

# UROLOGY FOR THE PRACTITIONER NOVEL CONCEPTS IN THE TREATMENT OF LOCALIZED RENAL CELL CARCINOMA

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**ABSTRACT :** The understanding of renal cell carcinoma has undergone significant advances in the past several years. These have included advances in imaging procedures and surgical approaches, allowing for more precise staging, and individualized approaches to therapy. Furthermore, there has been an increase in the diagnosis of incidental tumors and currently the majority of RCCs are incidentally diagnosed on routine imaging procedures. In this manuscript, we review the surgical options for renal cell carcinoma with specific emphasis on the algorithm for approaching these tumors, in order to ensure maximal cancer specific survival, without threatening the overall renal function.

## INTRODUCTION

Renal cell carcinoma (RCC) accounts for 3% of all adult malignancies and 90-95% of neoplasms arising from the kidney. It is the sixth leading cause of cancer deaths and is the most lethal urologic cancer accounting for 40% mortality compared to 20% mortality rate associated with prostate and bladder cancers. It is estimated that 31,200 new cases of RCC are diagnosed annually and more than 11,900 deaths occur from this disease each year in the United States [1]. Significant advances in imaging procedures during the last two decades have increased the incidental detection of RCC leading to a change in the known surgical therapeutic modalities. The percentage of incidental tumors has increased from 13% during 1982 and 1983 to 59.2% during 1996 and 1997. T1/T2 tumors have been detected in 74.3% of incidentally discovered RCC compared to only 49.1% of symptomatic RCC [2-3].

RCC continues to be difficult to treat because of its ability to spread without producing symptoms and its inherent resistance to conventional chemotherapy. However, advances in molecular biology and the promise of

novel chemotherapeutic agents, together with advances in nephron-sparing surgery and less invasive surgical techniques, have improved the management of this malignancy.

In this manuscript we review the management of strategies and surgical options in the management of RCC (Figure 1).

## TREATMENT OPTIONS

### 1. Radical Nephrectomy (RNx)

Traditionally, radical nephrectomy remains the treatment of choice for localized RCC with normal contralateral kidney [4], but with the increasing use of modern radiologic imaging in recent years, incidental detection of RCC has increased in asymptomatic patients. Incidentally diagnosed RCC tends to be smaller and of lower stage in comparison to symptomatic ones [2-3]. Thus, interest in less invasive surgical management of RCC has increased, and the number of patients undergoing radical nephrectomy has decreased over the last two decades [5-6]. The risk of renal insufficiency, which might develop after radical nephrectomy, raises several concerns. Studies done on renal transplant donors with long-term follow-up have revealed that normal renal function can be preserved with a solitary kidney [7]. However, kidney donors are usually young, well selected and do not have other risk factors that might affect their future renal function such as diabetes or hypertension. Patients with RCC are usually older, and have multiple risk factors. It was shown that a significant rise in serum creatinine occurs in patients undergoing radical nephrectomy for renal cell carcinoma [8-9]. Novick et al. showed that loss of 50% or more of renal mass puts such patients at greater risk of progressive renal failure [10]. On the basis of current literature, it is preferable to perform partial nephrectomy whenever feasible rather

### TREATMENT OF RENAL CELL CARCINOMA

- Open radical nephrectomy (ORN)
- Laparoscopic radical nephrectomy (LRN)
- Open partial nephrectomy (OPN)
- Laparoscopic partial nephrectomy (LPN)
- Energy ablative procedures
  1. Cryoablation
  2. Radiofrequency ablation
  3. High intensity focused ultrasound (HIFU)

FIGURE 1. Treatment options for localized RCC

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than radical nephrectomy in cases of RCC with risk factors that can affect the overall renal function.

