



Partial Nephrectomy for Clinical T2 Renal Tumors: Current Evidence in Perspective

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Abstract

Renal tumor is one of the most important urological malignancies with a rising worldwide incidence. There is advocacy for nephron sparing surgery (Partial nephrectomy (PN)) in the management of renal tumors because of studies that have demonstrated impaired renal function after radical nephrectomy with an associated increased risk of overall mortality. Renal tumors with size less than 4 cm, clinical stage T1a (cT1a), had been the focus for PN. However currently, clinical stage T2 (cT2) renal tumors which are renal tumors larger than 7 cm but confined to the kidneys are being managed with partial nephrectomy. This expanding use has been attributed to advances in tumor biology, radiological imaging and surgical technology. We explore the current evidence in support of this emerging practice.

Background

Renal tumor is one of the most important urological malignancies accounting for 2.4% of all adult malignancies. Its incidence is noted to be rising with an early stage at detection due to current wide spread use of cross sectional imaging in the evaluation of patients [1,2].

Currently, the diagnosis and staging of renal tumors involves the use of cross sectional imaging such as ultrasound, CT scan and magnetic resonance imaging. These have been found to be mostly accurate though some benign lesions have been inaccurately diagnosed as malignant [3]. Percutaneous renal biopsies have been found to be safe and able to differentiate malignant lesions from benign lesions and determine the potential for tumor growth and metastasis by determining the cell subtype and the fuhrman grade [4-6].

However, it must be noted that the smaller the renal mass the more likely it would be benign [7] and hence clinical stage T2 (cT2) renal tumors which are larger might have a higher percentage of them being malignant as compared to the finding by some investigators that between 8% - 27% of resected renal tumors tended to be benign [6,8].

The diagnosis of renal tumors at an early stage has contributed to the increasing call for nephron sparing surgery for the management of these tumors. Though this observation is true of developed countries, in developing countries renal tumors tend to be seen in a more advanced stage limiting the use of nephron sparing procedures, thus radical nephrectomy (RN) tends to be the norm [9]. The advocacy for nephron sparing surgery (Partial nephrectomy (PN)) in the management of renal tumors is because of studies that have demonstrated impaired renal function after RN with an associated increased risk of overall mortality and a greater risk of cardiovascular events that arise from loss of renal function [10].

The need to remove or ablate renal tumors stem from the fact that renal cell carcinoma, the predominant histological type (70%), is not effectively treated with chemotherapy and radiation therapy. The use of immunotherapy using cytokines like interferon alpha and interleukin 2 has demonstrated variable results with IFN- α providing a response rate of 6% to 15% and a survival benefit of 3–5 months and Interleukin-2 (IL-2) with documented response rates from 7% to 27% [11]. Other agents such as vascular endothelial growth factor-targeting (VEGF) antiangiogenic agents, mammalian target of rapamycin inhibitors, temsirolimus, and sorafenib have largely shown no statistically significant improvement in overall survival which has led to the introduction of Nivolumab, a programmed death-1 (PD-1) monoclonal antibody, which is under study [12].

Expanding Indications for partial Nephrectomy to include clinical T2 renal tumors

Partial nephrectomy (PN) for renal tumors has been in practice for some period. Renal tumors

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Received Date: 19 Sep 2017

Accepted Date: 25 Oct 2017

Published Date: 02 Nov 2017

Citation:

Kyei MY, Mensah JE. Partial Nephrectomy for Clinical T2 Renal Tumors: Current Evidence in Perspective. Clin Surg. 2017; 2: 1709.

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Figure 1: Left cT2 renal tumor with hardly any uninvolved renal parenchyma.

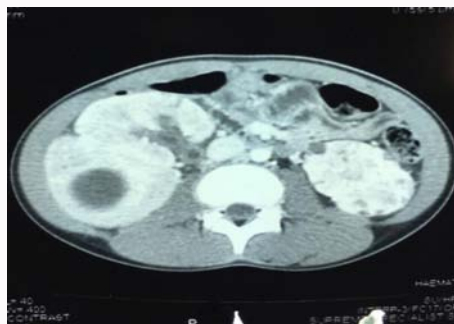


Figure 2: CT scan showing a cT2 right renal tumor, initial plan of performing open partial nephrectomy was abandoned as the hilum was found intra-operatively to be involved by tumor.

with size less than 4 cm, clinical stage T1a (cT1a), had been the focus for PN. Other considerations for a safe PN that ensures complete tumor removal included a peripherally located tumor, a unilaterally functioning kidney and presence of bilateral renal tumors [13]. This procedure is increasingly done using minimally invasive methods such as laparoscopic [14] and robotic [15]. The oncology outcomes have been similar comparing these minimally invasive procedures and the open partial nephrectomy but with shorter hospital stay and less transfusion in the former [14,15].

