REVIEW ARTICLE

Nephron Sparing Surgery for Renal Carcinoma

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Radical nephrectomy remains the accepted standard treatment for localized renal cell carcinoma with an anatomically normal opposite kidney [1]. The concept of nephron sparing surgery for the treatment of renal tumours is not new. In 1984, Wells performed the first partial nephrectomy for removal of a perirenal fibrolipoma. Three years later, Czerny did the first partial nephrectomy for a renal neoplasm. This procedure was soon abandoned because of excessive postoperative morbidity which included haemorrhage, sepsis, fistulae etc. [2]. In 1950, Vermooten revived the concept of partial nephrectomy and suggested that partial nephrectomy could be performed for renal cell carcinoma even in the presence of normal contralateral kidney [3]. Robson *et. al.* in late 1960s established that nephrectomy performed outside Gerota's fascia yielded improved survival over pericapsular nephrectomy [4]. This again diminished the trend towards conservational renal surgery in cancer.

Recent interest in nephron sparing surgery for renal cell carcinoma has been stimulated by advances in renal imaging, improved surgical techniques, the increasing number of incidentally discovered low stage renal cell carcinoma and good long term survival in patients undergoing this form of treatment. Nephron sparing surgery entails complete local resection of a renal tumour while leaving behind the largest possible amount of nomally functioning parenchyma in the involved kidney.

Indications of nephron sparing surgery

The classical indications of nephron sparing surgery include conditions in which radical nephrectomy would render the patient anephric with subsequent need for dialysis. These are :

- Bilateral synchronous renal cell carcinoma.
- renal cell carcinoma in a solitary functioning kidney.

In the above two indications, the aim is to preserve as much functioning renal tissue as possible. A functioning renal remnant of atleast 20% in one kidney is necessary to avoid end stage renal failure.

- Unilateral renal cell carcinoma and a functioning opposite kidney that is affected by conditions that might threaten its future functioning e. g. Renal artery stenosis, hydronephrosis, chronic pyelonephritis, ureteral reflux, calculus disease, diabetes, nephrosclerosis.

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Of late, indications of nephron sparing surgery have been extended to include the small, solitary, peripheral renal cell carcinoma which is low grade and low stage in a patient with a normal contralateral kidney. This indication is the most debatable. It is however supported by the following arguments.

* There is dramatic increase in the incidental discovery of small, totally asymptomatic renal tumours due to advancement in imaging techniques [5–9].
* There is some evidence that unilateral nephrectomy causes sustained hyperperfusion to the contralateral kidney, which may lead to development of proteinuria and tubular injury [10]. However this damage is more likely if there is less than one kidney [11, 12].
* The pre-operative unknown malignant potential of solid renal tumour [13].
* Possibility of a contralateral tumour development ; this has been reported in upto 4% and it may occur upto 20 years after nephrectomy [14, 15].
* Possible need of cytotoxic drugs for metastatic disease in future [16].
* Excellent results of nephron sparing surgery in renal cell carcinoma which is of low clinicopathological grade and low stage [17–21].

Perioperative and intraoperative requirements and considerations

Patient undergoing nephron sparing surgery should be evaluated properly to rule out locally extensive or metastic disease.

* A renal angiogram should be done to delineate the main renal artery and its branches and to document the presence of polar vessels. Knowledge of the number and location of these vessels help greatly in removing the tumour with minimal blood loss and avoids injury to adjacent parenchyma. All efforts should be made to preserve segmental arteries supplying the tumour free parenchyma.
* Renal venography is performed in patients with large or centrally located tumour to evaluate for intrarenal venous thrombosis secondary to malignancy [22]. If thrombosis is present, it implies a more advanced local tumour and also increases the technical complexity of tumour excision.
* The surgeon should give enough attention to minimize intraoperative ischaemic renal damage. A number of measures have been suggested. Patients should undergo volume expansion by hydration with salt containing solutions for atleast 12 hours preoperatively to ensure optimal renal perfusion at operation ; use of allopurinol in experimental studies has been found to prevent the generation of free radicals after reperfusion of the kidney [23]. Temporary renal artery occlusion, required for bloodless field at surgery, can damage renal parenchyma due to renal ischaemia.

