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ORIGINAL ARTICLE

Radical nephrectomy and intracaval thrombectomy for advanced renal cancer with extensive inferior vena cava involvement utilising cardiopulmonary bypass and hypothermic circulatory arrest: Is it worthwhile?

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KEYWORDS

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Cardiopulmonary bypass;
Hypothermic circulatory arrest

Abstract ***Objective:*** To report our long-term outcomes of surgical treatment of renal tumours with inferior vena cava (IVC) tumour thrombus above the hepatic veins, utilising cardiopulmonary bypass (CBP) and hypothermic circulatory arrest (HCA), as surgical resection remains the only effective treatment for renal cancers with extensive IVC tumour thrombus.

Patients and methods: We retrospectively reviewed 48 consecutive patients (median age 58 years) who underwent surgical treatment for non-metastatic renal cancer with IVC tumour thrombus extending above the hepatic veins. Perioperative, histological, disease-free (DFS) and overall survival (OS) data were recorded.

Results: Tumour thrombus was level III in 23 patients and level IV in 25 patients. The median (range) CBP and HCA times were 162 (120–300) min and 35 (9–64) min,

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ABBREVIATIONS

ASA, American Society of Anesthesiologists;
CPB, cardiopulmonary bypass;
DFS, disease-free survival;
HCA, hypothermic circulatory arrest;
IVC, inferior vena cava;
MOF, multi-organ failure;
OS, overall survival

respectively. Three patients underwent synchronous cardiac surgical procedures. There were three (6.3%) perioperative deaths. American Society of Anesthesiologists grade and perioperative blood transfusion requirement were significant factors associated with perioperative death ($P < 0.05$). Despite extensive preoperative screening for metastases the median (range) DFS was only 10.2 (1.2–224.4) months. The median (range) OS was 23 (0–224.4) months. Cox regression analysis revealed that perinephric fat invasion conferred a significantly poorer DFS ($P = 0.005$).

Conclusions: Radical surgery for patients with extensive IVC tumour thrombus has acceptable operative morbidity and mortality. It provides symptom palliation and the possibility of long-term survival. Improvements in preoperative detection of occult metastasis may improve case selection and newer adjuvant therapies may improve survival in this high-risk group.

Introduction

RCCs have the ability to form venous tumour thrombi, which extend into the inferior vena cava (IVC) in 4–10% of cases [1]. Tumour thrombi may extend above the hepatic veins up as far as the right atrium in a quarter of these patients. In the absence of regional nodal or distant disease, surgical resection is the only effective treatment.

Disease extending above the hepatic veins is a considerable surgical challenge. Marshall et al. [2] first described the technique of cardiopulmonary bypass (CPB) and hypothermic circulatory arrest (HCA) to facilitate the removal of bulky IVC tumour thrombi extending above the hepatic veins.

We have previously reported our initial experience and short-term follow-up utilising this technique [3]. In terms of cancer-specific survival, some reports suggest that the extent of IVC involvement may act as a prognostic factor for outcome [4–9].

We assessed our long-term results for resection of tumours extending above the hepatic veins and applied regression analysis to identify prognostic factors influencing disease-free (DFS) and overall survival (OS) in this group of patients.

Patients and methods

From March 1989 until January 2009, 48 patients with level III (above hepatic veins; infradiaphragmatic) and level IV (supradiaphragmatic; into right atrium) IVC involvement (as defined by the Mayo Clinic definitions [10]), underwent surgical treatment for non-metastatic RCC utilising CPB and HCA.

All patients underwent preoperative evaluation to exclude metastases and determine the proximal level of tumour thrombus. Assessment included routine laboratory and radiological investigation with chest X-ray, CT, Doppler ultrasonography and/or MRI. All patients had formal cardiology review to assess their fitness before treatment (including an exercise stress test, echocardiography and further investigation with coronary angiography, as indicated by their stress test findings).

Surgery was performed as a joint case with the cardiac surgeons utilising CPB and deep HCA to allow complete surgical excision. Preoperative embolisation of the kidney was employed in selected cases.