Open partial nephrectomy however continues to be performed for larger tumors in situations where there is decreased performance status and for tumors in solitary kidney seven in centers with minimally invasive setups [14]. Partial nephrectomy has been expanded to include clinical stage T1b (cT1b) and currently clinical stage T2 (cT2) renal tumors in the existence of good contralateral kidneys. cT2 renal tumors are renal tumors with size greater than 7 cm but confined to the kidney (Figure 1).

This expanding use has been attributed to advances in tumor biology, radiological imaging and surgical technology [13].

Though initial results were conflicting as to the superiority of PN over RN with regards to overall survival, Kopp et al. [16] in a study found no significant difference in 5 year cancer specific survival, progression free survival and overall survival between PN and RN for cT2 renal tumors using the R.E.N.A.L nephrometric score to achieve satisfactory matching so as to eliminate inherent biases in tumor characteristics that influence the choice of either PN or RN [16]. In a meta-analysis by Amir et al. [17], they identified four studies on cT2 renal tumors that compared PN (n=212) to RN (n=1792). In these patients, they found that the estimated blood loss was higher for PN ($p<0.001$), as was the likelihood of complications (RR 2.0; $p<0.001$). However, the recurrence rate (RR 0.61; $p=0.004$)

and cancer-specific mortality (RR 0.65; $p=0.03$) were lower for PN with the better likelihood of renal function preservation [17]. They concluded that despite these advantages, there was the need for good patient selection to achieve the intended benefits for choosing PN for cT2 renal tumors [17]. Similar conclusion was arrived at after the review of oncological and functional outcomes for PN in the setting of cT2 tumors by Nahal et al. [18]. They also affirmed the advantages of PN over RN for cT2 tumors indicating that PN has emerged as an acceptable alternative for surgical management of cT2 renal tumors over the last decade [18].

Points of concern

The need for cross sectional imaging with 3D reconstruction as part of the pre-operative planning is important in these large tumors especially in assessing the nearness to/ involvement of the renal hilum and in the determination of renal parenchyma that is likely to be left behind after the procedure (Figure 2).

Warm ischaemia have a negative impact on renal function. The median warm ischaemic times have been noted to be longer in larger renal tumors undergoing PN compared to smaller tumors [15]. Therefore, efforts at reducing the effect of warm ischaemia need special consideration in these larger tumors. A study of 360 solitary kidneys that had PN showed that each additional minute of warm ischemia correlated with a 6% increased incidence of de novo severe CKD and that suggested a cause/effect relationship [19]. In current practice, a warm ischaemic time of 30 min is considered safe. However, for procedures anticipated to go beyond this time, various methods have been employed to reduce the ischaemic time, with hypothermia being one of the foremost modalities used to preserve renal function. The clinical effectiveness of pharmacological agents such as intravenous mannitol infusion, dopamine, fenoldopam and use of antioxidants such as allupurinol, vitamin C and vitamin E in preventing ischaemic renal damage during PN have been challenged [20]. Thus nephron sparing surgeries for cT2 tumors requires one to be technically experienced in order to perform the procedure in an acceptable time period to avoid a prolonged warm ischaemic time or if need be institute some of the preventive methods early to save renal function.

Tumor recurrence either local or metastatic is of great concern when PN is performed for cT2 renal tumors. Percutaneous renal biopsies on these large renal tumors prior to intervention could identify benign lesions or less aggressive lesions that will assist in the clinical decision as regards the extent of resection at PN in cT2 renal tumors. There is however the need for a lifelong follow up or surveillance to diagnosis or detect local recurrence early for intervention.

There is no consensus on the follow up plan of patients after PN for small renal masses and less so for cT2 renal tumors. Kopp et al. [16] in their study used physical examination, chest X-ray and abdominal CT/MRI every 6 months for 3 years, then yearly afterwards after PN for cT2 renal tumors with long term follow-up continuing indefinitely [16]. This may be modified if the histology report comes as a benign lesion.

Further studies on PN for cT2 renal tumors will lead to the procedure being performed more safely supported by robust and standardized predictor of success and recurrence. Increasing experience, will also allow more of these large tumors to be managed by minimally invasive techniques.

Conclusion

Partial nephrectomy for Renal tumors have been demonstrated to be safe in well selected patients with cT2 renal tumors offering long term tumor control with the advantage of preserving renal function. These tumors have heterogeneous characteristics and so require careful consideration of the patient and tumor characteristics as well as the surgeons experience in its pursuit. The call for prospective randomized studies is in order as it will firmly place this approach as a viable and probably the preferred option in the management of patients with cT2 renal tumors.

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