Ischaemic renal damage can be decreased by either topical cooling or by continuous in situ cold perfusion. Human kidney can tolerate ischaemia for 30 minutes without topical cooling but with topical cooling, it can tolerate ischaemia for upto 3 hours. Because of its ease and low cost, surface cooling is the most popular method of in situ renal hypothermia and is most commonly employed. In this technique, saline slush is placed around the kidney and the kidney is allowed to cool for about 10–15 minutes after occlusion of the renal artery. This time is needed to attain a core renal temperture of 15°C–20°C which optimises renal preservation.

In addition, during the procedure, recooling is

recommended every 30 minutes because rewarming occurs due to removal of the slush from the operative area. This is especially true when the surgeon elects not to occlude the renal vein at the time of renal artery occlusion to identify venous branches more easily during dissection.

In contrast to topical cooling, in situ continuous perfusion by cold fluid ensures homogenous cooling of the entire kidney. In continuous cold perfusion there is no time limit for ischaemia tolerance of the kidney ; it thus allows time for painstaking reconstruction of pelvicalyceal system and damaged blood vessels. This technique eliminates the need for bench surgery and risk of loss of renal function. It also washes out vasoactive metabolites and free radicals. The renal artery is occluded with vascular clamp and a longitudinal arteriotomy is made. A 10–12F perfusion catheter is used for cold perfusion. Drainage of the fluid is done by a longitudinal renal venotomy after clamping the renal vein or via the gonadal veins on the left side. Perfusion of kidney is done at hydrostatic perfusion pressure of 55–75 cm of H_2O. Within a few seconds, the entire kidney is cooled to 4°C –8°C and becomes pale and bloodless. Continuous perfusion is maintained throughout the ischaemia time. Disadvantages of this technique includes possible injury to renal vessels and the theoretical risk of tumour dissemination and in situ perfusion should not be used in routine cases. In the present scenario, the only indication for in situ perfusion is a locally extensive tumour in a solitary kidney involving the hilum.

* Mannitol, given intravenously 5 to 10 minutes before arterial clamping has been shown to aid in preventing ischaemic renal damage by decreasing intracellular oedema, flushing cellular debris and myoglobin from tubules and arresting mitochondrial calcium accumulation. [24]
* Use of systemic anticoagulation (Heparin 5000 IU) at the induction of anaesthesia or before clamping the renal artery to minimize risk of intrarenal clotting and subsequent renal arterry thrombosis is used but its benefit is debatable.
* Use of intraoperative ultrasound and frozen section of the margin to decrease local recurrence is recommended. [25, 26] Use of intraoperative sonography has two advantages ; first, it confirms the location of the tumour and secondly, it inspects the remaining parenchyma for satellite lesions. It can demonstrate satellite lesion of upto 1–1.5 cm size.
* Use of the Argon beam infrared coagulator of CUSA (cavitron ultrasonic surgical aspirator) has got two distinct advantages. It achieves renal parenchymal haemostasis and produces tissue necrosis to a depth of approximately 2 mm, thereby killing tumour cells at the margin, so decreasing the incidence of local recurrence [27,28]. Fibrin glue, a concentrated mixture of fibrinogen and thrombin has also been used successfully to control bleeding during nephron sparing surgery [29].
* Goldwasser *et. al.* have devised a kidney tourniquet which when placed circumferentially around the parenchyma just proximal to the line of resection, achieves haemostasis by compression while obviating the need for occlusion of the renal artery [30].

A variety of nephron sparing surgical techniques have been described

* Enucleation.
* Wedge resection.

* Segmental polar nephrectomy.
* Major transverse resection.
* Extra corporeal partial nephrectomy with autotransplantation.

