

Mini-reviews

In this section there are two mini-reviews which act as updates on the modern surgical management of RCC, specifically relating to laparoscopic radical nephrectomy and partial nephrectomy. It is clear that the somewhat outdated idea of an open radical nephrectomy for all cases of RCC is no longer acceptable to patients, so it behoves us to adopt the newer treatment methods. The other mini-reviews describe the use of three-dimensional imaging in urology and the surgical alternatives for treating Peyronie's disease.

The expanding indications for laparoscopic radical nephrectomy

NEIL J. FENN and INDERBIR S. GILL*

*Department of Urology, Morriston Hospital, Morriston, Swansea, UK, and *The Minimally Invasive Surgery Center, Section of Laparoscopic & Minimally Invasive Surgery, Glickman Urological Institute, The Cleveland Clinic Foundation, Cleveland, Ohio, USA*

Accepted for publication 14 March 2004

INTRODUCTION

The first laparoscopic radical nephrectomy (LRN) was performed by Ralph Clayman in 1990 [1]. Since then LRN has gained popularity and is now arguably the treatment of choice for early stage (T1N0M0) RCC unsuitable for nephron-sparing surgery. Underpinning this development have been the meticulous attempts of laparoscopic urologists to ensure that established principles of open cancer surgery are reproduced in the laparoscopic setting. These important principles include appropriate patient selection, perioperative safety and confirmation of oncological effectiveness.

Numerous centres worldwide [2–8] have shown a clear advantage of LRN over open radical nephrectomy (ORN) in terms of reduced perioperative morbidity. Improvements, including reduced blood loss, postoperative analgesia requirement, length of hospital stay and duration of convalescence, are clearly advantageous to both the patient and urologist (Table 1). Despite these benefits, concerns about oncological effectiveness were expressed, as the initial series had a limited mean follow-up of only 2 years. Several groups have now combined their experience and recently published their long-term follow-up [7,9,10]. These data now confirm that LRN provides long-term oncological control comparable to

ORN, with a 5-year recurrence-free survival of 92% and 91%, and 5 year cancer-specific survival of 98% and 92%, for LRN and ORN, respectively [10].

As experience and techniques have improved, urologists have turned their attention and expertise to cases initially considered to have relative contraindications to the laparoscopic approach. These expanding indications for LRN in selected patients are:

- Larger tumours (>7 cm, pT2);
- Level I renal vein tumour thrombus;
- Cytoreductive nephrectomy;
- Limited locally invasive tumours into psoas or diaphragm;
- Concomitant lymphadenectomy for small volume disease;
- Morbidly obese patient with RCC;
- Laparoscopy in the previously operated abdomen.

In this review we explore these expanding indications for LRN, including the techniques and reported data which support their continuing development. The Medline and EMBASE databases were used to search for relevant English articles published between January 1990 and December 2003. MESH words used for the search included: renal cancer; nephrectomy; laparoscopy; large tumour; advanced disease, cytoreduction, immunotherapy, multiple procedures.

TABLE 1 LRN; worldwide experience published in peer-reviewed journals

Variable	[2]	[3]	[4]	[5]	[6]	[7]	[8]
No. of patients	72	60	61	73	50	67	100
Laparoscopic approach	Trans 72	Trans 35 Retro 15	Trans 55 Retro 3 Both 3	Trans 73	Retro 50	Trans 66 Retro 1	Trans 27 Retro 73
Open conversion, n (%)	6 (8)	1 (1.6)	–	3 (4)	3 (6)	1 (1.5)	2 (2)
Extraction method	M	M	M and I	I	I	M and I	M and I
Estimated blood loss, mL	–	255	172	170	150	289	212
Surgical time, h	2.9	5.2	5.5	2.4	2.4	4.2	2.8
Analgesia, mg morphine (sulphate equivalent)	–	29	27	–	–	–	22
Complications, %	10	9	5	4	8	15	3
Hospital stay, days	4.4	–	3.4	7.4	6	3.8	1.6
Convalescence, weeks	–	3.2	8.2	–	–	–	4.2
Local or port site recurrence	1	0	1	0	1	0	0

M, morcellation; I, intact.

