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Clear Cell Renal Cell Carcinoma: What's New And What's Proven?

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Abstract

In the last three decades, presentation of renal tumors has changed greatly and knowledge of their biology has advanced notably. The widespread use of imaging techniques, such as ultrasound, magnetic resonance imaging and computed tomography, has changed the landscape of renal cancer. We now observe more and more incidental and asymptomatic small, low-grade renal masses, up to more than 70%, and treatment has moved away from radical nephrectomy to nephron-sparing approaches, such as open, laparoscopic and robot-assisted partial nephrectomy (PN) and thermoablation. Several reports have provided evidence that nephron-sparing surgery is oncologically efficacious as radical nephrectomy (RN) for a small renal mass. However, in younger patients, RN was associated with decreased overall survival, which was probably due to its negative impact on the global renal function and increased cardiovascular events. In a very large study, the European Organization for Research and Treatment of Cancer compared outcomes and complications of elective PN versus RN for low stage renal cell carcinoma and demonstrated that oncological outcomes were similar, but functional results were better for PN. The complication rate was not so high in terms of leakage, intraoperative and postoperative bleeding, and need for reintervention. For several years elective PN was limited to T1a masses < 4 cm in size. However, several reports have recently shown that although T1b diseases are associated with higher progression rates than T1a, the different outcomes do not depend on whether radical or partial nephrectomy was used. We can therefore say that prognosis is linked to tumor biology rather than to the type of surgery. In conclusion it is reasonable to state that PN should be considered for all organ-confined renal tumors. Open surgery, laparoscopic or robot-assisted approaches to PN seem to provide similar oncological results, with overlapping complication rates and operation times. Regarding mini-invasive techniques, such as radiofrequency or cryotherapy, recent meta-analysis compared PN with these minimal invasive treatments and showed that PN seemed to be the best approach in terms of recurrence rates. Consequently, the other two strategies should not be considered as alternatives to surgery but should be reserved for patients who, for whatever reason, cannot undergo surgery. In conclusion, RN is associated with a greater risk of developing chronic kidney disease. Since PN provides similar oncological results, better functional outcomes and better overall survival than RN, it is indicated for the great majority of T1 tumors. Expanding indications to T1b malignancies is associated with a higher complication rate. Thermoablative treatment provides long-term results that are not as good as PN and so it is indicated only for patients who cannot withstand surgery.

Content

Epidemiology

The incidence of clear cell renal cell carcinoma (CCRCC) has increased by about 2% annually in recent years with the greatest incidence in Europe, North America and Australia. It is the 14th most common form of cancer with 200,000 new cases diagnosed in 2002. Despite earlier diagnosis with ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), 20-30% of patients have metastases at diagnosis and the same number relapse and/or develop metastases after surgery (1, 2).

Etiology

CCRCC is still found predominantly in men. Distribution in ethnic groups is linked mostly to different lifestyles, approaches to diagnosis and to therapy. The 70-75-year-old age group is most affected in Europe and the USA. Cigarette smoking is recognized as a risk factor, increasing risk by 54% for men and 22% for women (3). Obesity and hypertension are also well-known risk factors. It is worth noting that all three factors can be modified and eliminated (4, 5).

About 2-3% of CCRCCs are due to inherited genetic defects. Von Hippel-Lindau (VHL) syndrome is the most frequent and should be considered in young patients with CCRCC and/or when lesions are multifocal/bilateral. These forms have a relatively low risk of metastasis. Localized on chromosome 3p25-26 the *VHL* gene under normal conditions produces a protein that degrades hypoxia-inducing factors (HIFs) leading to neoangiogenesis as its final product. Inherited papillary CCRCC is caused by activation of the c-met proto-oncogene on chromosome 7q31, which encodes for growth factor receptors (6).

Other risk factors for CCRCC are acquired renal cystic disease in dialyzed patients (7) and possibly in patients with diabetes (8), with urinary tract infections and occupational exposure to carcinogens (asbestos, aromatic polycyclic hydrocarbons, solvents, cadmium) (9).