The basic surgical principles [3] involved in performing Nephron sparing surgery are :

* Early vascular control.
* Preservation of the function of the kidney without ischaemic damage.
* Complete tumour excision with negative surgical margins.
* Watertight closure of the collecting system.
* Careful haemostasis.
* Closure of renal defect with perirenal fat or haemostatic material.

The choice of surgical approach and incision differs from surgeon to surgeon.

Enucleation

Some renal cell carcinoma are completely encapsulated by a distinct pseudocapsule of fibrous tissue which allows avascular tumour removal by enucleation with maximum conservation of renal tissue. These types of tumours are small, of low histological grade and diploid by flowcytometery.

Technique–A circumferential incision around the tumour is given after identifying the plane between the pseudocapsule and the adjacent uninvolved parenchyma. By blunt dissection, the lesion is shelled out of the kidney and haemostasis is obtained by figure of eight sutures or by gentle digital compression. Fatty tissue from the surrounding perinephric area can be placed to obliterate the cavity and to ensure additional haemostasis. This technique should be used for tumours which have a pseudocapsule which can be identified by preoperative CT scan and arteriography used in combination.

Advantages of enucleation are :

* Simple and rapid to perform.
* Renal artery occlusion is not often required.
* Maximum functioning renal parenchyma is preserved.
* Multiple tumours can be removed with this technique e. g. in Von Hippel Lindau's disease. The likelihood of residual cancer following enucleation with follow up period of 5 years is 0–9%.

Table 1 : Results of Nephron Sparing Surgery for Renal Cell Carcinoma

Reference	No. of Pts.	Disease Specific Survival (%)	Followup	Local Tumour Recurrence (%)
Jacobs *et. al.*	51	84.4	5 years	10.2
Marbergers *et. al.*	72	77.8	36 to 142 mths	8.3
Marberger *et. al.*	04	100	Mean 40 mths	0
Bennet *et. al.*	07	71.4	44.6 mths	0
Palmer *et. al.*	07	57	62-85 mths	0
Marshall & Walsh	10	90	Mean 24.5 mths	10
Bazeed *et. al.*	51	96	Mean 35.8 mths	4
Carini *et. al.*	35	88.6	Mean 45.8 mths	3
Novick *et. al.*	100	84	5 years	9
Gohji *et. al.*	21	100	1 to 76 mths	0
Morgan & Zincke	104	88.9	5 years	6
Van Poppel *et. al.*	31	93.5	Mean 41 mths	0
Provet *et. al.*	44	88	Mean 36 mths	2
Steibach *et. al.*	106	93	3 to 4.5 yrs.	2
Selli *et. al.*	57	89.5	Mean 46.2 mths	4

Wedge resection

It is the appropriate technique for removing peripheral tumours on the surface of the kidney, particularly those which are larger and not encapsulated or both. This technique is associated with heavier bleeding ; it is best performed with temporary renal occlusion and surface hypothermia.

In wedge resection, the tumour is removed with a 1–2 cm margin of grossly normal parenchyma. Parenchyma is divided with a combination of sharp and blunt dissection. Invariably, the tumour extends deeply into the kidney and the collecting system is entered. As the parenchyma is incised, prominent intra renal vessels are identified and ligated. When wedge resection involves significant amount of parenchyma removal, a double J stent is placed with the proximal end positioned in the pelvis. This will decrease the risk of urine extravasation. The collecting system is closed with a 4/0 chromic catgut (interrupted or continuous) suture. The renal defect can be closed in two ways. The kidney may be closed upon itself if there is no tension with 2/0 or 3/0 chromic catgut, simple interrupted sutures. A portion of perirenal fat may be placed in the base of the renal defect as a haemostatic measure and sutured to the parenchymal margin with interrupted 4/0 chromic catgut.