Robson introduced radical nephrectomy in 1969 [4], which encompasses four basic principles : 1) early ligation of the renal artery and vein, 2) removal of the kidney outside Gerota's fascia, 3) removal of the ipsilateral adrenal gland and 4) performance of lymphadenectomy from the ipsilateral crus of the diaphragm to the aortic bifurcation. The most important part is the removal of the kidney outside Gerota's fascia, since the renal capsule turns up to be involved in 25% of the cases. Ipsilateral adrenalectomy seems to be warranted when the tumor involves the upper pole of the kidney, or when the kidney is extensively involved by cancer [11]. Routine performance of lymphadenectomy is still debatable, and seems to be more important for prognostic evaluation but has little therapeutic benefit [12]. Complications following radical nephrectomy may occur in 20% of the cases, with around 2% operative mortality [13]. Post-operative recurrence following radical nephrectomy for RCC is stage-dependent (7.1% for T1N0M0 to 39.4% for T3N0M0 tumors) [14].

## 2. Laparoscopic Radical Nephrectomy

Laparoscopic radical nephrectomy has been shown recently to be an excellent minimally invasive alternative to open radical surgery for most patients with organ confined T1-T3aN0M0 renal tumors [15]. This procedure should be offered to patients who are not candidates for nephron-sparing surgery. In the past, larger tumors and tumors involving renal vein were considered as absolute contraindication for laparoscopic radical nephrectomy, but nowadays these are amenable to this technique. Steinberg et al. reviewed the overall experience at the Cleveland Clinic [16] : Of 300 patients who underwent laparoscopic radical nephrectomy, 33 were performed for tumors larger than 7 cm (17 tumors between 7 and 10 cm, and 16 tumors over 10 cm), and these were compared in a historical cohort fashion with 34 cases who underwent open radical nephrectomy for tumors larger than 7 cm. No statistical difference in complication rates were found between the two groups, although there were less surgical complications in the laparoscopic group. Therefore, laparoscopic radical nephrectomy has proved to be a safe procedure with a low incidence of complications especially in the hands of urologists who are experienced in laparoscopic surgery [15]. Overall, laparoscopic radical nephrectomy does not increase the risk of port site seeding. Nevertheless, one must be careful to avoid the rare complication of sack perforation with potential tumor spillage [17]. This complication is more prevalent with tumor morcellation within the endocatch bag. We prefer to extract the specimen intact after full entrapment in the endocatch bag, and to widen the incision as needed to achieve easy extraction.

Long-term oncologic data on laparoscopic radical nephrectomy are promising. Portis et al. reviewed the

experience with 64 patients operated before 1996. These were compared with a cohort of 69 patients who were operated by open radical nephrectomy, with a 5-year disease free survival of 92% and 91% for laparoscopic and open radical nephrectomies respectively. The authors concluded that laparoscopic radical nephrectomy confers long-term oncologic efficacy that is comparable to open technique [18], and could now be considered as the gold standard treatment for localized renal cell carcinoma that is not amenable for nephron sparing surgery.

## 3. Partial Nephrectomy

The first partial nephrectomy for RCC was performed in 1887. However, interest in nephron-sparing surgery greatly increased in the last 2 decades with the advancement in renal imaging and reno-vascular surgery. Besides the absolute indications for partial nephrectomy, where the patient will be at risk for renal replacement therapy after radical nephrectomy, such as bilateral renal tumors or a tumor in solitary kidney, the relative indications expanded to include cases with calculus disease in the contralateral kidney, infections, vascular problems, hypertension and diabetes. Recently, the indications expanded further to include patients with small-localized tumors and normal contralateral kidney. All comparative studies have shown excellent local control, a low local recurrence rate (amenable for curative surgery) and similar 5-year cancer specific survival and overall survival rates [19-20]. Although partial nephrectomy exposes patients to a higher complication rate, these complications have decreased significantly over the years with growing experience with the procedure, which is considered technically more demanding than radical nephrectomy. However, even with improved operative techniques, immediate or delayed hemorrhage from the tumor bed can occur. Urinary fistulas occur rarely but most respond to conservative management [21]. The major concern is the occurrence of local relapse in the tumor bed as a result of incomplete removal, which can occur in about 10% of cases [22].