Our surgical technique has been previously reported [3], but in brief surgery commences with a midline laparotomy to confirm operability and then proceeds to median sternotomy and CPB. Little attempt is made to mobilise the kidney or IVC before the patient is on by-pass in order to reduce the risk of tumour embolisation. Cooling is commenced and during this phase the IVC is exposed. Once the body core temperature has reached 15 °C, perfusion is maintained for 20 min to ensure uniform cooling of the brain before circulation is arrested. During cooling (typically taking 20–30 min) and the subsequent 20 min when the core is maintained at 15 °C, mobilisation of the IVC and the kidney is continued.

Once the circulation is arrested the IVC is opened to allow all visible tumour thrombus to be removed. On occasions when there is very extensive IVC tumour, dissection is carried out from above and below the diaphragm simultaneously. The IVC is then repaired, circulation re-started and re-warming begins. During this phase a standard radical nephrectomy is performed. Once off CPB any residual coagulopathy is corrected.

In our current practice we aim to identify and ligate the renal artery early, then completely mobilise the kidney. For right-sided tumours, the right renal artery is ligated between the aorta and IVC, whilst for left-sided tumours this is ligated behind left renal vein. The IVC is mobilised and the kidney is ready for removal except for the renal vein prior to cooling aiming

to minimise the time on CPB and HCA. Also patients are cooled to 18 °C only.

A retrospective notes review was performed extracting data onto a standardised pro forma, which was later transferred to an anonymised database for analysis.

Preoperative details recorded included: age, presenting features, preoperative staging, maximum diameter of primary tumour and IVC tumour thrombus, level of proximal tumour thrombus, and preoperative blood results. Operative details recorded included preoperative embolisation, CPB time, HCA time, HCA temperature, other procedures performed, and total operating time. Data relating to CPB and HCA were taken from an independent perfusionist database.

Perioperative details recorded included: blood product requirements, intensive care/high-dependency stay, dialysis requirement, perioperative complications, perioperative mortality (death within 30 days), total hospital stay, and histopathological features. Blood product requirement within first 24 h of surgery was taken from an independent blood bank database.

All patients were reviewed at 6 weeks with histology results. Due to the tertiary referral nature of this work, many patients subsequently return to their referring consultant for follow-up.

Mortality data were obtained via the cancer intelligence units from the referring area, including date and cause of death for those who had died. Data on DFS were collected from hospital notes or contact with the patient's GP or referring consultant.

Kaplan–Meier curves were plotted and analysed using the Statistical Package for the Social Sciences (SPSS®) for Windows version 15.0 (SPSS Inc., Chicago, IL, USA), allowing further assessment of DFS and OS. Linear regression analysis was performed to identify factors influencing perioperative mortality. Cox regression analysis was performed to determine factors influencing DFS and OS, followed by Kaplan–Meier analysis using the log-rank Mantel-Cox test.

Results

Preoperative data

Of the 48 patients in this series, 33 were male and 15 were female with a median (range) age of 58 (14–76) years. The majority of these tumours were right sided ($n = 35$, 73%).

Patients presented with a variety of symptoms including: haematuria, loin pain, lower limb oedema, thromboembolic disease, and constitutional symptoms (Table 1).

On preoperative imaging the primary tumour had a median (range) diameter of 9.0 (2.5–16.0) cm with a median (range) IVC tumour thrombus diameter of 4.0 (2.0–7.0) cm. The proximal extent of the IVC tumour on preoperative imaging was level III in 25 patients and level IV in 23 patients (Mayo clinic classification [10]). The median (range) American Society of Anesthesiologists (ASA) grade was 3 (2–4).

Table 1 Presenting symptoms and signs.*

Symptoms	*N*
Haematuria	19
Loin/abdominal pain	16
Thromboembolic disease:	
Deep vein thrombosis	6
Pulmonary embolus	8
Mass	3
Constitutional symptoms:	
Weight loss	14
Lethargy	10
Anorexia	6
Anaemia	6
Night sweats	4
Unwell	2
Other symptoms:	
Lower limb oedema	3
Shortness of breath	2
Hypertension	2
Varicocoele	2
Varicose veins	1

* Some patients presented with more than one symptom or sign.

Operative data

Preoperative embolisation of the kidney was performed in eight patients (17%). The patients were selected based on examining preoperative imaging with the radiologist, it was selected mainly in left-sided tumours where anticipated difficulty in controlling the renal artery was expected either due to presence of large para-aortic lymph node, extensive tumour making access to the artery in earlier stages of surgery difficult, or extensive venous collaterals that were anticipated to bleed heavily during mobilisation of the kidney.

