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Performing Cytoreductive Nephrectomy following Targeted Sunitinib Therapy for Metastatic Renal Cell Carcinoma: A Surgical Perspective

Greg L. Shaw[a] Mahreen Hussain[a] Rajesh Nair[a] John Bycroft[a] Luis Beltran[a]
James S.A. Green[a] Thomas Powles[b] John L. Peters[a]

[a]Whipps Cross University Hospital and [b]St. Bartholomew's Hospital, London, UK

Key Words
Metastatic renal cell carcinoma · Cytoreductive nephrectomy · Neoadjuvant sunitinib · Operative safety

Abstract
Objective: To describe for surgeons contemplating performing cytoreductive nephrectomy (CRN) on patients after neoadjuvant sunitinib compared to a benchmark of open radical nephrectomy, describing technical difficulties, safety and feasibility. ***Patients and Methods:*** We compared measurable surgical parameters and perioperative complications in 22 patients with metastatic renal cell carcinoma (mRCC) undergoing CRN after neoadjuvant sunitinib, with 28 patients who underwent open radical nephrectomy for non-metastatic disease (nmRCC). ***Results:*** Median blood loss (320 vs. 775 ml), median operative time (128 vs. 195 min) and median length of stay (5 vs. 7 days) were greater in the mRCC group. Surgery after sunitinib was technically challenging due to fibrosis, loss of the tissue planes that usually facilitate radical nephrectomy and abnormal blood vessel formation. Side effects of sunitinib resulted in predictable complications. ***Conclusion:*** CRN after treatment with sunitinib is safe and feasible in our hands, although the surgery is more time-consuming and technically demanding. A multidisciplinary approach is mandatory.

Introduction

Renal cell carcinoma (RCC) is the commonest kidney cancer [1]. In the UK its incidence is rising, with 8,228 new cases in 2007 [2] and with 25% of cancers having metastasised at diagnosis [3]. 85% have clear cell carcinoma. The prognosis is poor with a 23% 5-year overall survival rate reported in the original study demonstrating superiority over interferon-α (IFN-α). Herein, Motzer et al. [4] demonstrated that sunitinib improved median progression-free survival (11 vs. 5 months) and overall survival (26.4 vs. 21.6 months) in patients with metastatic RCC (mRCC). Following this work, targeted therapies are the standard of care for mRCC in the UK with NICE recommending sunitinib as first-line treatment for advanced or mRCC in fit patients [5].

In the immunotherapy era, two prospective randomised trials (SWOG 8949 [6] and EORTC 30947 [7]) comparing cytoreductive nephrectomy (CRN) followed by IFN-α versus IFN-α without surgery, demonstrated the utility of CRN in improving overall survival. A combined analysis of these SWOG and EORTC trials confirmed a longer median survival in the nephrectomy/IFN-α group [8]. In theory, tumour bulk may act as a sink absorbing antibodies and anticancer cells [9] and/or tumour releasing pro-angiogenic factors (VEGF and PDGF)

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Mr. G.L. Shaw
University Department of Oncology
Box 279 (S4), Addenbrooke's Hospital
Cambridge CB2 0QQ (UK)
Tel. +44 7803 158 770, E-Mail gregshaw@doctors.org.uk

Table 1. Patient characteristics

Patient demographics	Open radical nephrectomy for nmRCC	Cytoreductive nephrectomy for mRCC
Number of patients	28	22
Median age (range), years	68 (42–90)	65 (45–81)
Male	20 (71%)	17 (77%)
pT stage		
T1a	0	0
T1b	0	1 (4%)
T2a	4 (14%)	1 (4%)
T2b	5 (18%)	3 (14%)
T3a	10 (36%)	12 (55%)
T3b	5 (18%)	3 (14%)
T3c	0	0
T4	4 (14%)	2 (9%)

Table 2. Surgical complications and operative outcomes

	nmRCC (n = 28)	mRCC (n = 22)
Surgical parameters		
Median blood loss, ml	320 (50–2,220)	775 (90–4,700)
Operating time, min	128 (66–390)	195 (70–420)
Hospital stay, days	5 (3–42)	7 (4–36)
Intra-operative complications		
Bowel-associated	1 small bowel enterotomy primary repair	1 hemicolectomy 1 duodenal reconstruction
Splenectomy	0	1
Hepatic resection	0	1
Vascular	0	1 (IVC injury)
Post-operative complications		
Clavien-Dindo grade 0/1	84%	80%
Clavien-Dindo grade 4/5	9%	15%
Death	0	1
Wound infection	1	1
Delayed wound healing	1	1
Endocrine disorders	0	1 (Addison's)
Lymphocoele	0	1

Ranges in parentheses.