Another issue of great importance is the multicentricity of RCC that predisposes to future recurrences. This is especially important in cases like Von Hippel Lindau syndrome, where multifocality rates could reach 25%, and higher rates of bilaterality either synchronous or metachronous, which should be taken into consideration in such cases. Multifocality, which is inherent to renal cell carcinoma, is not in itself an argument against nephron sparing surgery due to the comparable outcome of nephron sparing surgery to radical nephrectomy [22]. The quality of life in patients undergoing nephron-sparing surgery is superior to patients having radical surgery. In addition, it has a comparable cost-effectiveness and length of hospital stay to radical nephrectomy. Partial nephrectomy is now the gold standard of treatment for solitary tumors up to 4 cm in size, for tumors affecting anatomically or functionally solitary kidneys and in bilateral renal tumors [25].

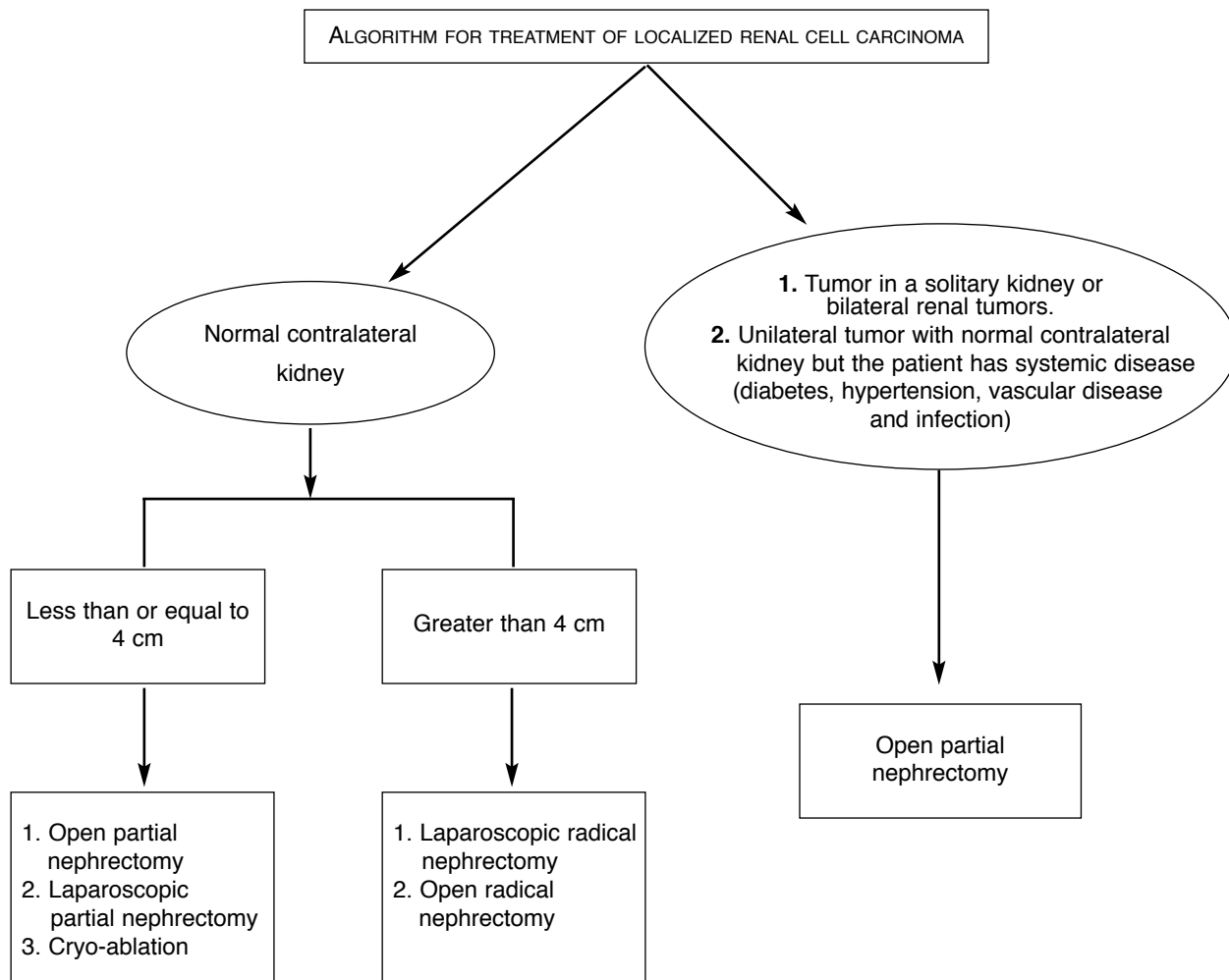


FIGURE 2. Treatment strategies for localized RCC

#### 4. Laparoscopic Partial Nephrectomy

Laparoscopic partial nephrectomy is a novel and challenging approach that involves significant steps as securing renal hypothermia, hemostasis, pelvicalyceal reconstruction, temporary occlusion of renal vessels. Laparoscopic partial nephrectomy has addressed all these issues to duplicate the open technique but has the advantage of being less invasive with shorter recovery and better cosmesis and comparable outcome. Recently, Guillanneau and his colleagues [24] evaluated laparoscopic partial nephrectomy for RCC in 28 patients, with median tumor size of 3.2 cm. They noted improved intra-operative visualization and were able to achieve consistent renal hypothermia by this technique. The long-term results regarding oncologic efficacy of this technique needs further follow-up. Gill et al., in a comparative study between open versus laparoscopic partial nephrectomy for solitary renal tumors of 7 cm or less in 200 patients, noted a higher complication rate in the laparoscopic group, with a higher incidence of positive margins [25]. The authors concluded that open partial

nephrectomy remains the gold standard for nephron sparing treatment for renal tumors [25].

#### 5. Cryoablation

Cryoablation encompasses rapid freezing of the targeted tissue, which is followed by sloughing of the devitalized tissues and healing by secondary intention. The lethal temperature for achieving reliable tissue death is around  $-40^{\circ}\text{C}$ . Cryoablation represents one of the treatment options for small peripheral renal masses. The procedure can be done laparoscopically or percutaneously. Lee and his colleagues [26] reported their experience in 20 patients with small tumors (1.4-4.5 cm) of whom 11 had no evidence of recurrence. Of the remaining patients, 50% had late resolution of the tumor at two years follow-up, and in the other half the mass remained stable during follow-up (2-23 months). Thus, cryoablation seems to be an excellent alternative for patients with small (less than 3 cm) peripheral lesions especially in patients with poor general performance status [27].