Diagnosis

In recent years presentation of renal tumors has changed greatly and knowledge of their biology has advanced notably. Today guidelines for therapy are changing rapidly for several reasons: increased incidence, a higher percentage of accidental diagnoses and a smaller mean size of diagnosed lesions. Furthermore, localized disease is more common, patients are elderly and more is known about the reduced risk of aggressive disease in small renal masses.

The gradual increase in accidental diagnosis of renal tumors has often been described elsewhere (10-11). Schlomer et al. observed that 74% of 349 treated renal tumors were diagnosed accidentally in the 5-year period from 2000 to 2005 (12). Accidental diagnosis is due to widespread use of imaging techniques such as ultrasound and CT scans (13). Indeed, recent data have shown that use of CT scans increased 141% between 1996 and 2005 and ultrasound 12% in the same period (14).

Consequent to the increase in accidental diagnosis is a reduction in mean lesion size of diagnosed tumors. Upon reanalysis of data in the National Cancer Database for the years 1996-2004 for 104,150 patients, Cooperberg et al. observed that the mean size of neoplasias had fallen from 4.13 to 3.69 cm, while tumors under 3 cm in size accounted for 32% of tumors in 1993 and 43.4% in 2004 (15).

Another review of the National Cancer Database showed that tumor stage had also been reduced over time (16). Stage I disease increased from 41.4% to 54.5% in men and from 45.6% to 61.5% in women in the 1993-2004 time period. The authors also reported a drop in cases with stage III and IV disease in the same period, while the percentage of metastases gradually fell from 26.3% (1988) to 16.7% (2003) (17).

Therapeutic Indications for Localized CCRCC

Active surveillance

Active surveillance of small renal masses has shown that a significant percentage are not CCRCC and that real CCRCC are often indolent, with only 1.3% evolving towards metastasis in some series in the years following diagnosis (18-22). Consequently, active surveillance is a reasonable option in patients who have renal masses < 4 cm in size as well as significant comorbidities or short life expectancy.

Nephron-sparing surgery

Even though small renal lesions are ideal candidates for nephron-sparing surgery or partial nephrectomy (PN), recent studies have reported that PN is still rarely used (23, 24). Concerns about a higher risk of local relapse because of insufficient resection, microscopic satellite tumors and multifocality have led surgeons to prefer radical nephrectomy (RN) as standard treatment for even small lesions in the renal cortex (25, 26). Today, however, RN is no longer the gold standard for small CCRCC and should be limited to cases that PN cannot treat.

Open partial nephrectomy (OPN) for CCRCC < 4 cm in size is preferable to RN because renal function is conserved and long-term survival is better, with a lower incidence of relapse and better quality of life (27-32). Furthermore, progress in recent years in laparoscopic surgery for partial nephrectomy and robotic PN have aroused such great interest in surgeons that they have become valid treatment options for this type of neoplasia in centers of excellence.

Using the glomerular filtration rate (GFR) to compare long-term renal function in 622 patients after RN or PN, Huang et al. recently demonstrated that RN was a significant risk factor for the development of chronic kidney disease (33). In a study comparing RN (n = 290) with PN (n = 358), Thompson et al. concluded that RN was associated with poorer overall survival in patients < 65 years of age (relative risk: 216, P = 0.02 vs. PN) (34).

Miller et al. compared cardiovascular and renal morbidity after RN and PN in patients with early-stage renal cancer and concluded that PN is associated with less occurrence of kidney failure, dialysis and kidney transplantation (35). Recent epidemiological and surveillance data show that compared with PN, RN is associated with a greater incidence of general non-cancer-related deaths in patients with T1aN0M0 renal carcinoma (36).

In conclusion, even though data indicate a substantial overlap between nephron-sparing surgery and RN as far as cancer control is concerned, PN is markedly better for preservation of renal function, prevention of chronic kidney failure and better quality of life (37, 38).

Indications for both OPN and laparoscopic PN (LPN) have been extended in the past 10 years to encompass lesions from < 4 cm in diameter, to lesions between 4 and 7 cm (39-46). OPN is the safest and most efficacious in patients with a single kidney. Both OPN and LPN are safe when lesions are in the hilus or the peripheral kidney (47, 48) and both can be used with large lesions (4-7 cm) in selected patients (43, 49, 50).