Segmental Polar Nephrectomy

If cancer is confined to one pole of the kidney, partial nephrectomy can be performed by isolating and ligating the segmental arterial branch while allowing unimpaired perfusion to the remaining kidney. After ligating the vessels, an ischaemic line of demarcation appears on the surface of the kidney and outlines the segment to be excised. If this is not obvious, then a few ml of methylene blue is directly injected distally into the ligated segmental artery to better outline the limits of the involved renal segment. An incision is then made on the renal cortex at the line of demarcation, which should be atleast 1–2 cm away from the visible edge of the cancer. Parenchyma is divided by blunt and sharp dissection and the polar segment is removed. Often a portion of the collecting system is also removed and should be carefully closed with interrupted 4/0 chromic catgut to ensure a water tight closure. Small transected vessels should be suture ligated. Edge of the kidney is then approximated as additional haemostatic measure using 2/0 or 3/0 chromic sutures inserted through the capsule and small amount of parenchyma. Before tying these sutures, one can insert perirenal fat or oxycel into the defect for inclusion in the renal closure. Renal defect can also be covered by a free peritoneal graft. If the collecting system is entered, a penrose drain is left in the perinephric space. Polar nephrectomy may also be accomplished by guillotine method, which includes complete vascular occlusion of the kidney and surface cooling with no attempt to identify segmental branches. This technique is most applicable to small lesions not involving the entire apical segmental branch where ligation of apical segmental branch will produce more parenchymal ischaemia than is necessary.

Major Transverse Resection

This is done to remove large tumours that involve the upper or lower portion of the kidney. This is performed under surface hypothermia after temporary occlusion of the renal artery. Surgical technique of tumour removal is the same as described above. While contemplating this technique, it is useful to obtain selective renal renography preoperatively to exclude tumour thrombosis of the major renal vein which may be missed by a CT scan, MRI or inferior venography. Presence of tumour thrombosis may make major transverse resection unfeasible.

Extracorporeal partial Nephrectomy and autotransplantation

This is indicated in large, hypervascular, centrally located renal cell carcinoma, not amenable to

in-situ excision. This approach gives optimum exposure and bloodless surgical field which will enable the surgeon to perform a more precise operation with maximal conservation of renal parenchyma and greater protection of kidney from prolonged ischaemia.

In this technique, the kidney is immediately flushed after removal with 500 ml of chilled perfusion solution and is kept in ice slush to maintain hypothermia. Wherever possible, it is best to leave the ureter attached to maintain distal blood supply and the extracorporeal operation is done on the patient's abdominal wall. After completing the resection, tumour free margin is verified by frozen section. At this point, the renal remnant is placed on the pulsatile perfusion unit primarily to facilitate identification and suture ligation of remaining bleeder points. Renal defect is closed by suturing the kidney upon itself. Autotransplantation into the iliac fossa is then done as in renal transplantation. Nephrostomy is done for postoperative drainage if there is extensive hilar dissection of vessels while removing tumour.

Complications of nephron sparing surgery [32]

Technical :

- Renal vascular thrombosis.
- Renal failure due to long ischaemia.
- Improper suturing technique

Risk of technical related complications are higher in solitary kidney, large tumour and centrally located tumour.

Renal related complications

- Urinary fistula.
- Bleeding.
- Acute renal failure.
- Wound infection.
- Perinephric abscess.
- Incidental splenectomy.
- Retroperitoneal fibrosis.
- Secondary nephrectomy.
- Tumour recurrence.

Post-operative bleeding and urinary fistula are the two common complications in most cases. Postoperative urinary fistula can be minimised if the anastomosis is verified with methylene blue.

Incidence of impaired renal function is 12.7% in all cases and 26% in solitary kidney mainly because of injury to renal vasculature. Compbell *et. al.* have identified various risk factors for renal failure which includes an operation performed in a solitary kidney, tumour size greater than 4 cm, ischaemia time greater than 60 minutes and excision of greater than 50% parenchyma. Incidence of renal failure can be minimised by avoiding vascular spasm and putting the kidney in brisk diuresis.