## 6. High Intensity Focused Ultrasound [HIFU]

HIFU is the least invasive technique available for renal tumor ablation ; it employs ablative ultrasound frequency beams generated by piezoelectric elements reflected as in ESWL. Thermal destruction results, with local hemorrhage and coagulative necrosis. Most literature is experimental which demonstrates that tumors in the upper pole are not affected due to absorption of ultrasound energy by the bony ribs [28]. Preliminary results with this technique are encouraging, but long term follow-up is needed to better demonstrate its efficacy [29-30].

## 7. Radio frequency ablation

Radio frequency ablation provides heat-based tissue destruction that can be performed using the “dry” or “wet” technique. Uncertainty about the efficacy of radio frequency ablation still exists, and pathologic examination following radio frequency ablation showed viable tumor tissue in 5% of the tumor volume in 80% of cases one week following treatment [31]. Consequently, such treatment is still in the experimental phase at the time being.

Minimally invasive procedures such as cryoablation, microwave and laser therapies are expected to replace conventional open surgical procedures in the future. However, to date many of these procedures have been done for small tumors and considered investigational.

## STRATEGIES OF TREATMENT OF LOCALIZED RCC

With the advent of less invasive modalities for treatment of localized RCC the recommended treatment will probably change in the future. The availability and training in laparoscopic surgery is the most important parameter that might divert some surgeons from adhering to recommended modalities of treatment in certain situations.

To simplify the strategy of treatment of localized RCC as depicted in Figure 2, we divided patients into groups, those with normal or abnormal contralateral kidney and according to tumor size. Tumors up to 4 cm in size are best treated with elective open partial nephrectomy that continues to be considered the gold standard. When the tumor is larger than 4 cm, laparoscopic radical nephrectomy is the recommended treatment. Patients who have tumors in anatomically or functionary solitary kidney, like cases of bilateral renal tumors, or when the other kidney is normal but threatened by systemic diseases like diabetes or hypertension, are best treated with open partial nephrectomy. If this is not feasible, laparoscopic radical nephrectomy with renal replacement therapy should be considered.

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