EXPANDING INDICATIONS FOR LRN

ORGAN-CONFINED BULKY TUMOURS (T2/T3aN0M0)

The initial LRN series mainly report the surgical outcome for small tumours (mean tumour diameter 3.8–5.7 cm) with only a small proportion of tumours of >7 cm (Fig. 1), the current size threshold for T1/T2 tumours in the TNM classification [2–8]. It is therefore difficult to draw any conclusions about the oncological effectiveness of LRN for larger organ-confined tumours, because of the few patients involved. Surgically, as the specimen bulk increases, several unique technical issues arise. These include reduced working space, maintaining operator orientation, increased potential for adjacent organ involvement, significant parasitic vessels and difficulties with specimen entrapment/removal.

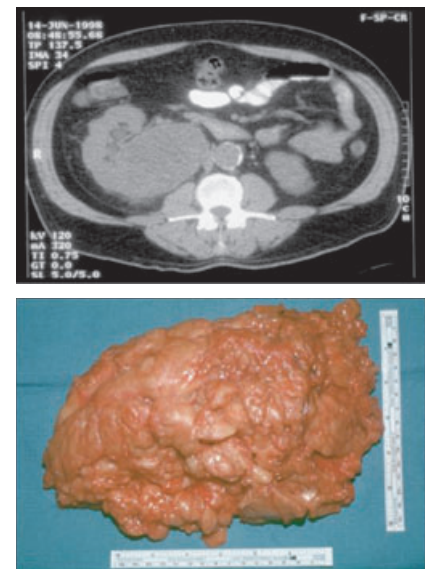
Case selection is important, with carefully selected larger tumours (>7 cm) prudently reserved for the experienced laparoscopist. The retroperitoneal route has a comparatively limited working space, making the transperitoneal approach the preferred route of most. A novel concept of combining the thorascopic transdiaphragmatic and laparoscopic transabdominal approaches for large upper pole tumours has also been explored [11]. Using the porcine model, these authors successfully performed eight nephrectomies thorascopically with excellent visualization of the adrenal, upper

pole kidney and renal vessels; however, this approach has yet to be attempted clinically.

As tumour size increases so does the potential for adjacent organs to interfere with laparoscopic dissection. The use of additional ports for appropriate padded retraction (soft bowel clamps, fan retractors, etc.) minimizes the chances of organ damage. After nephrectomy, specimen extraction may prove difficult because the specimen is larger. In the absence of metastatic disease, intact tumour extraction is preferable to allow full pathological assessment. This is best achieved using an Endocatch II device (US Surgical, Norwalk, CT) and removal through a muscle-splitting lower abdominal modified Gibson incision, Pfannenstiel incision or transvaginal extraction [12].

Laparoscopic surgical results and the follow-up for large tumours are limited [10,13]. The most recent data [13] compared LRN and ORN for tumours of >7 cm. A group of 33 LRN for large tumours (mean 9.8 cm) were compared with 34 ORN for large tumours (mean 10 cm) and 171 LRN for small tumours (≤7 cm; mean 4.5 cm). Surgical outcomes for LRN in large were comparable with those for LRN in smaller tumours in terms of operating time, complications and length of hospital stay. Blood loss was significantly greater for the larger tumours (229 vs 294 mL; $P < 0.001$). Surgical outcomes in both LRN groups offered advantages in blood loss and hospital stay over ORN. Portis *et al.* [10] identified nine of

FIG. 1. CT scan and operative specimen of a 12 cm medially located, organ-confined RCC excised by retroperitoneal LRN. (operative duration 2.2 h, specimen weight 1.2 kg, hospital stay 23 h, pathology was RCC with negative surgical margins).



64 patients undergoing LRN with tumours of >7 cm and compared them with 24 ORN in similar sized tumours. Five-year Kaplan-Meier actuarial recurrence-free (87% vs 83%) and cancer-specific survival rates (100% vs 87%) provided limited confirmation of oncological safety. The ongoing follow-up will provide a definitive answer.