Surgical Approaches

The best access route for OPN is the retroperitoneal approach. The renal hilus vessels were clamped in 50-99% of patients with a mean ischemia time ranging from 14.0-20.1 min (43, 48, 51-55). In most OPN in patients with a single kidney, ischemia times were longer (38.1 ± 20.9 min), probably because resectioned tumors were larger (48). Cooling was used in 18-60% of cases to prevent renal damage, particularly in patients with a single kidney (48, 53, 54).

In laparoscopy, the transperitoneal approach is generally preferred; it is the most suitable for anterior and medial lesions. Restricted retroperitoneal space makes LPN more difficult technically, but this approach provides direct access to posterior masses, particularly to posteromedial lesions (56). Factors that appear to ensure the success of LPN are routine closure of the hilar vessels, use of hemostatic agents and parenchymal sutures (57).

Unfortunately, warm ischemia times are 10 minutes longer in LPN than in OPN (30.7 vs. 20.1 min) as shown by a comparative analysis of 1,800 patients with solitary tumors (52). Since cold ischemia is more complex during LPN, several methods have been proposed to facilitate and optimize it (58-61); retrograde ureteral infusion of freezing saline solution has recently been suggested to prevent parenchymal edema and protect the nephrons (62, 63).

The suture technique for reconstituting the renal parenchyma in LPN is still being developed (64, 65) and several biological agents have been used, not only to control hemostasis (66, 67) but also to reduce the overall complication rate (37 vs. 16%, $P = 0.008$) in terms of postoperative hemorrhage (12 vs. 3%, $P = 0.08$) and urinary fistula (6 vs. 1.5%, $P = 0.12$) (68).

Finally, comparative studies have shown that operating times are significantly shorter with LPN than with OPN: 85/225 vs. 150/275 min (52, 69, 70).

Robot-assisted partial nephrectomy

Robot-assisted PN (RPN), using the Da Vinci robot system, was first described by Bhayani (71) and Kaul et al. (72). The robot-assisted technique uses a hybrid approach with the first part of the operation being based on the standard laparoscopic transperitoneal dissection (73-77).

Sliding-clip renorrhaphy provides an efficient system for fashioning a hemostatic tenorraphy, thus eliminating the need for knots inside the human body (78, 79). Interestingly, overall operating times for uncomplicated lesions were longer with RPN than with LPN (185 vs. 158 min, $P < 0.01$) (80).

Oncological Results

At present, the European Organization for Research and Treatment of Cancer (EORTC) is still conducting the first randomized, prospective, phase III study comparing complications after elective PN and RN in patients with low-grade CCRCC under 5 cm in size who have a normal contralateral kidney.

In nonrandomized studies on CCRCC < 4 cm in diameter, oncological results were similar after OPN and RN (28, 48, 81, 82), with 5- and 10-year cancer-specific survival rates of 98.5 and 96.7%, respectively. The overall incidence of local relapse was very low in all series (0-5.9%). Similar results were achieved with PN for tumors > 4 cm (39-46, 82, 83), which encourages extending indications to neoplasia that are up to 7 cm in diameter. A recent article by researchers from the Mayo Clinic on this issue demonstrated that, in the absence of metastases and relapse, cancer-specific survival falls significantly with each 1-cm increase in the size of the tumor mass (84). When tumors range in size from 4-7 cm, the surgeon's decision to opt for PN should depend on tumor localization and resectability rather than size (42, 44, 85).

The earliest data on the laparoscopic and robot-assisted techniques report 5-year cancer-specific survival rates of 100% after LPN with a local relapse rate of only 2.7% (86). Similar results were reported by Gill et al. (52) with a 3-year cancer-specific survival rate of over 99%. These results overlap with OPN outcomes. The overall local relapse rate after LPN in a recent series was a low 0-2.4%, while the positive margin rate ranged from 0-2.9% (69, 86-89). Moreover a retrospective analysis of LPN and OPN (200 patients) reported 5-year overall survival rates of 96 and 85% and local relapse-free rates of 97 and 98% respectively (70).