Postoperative follow up

Since local recurrence after nephron sparing surgery has been reported in 6%–9%, patients must be closely followed up. In order to ensure early detection of local recurrence, six monthly ultrasonogram and yearly CT scan have been recommended. Patients who develop local recurrence without metastasis may be considered for secondary surgical treatment. In some cases, another partial nephrectomy can be done with preservation of renal function. If this is not technically possible, total nephrectomy with initiation of the chronic dialysis and subsequent renal transplantation is an alternative. Patients

with greater than 50% reduction in over all renal mass are at greater risk for proteinuria, glomerulopathy and progressive renal failure ; therefore patient follow up should include 24 hours urinary protein measurement in addition to creatinine assay. Patients who develop proteinuria (>150 mg/day) may be treated with a low protein diet and a converting enzyme inhibitor, which in experimental studies has prevented glomerulopathy caused by reduced renal mass [45,46].

Results of various clinical trials have shown excellent long term cancer free survival rate with nephron sparing surgery for localised renal cell carcinoma.

Lerner *et. al.*[33] analysed the outcome of nephron sparing surgery in 185 patients and compared it with 209 patients, who were treated with radical nephrectomy. Patient in both group were well matched for age, sex, stage and grade of tumour. No significant difference was observed in both groups with respect to overall survival. Respective 5 and 10 years crude survival rate were 77% and 56% for the radical nephrectomy group and 77% and 53% for the nephron sparing surgery group. The respective 5 and 10 year metastasis free survival rates for radical nephrectomy patients were 84% and 82% compared to 85% for the nephron sparing group. Overall ipsilateral local recurrence rate was 5.9%, the highest (19%) in the ex-vivo sub-group of nephron sparing procedure. No patient had a renal fossa recurrence after radical nephrectomy. The author also compared the results of different treatment modalities for tumour 4 cm or smaller in diameter and found no significant difference in the crude survival of patients treated with enucleation and in-situ partial nephrectomy.

In the second largest series, Steinbach *et. al.* [34] published their retrospective analysis of 140 patients who underwent a conservative operation for renal tumour between June 1969 and December 1990. In their study, 53 patients had an imperative indication and 87 patients had an elective indication for nephron sparing surgery. Out of these 87 patients, 72 had renal cell carcinoma in the presence of normal contralateral kidney. In the imperative group, 32 of the 49 patients (65.3%) with renal cell carcinoma had no evidence of disease after a mean follow up of 4.6 years, 7 patients in this group died, 4 had known metastasis. Of the 72 patients with renal cell carcinoma who underwent elective operations, 68 (94.4%) had no signs of tumour progression after a mean follow up of 3.3 years. One patient died of surgery in the nephrectomy and enucleation group respectively. The 5 years cause specific survival rates for the imperative and elective groups were 84% and 96% respectively. In this study, patients with a local stage T3 were characterised by a significantly worse survival rate than those with a T1 or T2 tumour.

Butler *et. al.* [35] in the Cleveland series had collected details of 88 patients from 1975 to 1988, having small (less than 4 cm), single localised, unilateral, sporadic renal cell carcinoma who were either treated with radical nephrectomy (n=42) or nephron sparing surgery (n=46). The mean postoperative follow up was 48 ± 29 months. The authors found no difference between the two group in terms of mean hospital stay, requirement for blood transfusion or the occurrence of surgical complications. There was no difference in the mean preoperative and postoperative serum creatinine levels in the nephron sparing group, but this difference was significant in patients with radical nephrectomy group ($p<0.001$). A single patient in each group developed recurrent RCC postoperatively. The cancer specific 5 years survival rate for partial nephrectomy and nephron sparing surgery groups were 97% and 100% respectively. The authors concluded that both radical nephrectomy and nephron

sparing surgery were safe and equally effective curative treatment for patients with single, small unilateral localised RCC. Although 41 patients treated with radical nephrectomy showed significant rise in mean postoperative serum creatinine ; the long term renal functional advantage of nephron sparing surgery with a normal opposite kidney remains unproven.