[10]. The role of nephrectomy in the management of mRCC is less well established in the era of targeted therapies.

Debate continues as to which is best – adjuvant or neoadjuvant sunitinib. The EORTC 30073 phase 3 trial is designed to address this issue, with mRCC patients randomised to sunitinib then nephrectomy or CRN then sunitinib. There are at present 14 phase 2 trials of neoadjuvant treatment using various targeted therapies (including sunitinib, sorafenib, bevacizumab and everolimus) listed on clinicaltrials.gov. Those trial patients who are well enough after sunitinib will undergo CRN, performed by urologists who may have relatively little experience of nephrectomy in this context. Here we describe the experience of a single operating surgeon with this type of surgery through comparison with conventional radical nephrectomy, with which all urologists contemplating performing this type of surgery should be familiar. We have published data regarding the safety and efficacy of neoadjuvant sunitinib [11]. Here we focus on the surgical perspective of this approach.

Methods

Data was collected prospectively for 22 post-sunitinib patients with mRCC (as part of the SuMR trial – NCT01024205); all had received 3 cycles of neoadjuvant sunitinib prior to nephrectomy for biopsy confirmed clear cell RCC. CRN was performed 14 days after finishing sunitinib (day 28 cycle 3).

Data was collected retrospectively for the comparison group (n = 28) that had undergone open radical nephrectomy for non-metastatic RCC (nmRCC) from October 2008 to October 2010 by the same lead surgeon (J.L.P.).

Radical nephrectomy specimens were staged according to the Tumour Nodes Metastases (TNM) classification, by the same histopathologist (L.B.). Statistical significance was tested using Student's paired t test.

Results

Table 1 demonstrates preponderance in both groups of renal vein involvement (stage pT3a). There is no significant difference between the two groups of patients in terms of pathological T-stage or patient demographics.

Table 2 shows a comparison of surgical parameters and post-operative complications in the patients with nmRCC and those with mRCC. The results indicate significantly greater blood loss and operating time in the post-sunitinib group.

Although the surgery was more technically demanding in the mRCC group, the rate of post-operative complications was similar. One death occurred in the mRCC group. This patient was known to have extensive lung metastases prior to undergoing surgery. He opted for surgery despite being fully informed regarding the significant risks and limited potential benefits of surgery. One pa-

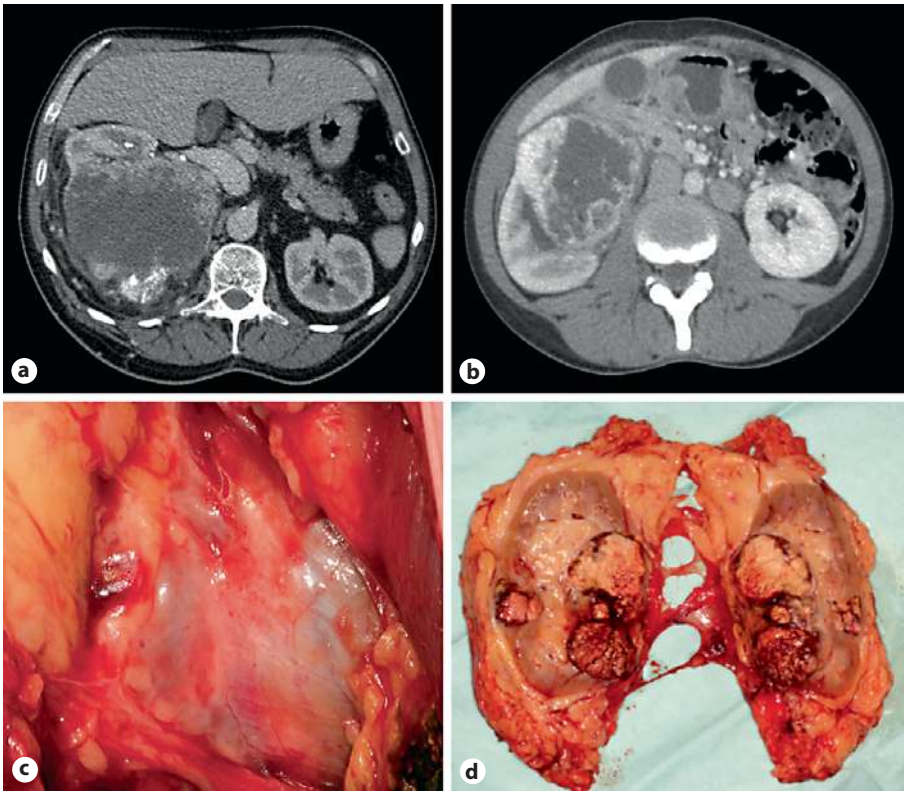

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Fig. 1. a, **b** Contrast-enhanced coronal section of CT scans of two typical post-sunitinib tumours. Large tumour size with extensive necrosis and fibrosis is demonstrated. **c**, **d** Photographs of surgical specimens post-sunitinib demonstrating extensive fibrosis around the periphery of the kidney and necrosis of the tumour.