RENAL VEIN/INFERIOR VENA CAVAL INVOLVEMENT

A unique feature of renal cell cancer is its propensity to develop intravascular tumour thrombus in 5–10% of cases. Tumour thrombus involving the renal vein is most common, although there can be extension into the inferior vena cava (IVC) and further cephalad to the right atrium. In the absence of nodal or metastatic disease, radical surgery involving radical nephrectomy with caval thrombectomy (when required) provides the best chance of long-term cure [14]. The presence of venous tumour thrombus was earlier considered a relative contraindication to the laparoscopic approach. With increasing experience and improved laparoscopic techniques several isolated case reports showed the feasibility of LRN in patients with level I tumour thrombus [15–17]. A series of eight consecutive patients with preoperatively diagnosed level I renal vein tumour thrombus treated with LRN was also reported, confirming the initial success [18].

For level I tumour thrombus, the approach is similar to a standard LRN. After renal artery clipping and division, the renal vein is mobilized as proximally as possible towards the IVC, more than for a typical LRN, to allow adequate room for proximal placement of the vascular stapling device. The tumour thrombus is often clearly visible within the bulky looking, non-collapsing segment of renal vein. Care is taken not to manipulate the tumour thrombus. The size and extent of the intravascular tumour thrombus can be confirmed by intraoperative real-time ultrasonography. This allows controlled positioning of the vascular stapler proximal to the tumour thrombus allowing good oncological clearance [17,18]. The stapling device may be used to 'milk' the tumour thrombus back towards the kidney, allowing adequate uninvolved vein for stapler placement and division [18].

In the largest series from The Cleveland Clinic, seven of eight patients were treated successfully, with a mean operative duration of 3.3 h, estimated blood loss of 354 mL and hospital stay of 2.3 days [18]. One patient required open conversion because of bleeding, with a primary tumour of 20 cm. In all cases the surgical margins were negative for cancer. During the short follow-up reported (mean 9.4 months, range 5–16) one patient developed pulmonary metastases,

treated with immunotherapy. Additional cases and longer follow-up data are awaited.

Extension into the IVC (level II–IV) requires vascular control of the infrarenal and supra-thrombus IVC, the contralateral renal vein, and the lumbar vessels. Traditionally this involves major open surgery including venovenous or cardiopulmonary bypass, with hypothermic circulatory arrest in some cases [13]. Recently, in a porcine model a simulated IVC tumour thrombus was developed by injecting a mixture of cryoprecipitate, bovine thrombin and calcium [19]. Thereafter, LRN and laparoscopic caval thrombectomy (level II) was successful. Simulated tumour thrombus extending into the right atrium was successfully managed laparoscopically in the calf model [20]. Using a combined laparoscopic and thoracoscopic approach with deep hypothermic circulatory arrest and cardiopulmonary bypass, two simultaneously working teams successfully completely cleared the caval and right atrial intravascular thrombus in six acute calves. Complete thrombus extraction was confirmed by laparoscopically directed angioscopy of the IVC and right atrium, which were then suture-repaired laparoscopically. All six calves were re-warmed and successfully taken off the cardiopulmonary bypass. Clearly further work is necessary before transferring these exciting concepts to humans.

CONCOMITANT LYMPHADENECTOMY

Routine lymphadenectomy is an integral part of most oncological surgery, although its role in radical nephrectomy is much debated. In the era before CT, up to 25% of patients had positive nodes discovered at surgery, and were treated with lymphadenectomy, as no effective systemic treatment was available. The development of accurate cross-sectional imaging techniques and adjuvant immunotherapy has resulted in a reappraisal of the role of lymphadenectomy at the time of nephrectomy. Pantuck *et al.* [21] reviewed over 900 patients undergoing radical nephrectomy with retroperitoneal lymph node dissection, over an 11-year period. They concluded that regional lymph node dissection appears to be unnecessary in patients with clinically node-negative disease, as it offers extremely limited staging information and no benefit in terms of decreasing disease recurrence or improving survival. In selected patients with positive nodes a formal node dissection may be

associated with improved survival when used in carefully selected patients undergoing cytoreductive nephrectomy and postoperative immunotherapy.

