 months in a patient with initial pathologic stage I[64]. The Johns Hopkins' group recently reported their long-term data of laparoscopic RPLND in 29 patients with high-risk clinical stage I, nonseminomatous germ cell testicular tumor (NSGCTT). A modified template dissection was performed as well. Lymph nodes were negative in 17 of 29 patients. Of these 17 patients, 15 had no recurrence and were free of disease with 5.8 years of follow-up. Two patients had recurrence, one in the chest, and one biochemical, and both were free of disease after chemotherapy. Ten out of 12 lymph node positive patients underwent adjuvant chemotherapy and were free of disease with 6.3 years of follow-up. One patient had a biochemical recurrence and was salvaged with chemotherapy. The only long-term complication was retrograde ejaculation in one patient[65].

Although challenging, laparoscopic RPLND is also feasible after chemotherapy for clinical

stage IIA or higher. Palese et al. reported on seven such patients. Post-chemotherapy laparoscopic RPLND was successfully completed in 5 (71.4%) patients. The overall complication rate was 57.1%, with a major complication incidence of 42.8%[66]. Janetschek et al. performed post-chemotherapy laparoscopic RPLND in 24 patients. There were no conversions to open surgery. Postoperative chylous ascites developed in five patients and resolved with conservative management. Antegrade ejaculation was preserved in all patients. All patients were well without evidence of disease at a mean follow-up of 24.4 months[67].

Laparoscopic RPLND is only diagnostic at the present time. Its therapeutic efficacy has not been proven. The long and steep learning curve remains the biggest obstacle in laparoscopic RPLND.

CONCLUSION

Today, there is a growing need to treat urologic malignancies in a minimally invasive fashion. Unfortunately most centers specializing in the treatment of these diseases are not trained in laparoscopic surgery and vice versa. Hence, uro-oncologists must become endo-oncologists.

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