In a recent review, Shapiro et al. observed that oncological results had been excellent since their first attempts at RPN (N = 211) (77), and indeed overlapped with results achieved in LPN studies (90, 91).

It is still not clear whether simple enucleation or enucleus-resection with a margin of apparently healthy tissue provides better results with regard to risk of positive surgical marginsand local relapse (25, 26, 92, 93). For the prognosis, margin positivity is a more important factor than margin size, even though a positive surgical margin is not always a factor in local relapse and/or disease progression (94). Today, however, tumor enucleation appears to be more accepted since no correlation emerged between the width of resection margins and risk of local relapse (95, 96).

Local relapse rates range from 0-5% after OPN, from 1.8-2.4% after LPN (97, 98) and are reported to be 3.3%. after RPN (77). A recent multicenter study suggested that positive surgical margins are rare after PN and should only require more frequent check-ups in an in-depth surveillance program (99). Some reports showed that positive surgical margins did not impact negatively on cancer-specific survival and that only a small percentage of patients relapsed clinically a short time after surgery (100).

Functional Results and Complications

Thompson and Blute recently reported that when the warm ischemia time did not exceed 20 min, renal injury was minimal (101). Despite this, the optimal warm ischemia time is still open to debate (101, 102). Data on OPN indicated full recovery of renal function within 30 minutes of ischemia (103). Renal failure occurred in 0.5-12.7% of cases (104). Although serum creatinine concentration is a useful parameter for monitoring changes in renal function in a patient with solitary kidney, it is not helpful in patients who have a normal contralateral kidney (105). A prospective study using CT scan to investigate renal function separately was able to demonstrate that 25 minutes warm ischemia time was the cutoff for irreversible renal damage (105). Furthermore, recent reports assessing the effects of ischemia during OPN in patients with a single kidney concluded that, when vessel clamping was needed, the warm ischemia time should not exceed 20 minutes and the cold ischemia time should be limited to 35 minutes so as to reduce the risk of acute and chronic kidney failure. Caution should be applied when analyzing these findings as only patients with single kidneys were included in the studies and serum creatinine levels were the only parameter for kidney failure (54).

Mean ischemia time is longer in LPN than in OPN. Some reports proposed a rapid declamping technique which included an initial renal parenchymal suture during ischemia; renorrhaphy was concluded only after organ revascularization. This technique not only reduced ischemia times by over 50% (13.9 vs. 31 min) but also improved the complication rate, as confirmed by other authors (106-108).

Early observations of RPN reported that ischemia times were satisfactory at 21.0-32.1 min (72, 77, 90, 91) and that postoperative renal function was similar after RPN and LPN (77).

Lane et al. (109) compared renal function results after OPN (n = 169) or LPN (n = 30) for renal neoplasia in patients with one kidney. LPN was associated with a 9-minute longer warm ischemia time ($P < 0.0001$) and a higher rate of postoperative dialysis (10 vs. 0.6% respectively, $P = 0.01$). The GFR dropped by 21 and 28% respectively after OPN and LPN (P = NS). Consequently, even if LPN is technically feasible in patients with one kidney, OPN should still be considered the best approach in patients who are at high risk of chronic kidney failure (109).

OPN-related complications have clearly been reduced in recent years. Even though OPN is technically more demanding than RN, perioperative morbidity is similar in cases of small renal tumors (81). In a randomized prospective study Van Poppel et al. demonstrated that OPN had a slightly greater complication rate than RN (110).

General complications ranged from 4.1-38.6%.Urinary fistulas accounted for 0.7-17.4%, and various types of hemorrhage for 0 and 7.5%. (42, 52, 111-113). In a recent multicenter study, Patard et al. reported that blood loss requiring transfusions and the appearance of urinary fistulas increase significantly after OPN for tumors > 4 cm in size. Increased perioperative morbidity is, however, still acceptable for these large masses (43).