Formal lymphadenectomy during LRN is not routine, as case selection has been limited to localized organ-confined disease. A formal lymphadenectomy includes removing the interaorto-caval and supra-hilar lymphatic tissue. It is unlikely that such an extended lymphadenectomy can be effectively done at the time of LRN. However, in our experience, lymphatico-fatty tissue clearance along the ipsilateral side of the great vessel can be routinely incorporated during LRN if required.

CYTOREDUCTIVE LRN

The treatment of metastatic RCC has generally produced disappointing results. Surgery alone has no effect on survival although it may control symptoms attributable to the primary tumour, e.g. pain, haematuria, paraneoplastic syndromes, or compression of adjacent viscera. RCC is resistant to traditional systemic chemotherapy, with objective response rates of <9%. The use of immunotherapy regimens represents an encouraging option, although response rates are modest at best. A review of 1411 patients receiving interferon- α and interleukin-2 in phase I and II trials indicated an overall objective response of 20.6%, with a 4.4% complete response rate [22]. Response rates and tolerance to treatment have been higher in patients undergoing nephrectomy before immunotherapy but these differences have not been statistically significant [23]. Most immunotherapy protocols and experimental regimens (requiring tumour-infiltrating lymphocyte isolation) involve nephrectomy before starting treatment. However, surgery in these patients is technically demanding, with high perioperative morbidity and mortality, which may also prevent 20–25% of patients from receiving additional treatment. LRN, with its advantages of superior convalescence, would appear to be an attractive option for these patients.

The technical issues associated with operating on larger bulky tumours and vascular tumour thrombus were noted earlier. Local laterally based invasion into body wall musculature may be problematic. Intentional resection and intracorporeal suture repair, with or without a mesh, of the anterior abdominal wall or

diaphragm during LRN has been reported [24]. The options of laparoscopic resection of involved bowel segments, tail of the pancreas and splenectomy are also possible, although clinical experience is anecdotal.

Several groups have assessed the feasibility and safety of LRN in the cytoreduction setting [25,26]. McClellan *et al.* [25] compared cytoreductive LRN in 11 patients, with 19 cytoreductive ORN used as historical controls. The two groups were well matched for age, sex, metastatic sites, ECOG status and size of tumour. In the laparoscopic group (median tumour 9 cm) specimens were removed intact in five patients and morcellated in six. Overall, LRN with morcellation was best, with reduced analgesic requirements, earlier discharge and the shortest delay in receiving immunotherapy (median 39 days). There were complications of surgery in 14% of patients, although there was no difference between the groups. Abreu *et al.* [26] presented the Cleveland Clinic experience at the World Congress meeting 2003 in Montreal. Cytoreductive LRN (12 patients) or partial nephrectomy (one) were used before treatment with interleukin-2. All procedures were successfully completed laparoscopically with specimens (mean tumour size 7.7 cm, range 2.8–15) removed intact through a muscle-splitting Gibson incision. The surgical complication rate was 11%, mean stay after surgery 2.5 days and immunotherapy was initiated at 39 days.

The role of cytoreductive nephrectomy in metastatic RCC remains to be clearly defined by a randomized controlled trial. The laparoscopic approach offers the expected advantages of minimally invasive surgery, but should only be used at centres with considerable experience in laparoscopy.

OTHER APPLICATIONS

As the diversity of laparoscopic procedures increases across many specialities, situations occasionally arise for multiple laparoscopic procedures at one sitting. Long operating times initially were a problem, but as experience has increased operating times have decreased. The simultaneous management of three urological malignancies has been described [27]; Deng *et al.* performed concomitant LRN and laparoscopic cystoprostatectomy for RCC, TCC of the bladder and prostatic adenocarcinoma. The

total operative duration was 11 h, estimated blood loss 800 mL, hospital stay 6 days, and all surgical margins were negative for cancer. We have performed laparoscopic bilateral radical nephroureterectomy and radical cystoprostatectomy in a single operative session in three patients in the same sitting. Laparoscopic cholecystectomy and hernia repair are possible at the time of a transperitoneal LRN, although this decision should be made with careful consideration (personal communication, N.J.F.). LRN for indications other than RCC has also been described [28].