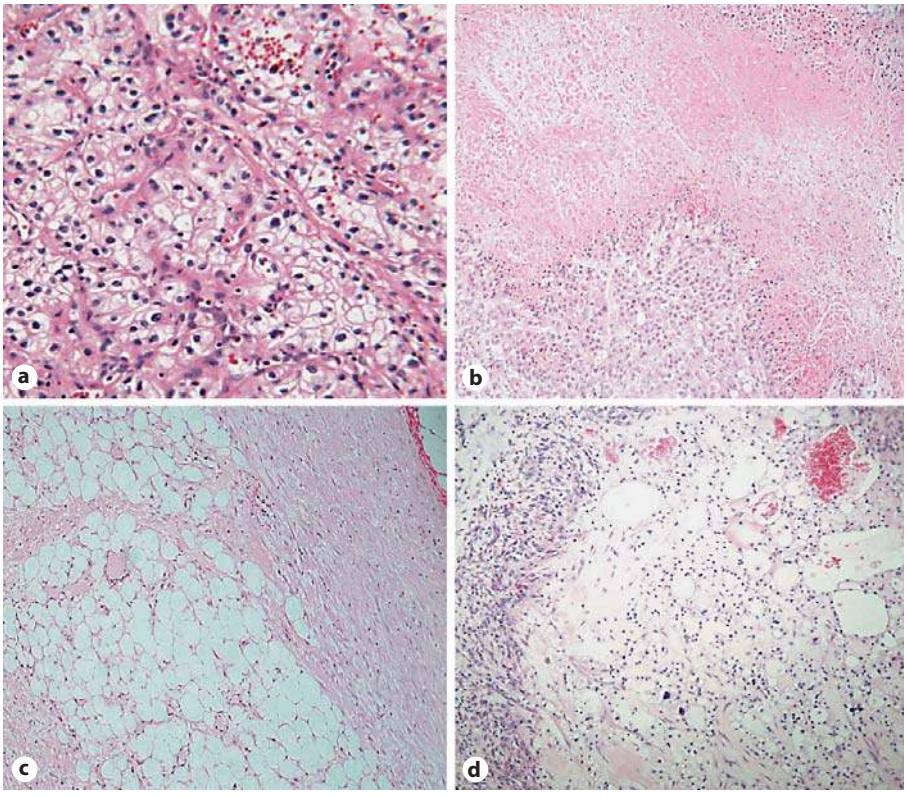

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Fig. 2. a Histology of conventional untreated clear cell renal carcinoma (×100). **b–d** Clear cell carcinoma after treatment with sunitinib (×200): necrosis within the tumour (**b**), fibrosis in the peri-renal fat (**c**), and neovascularisation with a rim of newly formed capillaries surrounding the tumour (**d**).

Table 3. Implications of neo-adjuvant sunitinib on peri-operative care during CRN

	Predictable effect of sunitinib	Implications for peri-operative management
Pre-operative	Anaemia Thrombocytopenia Neutropenia	Pre-operative transfusion Clotting dysfunction, platelet transfusion Vigilance regarding asepsis/antibiotic prophylaxis
Anaesthetic	LV dysfunction Prolongation of QT interval Hypertension ↓ Efficacy of analgesics and antibiotics	Invasive monitoring and post-operative HDU Interaction with ondansetron, droperidol (arrhythmia)
Intra-operative	Haemorrhage	Poor intra-operative vision, intra-operative blood/platelet transfusion
Post-operative	↓ VEGF activity Hypothyroidism Adrenal insufficiency Venous thromboembolism	Delayed wound healing (theoretical) Precipitated Addisonian crisis Prophylaxis, early LMWH treatment and mobilisation
Histopathological	Fibrosis Necrosis	Prolonged operative time, increased blood loss, increased risk of damage to adjacent viscera

tient had an Addisonian crisis post-operatively, probably due to adrenal suppression resulting from sunitinib treatment. This was managed successfully with steroid, fluid and electrolyte replacement.

Tumour necrosis and desmoplastic reaction, as seen in the post-sunitinib group, resulted in thickening of the capsule with fusing of tissue planes, making surgery technically more challenging with more frequent damage to adjacent viscera due to dense fibrotic adhesions. In 1 patient a simple enterotomy was made in the small bowel and repaired primarily. Another required duodenal resection following injury. A splenectomy was performed in 1 patient and (minimal) hepatic resection for bleeding in another. One patient required primary repair of an injury to the infra-hepatic inferior vena cava. This compares with one splenectomy and one small bowel enterotomy in the nmRCC group. Similar numbers of post-operative complications occurred in each group (table 2).