The LPN-related complication rate has also dropped sharply in recent years thanks to greater experience and improvements in suture technique over time. They range from 9-33%, with the most common being, once again, hemorrhage (1.5-9.5%) and urinary fistulas (1.4-10.6%) (113). In an analysis of their own experience, Turna et al. compared LPN in the years 1999-2002 and 2003-2006, finding the complication rate dropped from 29.6% to 16.9%. Urinary fistulas fell by 4.7% to 1.2% ($P = 0.01$), while no significant change was observed in postoperative hemorrhage (5.9 vs. 5.6%), probably because there were more technically difficult operations in the later series of patients (114).

Gill et al. compared LPN and OPN for neoplasms < 7 cm in size, reporting that LPN required prolonged warm ischemia times and was associated with greater postoperative complications. Urological complications respectively accounted for 9.2 vs. 5.0% ($P = 0.0006$) and postoperative hemorrhage for 4.2 vs. 1.6 ($P = 0.0002$) (52).

Although all authors reported a significantly lower complication rate for esophytic lesions (115, 116), data were divergent for neoplasm in a central or hilar position. In these cases, Frank et al. observed a greater incidence of complications that were linked to bleeding and prolonged ischemia times (117). On the other hand, Nadu et al. found that when LPN was performed by a surgeon who was skilled in laparoscopy, complication rates were similar for central neoplasms, those around the hilus and peripheral tumors (118).

Compared with OPN, LPN in patients with a tumor in a single kidney is associated with a 2.54-fold greater percentage of complications ($P < 0.05$) and a higher rate of postoperative dialysis (10 vs. 0.6% respectively, $P = 0.01$)(109).

A recent review observed that complication rates overlapped after RPN and LPN (77).

Cryoablation and Radiofrequency Techniques

The so-called mini-invasive techniques are based on the use of radiofrequency or cryotherapy. At present, radiofrequency treatment seems to provide results that are oncologically similar to nephron-sparing surgery with cancer-specific survival rates overlapping for stage T1a tumors (119, 120).

Data are, however, divergent on the methods that are currently available for evaluating efficacy. Some authors reported a high percentage of positive biopsies 6 months after therapy; others were of the view that biopsies, when performed less than 1 year after treatment, had no clinical or diagnostic value because radiofrequency provokes cell death through heat without altering tumor cytoarchitecture. On the other hand, loss of radiological enhancement does not definitely indicate successful outcome of treatment.

A recent meta-analysis compared outcomes after radiofrequency and cryotherapy for a total of 1.234 renal tumors in 46 retrospective studies from 44 centers. No significant differences emerged in lesion size (2.53 vs. 2.67 cm), age of patients (64.5 vs. 66.0 years) or length of follow-up (19.3 vs. 15.5 months).Pretreatment biopsies were performed in 82.3% of lesions receiving cryotherapy and in 62.2% treated with radiofrequency ($P < 0.0001$). Retreatment was more frequent after radiofrequency than after cryoablation: 8.5 vs. 1.3% ($P < 0.0001$) (121).

The local relapse rate was significantly greater after radiofrequency than after cryotherapy (4.7 vs. 12.3%; $P < 0.0001$). Disease progression to metastasis was documented in 1.8% of patients overall, with disease progressing in more cases after radiofrequency treatment (2.5%) than after cryotherapy (1%) in a trend that approaches statistical significance ($P = 0.06$).Even though univariate and multivariate analyses confirmed that risk of disease progression correlated with ablation modality, i.e., that cryoablation provides better oncological results than radiofrequency, retrospective data do not provide valid indications for the operator’s choice of which approach to choose.

Conclusion

At present, some evidence has emerged from recent studies about CCRC. The widespread use of imaging techniques, such as ultrasound and CT scans has increased accidental diagnosis in up to more than 70% of cases with a corresponding reduction in mean lesion size and stage.

As far as treatment is concerned, PN is definitely indicated as the gold standard for stage T1a for selected T1b tumors. It is associated with similar oncological outcomes, better functional result, better overall survival and better quality of life than radical nephrectomy. Open surgery, laparoscopic or robot-assisted approaches to PN seem to provide similar oncological results, with overlapping complication rates and operation times. Mini-invasive techniques like radiofrequency or cryotherapy are not yet indicated as alternatives to PN, particularly because efficacy is very difficult to evaluate.

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