CONCLUSION

Surgeons currently practise at a time when the expectations of the patient have never been greater. In addition to surgical cure, shorter hospital stays, smaller incisions, and a quicker return to everyday activity are expected by most. At the same time, many of these factors are also attractive to the health systems within which surgeons work. Laparoscopy has been able to fulfil many of these requirements. However, the introduction of new surgical practices requires clear evidence of surgical safety and excellent oncological outcomes. The success of LRN is firmly based on the ability of the laparoscopic approach to replicate the principles of ORN; as a result, LRN now has an increasingly expanding role in the management of clinically localized RCC.

With experience the laparoscopic repertoire has increased to include laparoscopic partial nephrectomy, nephroureterectomy, radical prostatectomy and radical cystectomy with urinary diversion to treat urological malignancies. In this milieu, expanding the indications for LRN to include organ-confined bulky tumours of >7 cm, level I renal vein tumour thrombus and cytoreduction all appear feasible in appropriately selected cases, with the realization of the limitation of each procedure. Longer term follow-up data are required for general acceptance of these methods into urological practice.

ACKNOWLEDGEMENTS

Neil Fenn thanks The British Urological Foundation and the BAUS section of Endourology for their generous funding of the Laparoscopic Preceptorship to The

Cleveland Clinic, and his consultant colleagues at the Morrision Hospital for their support and encouragement in allowing him to develop a laparoscopic urology service in Swansea.

CONFLICT OF INTEREST

N.J. Fenn has a British Urological Foundation Travelling Fellowship. Source of funding: Funding for Cleveland Clinic Fellowship – British Urological Foundation.

REFERENCES

- 1 Clayman RV, Kavoussi LR, Soper NJ *et al.* Laparoscopic nephrectomy: initial case report. *J Urol* 1991; **146**: 278–82
- 2 Barrett PH, Fentie DD, Taranger LA. Laparoscopic radical nephrectomy with morcellation for renal cell carcinoma: The Saskatoon experience. *Urology* 1998; **52**: 23–8
- 3 Ono Y, Kinukawa T, Hattori R *et al.* Laparoscopic radical nephrectomy for renal cell carcinoma: a five year experience. *Urology* 1999; **53**: 280–6
- 4 Dunn MD, Portis AJ, Shalhav AL *et al.* Laparoscopic versus open radical nephrectomy: 9 years experience. *J Urol* 2000; **164**: 1153–9
- 5 Janetshek G, Jeschke K, Peschel R *et al.* Laparoscopic renal surgery for stage T1 renal cell carcinoma. Radical nephrectomy and wedge resection. *Eur Urol* 2000; **38**: 131–6
- 6 Cicco A, Salomon L, Hoznek A *et al.* Results of retroperitoneal laparoscopic radical nephrectomy. *J Endourol* 2001; **15**: 355–9
- 7 Chan DY, Cadeddu JA, Jarrett TW, Marshall FF, Kavoussi LR. Laparoscopic radical nephrectomy: cancer control for renal cell carcinoma. *J Urol* 2001; **166**: 2095–100
- 8 Gill IS, Meraney AM, Schweizer DK *et al.* Laparoscopic radical nephrectomy in 100 patients: a single center experience from the United States. *Cancer* 2001; **92**: 1843–55
- 9 Saika T, Ono Y, Hattori R *et al.* Long term outcome of laparoscopic radical nephrectomy for pathological T1 renal cell cancer. *Urol* 2003; **62**: 1018–23
- 10 Portis AJ, Yan Y, Landman J *et al.* Long term follow up after laparoscopic radical nephrectomy. *J Urol* 2002; **167**: 1257–62
- 11 Meraney AM, Gill IS, Hsu TSH, Sung GT. Thoracoscopic transdiaphragmatic