Histopathological examination demonstrated necrosis in 94% of patients; this was extensive (>30% of tumour volume) in 50%. Figure 1a and b demonstrate typical CT appearances with central necrosis, figure 1c and d demonstrate the dense fibrosis found at surgery (fig. 1c) and after bisection of the resected kidney (fig. 1d). Hyalinisation was seen in 91% and neo-vascularisation in 74% of patients after sunitinib treatment. Figure 2a is a high-power photomicrograph of the histology (HE stain) of clear cell carcinoma for comparison with figure 2b–d which are photomicrographs of tumours after sunitinib with abnormal, thin-walled vasculature. A propensity for contact bleeding was common at CRN.

Discussion

There is no doubt that anti-angiogenic tyrosine kinase inhibitors have revolutionised the management of mRCC. With large-scale multicentre trials enrolling across Europe, more urological surgeons will be performing surgery in this setting. In table 3 we consider the predictable effects of sunitinib with respect to implications regarding the peri-operative care of these patients.

The thrombocytopenia and anaemia associated with sunitinib treatment as well as disseminated malignancy necessitated pre-operative optimisation with transfusion of blood products, in preparation for surgery in several patients.

Left ventricular dysfunction, prolongation of QT interval and hypertension all have implications for the anaesthetic, and in all post-sunitinib patients LV function was quantified with an echocardiogram pre-operatively.

The mechanism by which sunitinib causes hypertension may be through VEGF and PDGF inhibition decreasing vascular compliance and decreasing microvessel density leading to increased peripheral vascular resistance. The altered liver function seen with sunitinib resulting in altered drug metabolism necessitated care-

ful post-operative antibiotic and analgesic titration. Adrenal insufficiency can result from sunitinib therapy, and in 1 patient surgery precipitated an Addisonian crisis requiring aggressive steroid, fluid and electrolyte replacement.

Sunitinib inhibits tyrosine kinases anti-proliferative and anti-angiogenic effects. Our concerns regarding post-operative wound healing were unfounded despite pre-clinical evidence of delayed wound healing with sunitinib [12]. There was no wound dehiscence in either group.

Sunitinib is pro-thrombotic. In the immediate post-operative period this and the presence of disseminated malignancy renders the patients susceptible to thrombosis. We did not encounter any peri-operative thromboembolism. Prophylaxis was undertaken with the pre-operative application of thromboembolic deterrent stockings, intra- and post-operative pneumatic calf compression and post-operative subcutaneous low-molecular-weight heparin, with early mobilisation.

Published data regarding CRN after targeted therapy for metastatic clear cell RCC is limited but includes one report in which 44 patients were treated with a variety of targeted therapies before CRN. A total of 39 complications occurred in 17 (39%) patients treated with pre-operative targeted molecular therapy and in 16 (28%) who underwent up-front resection ($p = 0.287$) [13]. A second retrospective review of 19 patients treated with sunitinib, sorafenib or bevacizumab + interleukin and subsequent CRN. One patient had a significant intraoperative haemorrhage and disseminated intravascular coagulopathy from a concomitant liver resection. An anastomotic bowel leak and abscess were noted post-operatively in another patient who underwent en bloc resection of a retroperitoneal recurrence and adjacent colon. Two patients (11%) had minor wound complications, including a wound seroma and a ventral hernia [14]. A third describes 14 CRNs after sunitinib or sorafenib. These authors found that intraoperative adhesions were problematic, but in accordance with our findings did not observe any wound-healing problems [15]. This report is the first to describe the surgical perspective of treating patients treated only with sunitinib preceding CRN and reflects move towards sunitinib, rather than other tyrosine kinase inhibitors, as first-line treatment in metastatic RCC.

Although surgical complications and outcomes seem comparable between those patients who underwent open radical nephrectomy for nmRCC and those who underwent CRN post-sunitinib, we advocate interdisciplinary co-operation where surgical difficulties can be predicted based on relation to adjacent organs. Minimum requirements include: rigorous pre-operative assessment and patient optimisation, senior anaesthetic involvement, careful monitoring of post-operative analgesia and optimal surgical planning with assured support from general and vascular surgical colleagues. We hope that these data will be of value to the surgical team preparing to undertake this kind of surgery.

Conclusion

The potentially serious adverse effects associated with neoadjuvant sunitinib make subsequent CRN surgically and anaesthetically challenging. However, with adequate preparation and technique the risks might be minimised.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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