Licht and Novick [36] have summarised the results of nephron sparing surgery for renal cell carcinoma in 700 patients reported in the literature since 1980. They have shown a mean disease specific survival ranging from 57–100% with many series reporting long term disease specific survival rates of 90% or more. Post-operative local tumour recurrence rates have ranged from 0–10.2%.

CONTROVERSIAL ISSUES

Partial nephrectomy versus enucleation

Ability to perform enucleation successfully depends on the structural integrity of the pseudocapsule of compressed parenchyma that separates the tumour from normal kidney. Recent studies have compared the results of enucleation with partial nephrectomy for renal cell carcinoma. Authors have analysed the results between these groups and found no statistical difference in disease free survival between these two groups [18,42,17]. However, other studies have suggested a high risk of residual malignancy in the kidney when enucleation is performed ; these latter reports include several carefully done histopatholigic studies that have demonstrated frequent microscopic tumour penetration of the pseudocapsule that surrounds the neoplasm [48,50]. These data suggest that it is not always possible to be sure of complete tumour encapsulation prior to surgery. Tumour excision with a surrounding margin of normal parenchyma may be the safest approach to ensure the absence of malignancy in the preserved portion of the kidney.

Nephron sparing for the advanced renal cell carcinoma

The role of nephron sparing surgery in patients with locally extensive or metastatic renal cell carcinoma is not well defined.. Data suggests a higher incidence of post-operative tumour recurrence [18,22,37]. This approach may have wider application in the future if effective systemic chemotherapy for renal cell carcinoma becomes available.

Renal cell carcinoma in von Hippel Lindau's disease (VHL)

Renal cell carcinoma in VHL disease differs from its sporadic counterpart in that the diagnosis is made at a younger age and they are usually multiple and bilateral. Althogh these are generally low stage, they are capable of progression with metastasis and are a frequent cause of death. The results of nephron sparing for localised renal cell carcinoma in VHL is not as satisfactory as has been initially reported. The multicentric nature of renal cell carcinoma in this setting, may predispose to a high risk of postoperative local tumour recurrence [15]. However adequate surgical excision of all solid and cystic lesions and close post-opertive surveillance is required. Some patients will require repeat renal surgery. Bilateral nephrectomy with subsequent dialysis and transplantation is more likely to be curative for localized renal cell carcinoma in this setting.

Nephron sparing surgery with a normal contralateral kidney

Wide spread use of ultrasound and CT scanning has increased the number of incidentally detected renal cell carcinoma. Nephron sparing surgery can be considered for small (<4 cm.) solitary and peripheral renal cell carcinoma in this setting. Various studies have demonstrated results of nephron sparing surgery equivalent to radical nephrectomy in this

setting (Table-II). In most series the tumour size was less than 4 cm and the disease specific survival was more than 90% with local tumour recurrence less than 4%. Radical nephrectomy however, still remains the gold standard for larger unilateral renal cell carcinoma when there is a normal contralateral kidney.

Conclusions

Nephron sparing surgery is an effective treatment for patients with localized renal cell carcinoma in whom preservation of renal function is a relevant consideration. This can also be considered for small solitary and peripheral renal cell carcinoma with a normal contralateral kidney. In order to ensure early detection of local recurrence, patients should be stringently followed up. Role of nephron sparing surgery in patients with advanced renal cell carcinoma is currently limited, but this may change if effective chemotherapy becomes available.

Table 2 : Results of Nephron Sparing Surgery with normal contralateral kidney

Reference	No. of Pts.	Mean follow up (months)	Mean size of tumour (cms)	Disease specific survival (%)	Local recurrence (%)
Bazeed *et. al.*[37]	28	35.8	3.3	100	0
Carini *et. al.*[38]	10	30	3.45	90	0
Morgon *et. al.*[18]	20	46	3.07	100	0
Selli *et. al.*[39]	25	36.5	3.1	92	0
Herr[40]	41	60	3.5	95	2.4
Moli *et. al.*[41]	98	42	4.0	100	0
Steinbach *et. al.*	61	36	3.2	90	3.3

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