- nephrectomy: feasibility study. *Urology* 2000; **55**: 443–7
- 12 **Gill IS, Cherullo EE, Meraney AM, Borsuk F, Murphy DP, Falcone T.** Vaginal extraction of intact specimens following laparoscopic radical nephrectomy. *J Urol* 2002; **167**: 238–41
 - 13 **Steinberg AP, Desai M, Kaouk J et al.** The large (>7cm; pT2) renal tumour: laparoscopic versus open radical nephrectomy. *J Endourol* 2002; **16**: 160 (Abstract)
 - 14 **Glazer AA, Novick AC.** Long term follow up after surgical treatment for renal cell carcinoma extending into the right atrium. *J Urol* 1996; **155**: 448–52
 - 15 **McDougall E, Clayman RV, Elashry OM.** Laparoscopic radical nephrectomy for renal tumour: The Washington University experience. *J Urol* 1996; **155**: 1180;
 - 16 **Savage SJ, Gill IS.** Laparoscopic radical nephrectomy for renal cell carcinoma in a patient with level I renal vein tumour thrombus. *J Urol* 2000; **163**: 1243–5
 - 17 **Hsu TSH, Jeffery RB, Chon C, Presti JC.** Laparoscopic radical nephrectomy incorporating intraoperative ultrasonography for renal cell carcinoma with renal vein tumour thrombus. *Urology* 2003; **61**: 1246–8
 - 18 **Desai MM, Gill IS, Ramani AP et al.** Laparoscopic radical nephrectomy for cancer with level I renal vein involvement. *J Urol* 2003; **169**: 487–91
 - 19 **Fergany AF, Gill IS, Schweizer DK et al.** Laparoscopic radical nephrectomy with level II vena caval thrombectomy: survival porcine model. *J Urol* 2002; **168**: 2629–31
 - 20 **Meraney AM, Gill IS, Desai MM et al.** Laparoscopic inferior vena cava and right atrial thrombectomy utilising deep hypothermic circulatory arrest. *J Endourol* 2003; **17**: 275–82
 - 21 **Pantuck AJ, Zisman A, Dorey F et al.** Renal cell carcinoma with retroperitoneal lymph nodes. Role of lymph node dissection. *J Urol* 2003; **169**: 2076–83
 - 22 **Bukowski RM.** Immunotherapy in renal cell carcinoma. *Oncology* 1999; **13**: 801–10
 - 23 **Flanigan RC, Salmon SE, Blumenstein BA et al.** Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal cell cancer. *NEJM* 2001; **345**: 1655–9
 - 24 **Paulter SE, Richards C, Libutti SK, Linhan WM, McClellan MW.** Intentional resection of the diaphragm during cytoreductive laparoscopic radical nephrectomy. *J Urol* 2002; **167**: 48–50
 - 25 **McClellan WM, Lyne C, Libutti SK, Linehan WM.** Laparoscopic cytoreductive nephrectomy as preparation for administration of systemic interleukin-2 in the treatment of metastatic renal cell carcinoma: a pilot study. *Urology* 1999; **53**: 496–501
 - 26 **Abreu S, Kaouk J, Steinberg A et al.** Laparoscopic cytoreductive nephrectomy for local (N+) and distant (M+) metastatic renal cell cancer. *J Endourol* 2003; **17** (Suppl): A58
 - 27 **Deng DY, Meng MV, Grossfeld GD, Stoller ML.** Simultaneous laparoscopic management of 3 urological malignancies. *J Urol* 2002; **67**: 2125–6
 - 28 **Gill IS, Hobart MG, Kaouk JH, Aramovich CM, Budd T, Faiman C.** Leiomyosarcoma of the main renal artery treated with laparoscopic radical nephrectomy. *Urology* 2000; **56**: 669

Correspondence: Neil J. Fenn, Morriston Hospital, Morriston, Swansea SA6 6NL, UK. e-mail: neil.fenn@swansea-tr.wales.nhs.uk

Abbreviations: LRN, ORN, laparoscopic, open, radical nephrectomy; IVC, inferior vena cava.