At operation two of the tumours were upstaged from level III to level IV, none were down staged.

The median (range) operative time was 360 (225–480) min, with a median (range) CPB time of 162 (120–300) min. HCA lasted for a median (range) of 35 (9–64) min, at a median (range) temperature of 15 (10–22) °C. Three patients had synchronous cardiac surgical procedures, two patients with coronary artery disease underwent by-pass grafting and one patient with aortic stenosis underwent aortic valve replacement. Splenectomy was required in three patients and two patients with tumours invading the wall of the IVC required an IVC patch using bovine pericardium. Four patients were packed at the end of the procedure with packs being removed at 48 h.

The median (range) blood transfusion requirement in the first 24 h was 9.5 (1–46) units.

Postoperative data

Patients initially returned to Intensive Therapy Unit for a median (range) of 2 (0–37) days, with a median (range) overall hospital stay of 12 (7–103) days.

There were three perioperative deaths (6.3%), all of whom died of multi-organ failure (MOF). Linear regression analysis revealed that ASA grade and perioperative blood requirement were significant factors associated with perioperative death ($P = 0.044$ and $P = 0.008$, respectively).

In all, 25 (52%) patients experienced perioperative morbidity. Specific causes of morbidity are listed in Table 2, but the majority were short-lived. Only one patient required permanent renal replacement therapy.

The clinicopathological features for these tumours are shown in Table 3.

Survival data

Kaplan–Meier survival curves for DFS and OS are shown in Figs. 1 and 2.

Despite extensive preoperative screening for metastases, the median (range) DFS was only 10.2 (1.2–224.4) months. The 1-, 5- and 10-year DFS rates were 41%, 25%, and 22%, respectively. Sites of recurrence in these patients were lung (11), liver (seven), bone (six), brain (six), local recurrence (three), lymph nodes (two), colon (one) and unknown site (six), with some patients having more than one site of recurrence.

The median (range) OS was 23 (0–224.4) months with 1-, 5- and 10-year OS rates of 72%, 37%, and 16%, respectively. Cox regression analysis was performed to look at various factors that may affect DFS and OS. For DFS, age and perinephric fat invasion appeared to confer a worse prognosis. Also, Cox regression analysis was carried out to test if tumour diameter affects DFS or OS. The results of the hazard ratio showed that there was a slight reduction in both DFS and OS with an increase of tumour diameter. However, the reductions were not statistically significant, i.e. $P > 0.05$ (Table 4). However, when Kaplan–Meier analysis was performed only perinephric fat invasion appeared significant ($P = 0.005$; log-rank Mantel-Cox), reducing DFS at 5 years from 32% to 7% (Fig. 3).

For OS, only the HCA time appeared to significantly alter prognosis (Table 4). Kaplan–Meier analysis

Table 2 Perioperative morbidity.

Perioperative morbidity*	*N* (%)
Overall number of patients experiencing complications	25 (52)
Chest infection	8 (17)
Required dialysis	5 (10)
Temporary (1.57–10 weeks)	4 (8)
Permanent	1 (2)
Gastrointestinal bleeding	4 (8)
Re-exploration for bleeding	3 (6)
Atrial fibrillation	3 (6)
Confusion	3 (6)
Others: (PE, sternal dehiscence, wound dehiscence, prolonged lymphatic leak, pericardial effusion, *Clostridium difficile*)	6 (13)

* Some patients had more than one complication; PE, pulmonary embolus.

Table 3 Clinicopathological features.

Clinicopathological details (n = number reported in)	Value
Cell type ($n = 48$), n (%)	
Clear cell	34 (71)
Unclassified	8 (17)
Papillary	5 (10)
Chromophobe	1 (2)
Primary tumour diameter ($n = 47$), cm, median (range)	9.0 (2.5–16.0)
Invading perinephric fat ($n = 47$), n (%)	17 (36)
Fuhrman Grade ($n = 46$), n (%)	
Grade 2	18 (39)
Grade 3	19 (41)
Grade 4	9 (20)
Necrosis ($n = 40$), n (%)	29 (73)
Sarcomatous features ($n = 48$), n (%)	5 (10)
Pathological nodal status ($n = 48$), n (%)	
N0	13 (27)
N1	2 (4)
NX	33 (69)
IVC tumour diameter ($n = 39$), cm*, median (range)	4.0 (2.0–7.0)

* On CT scan.

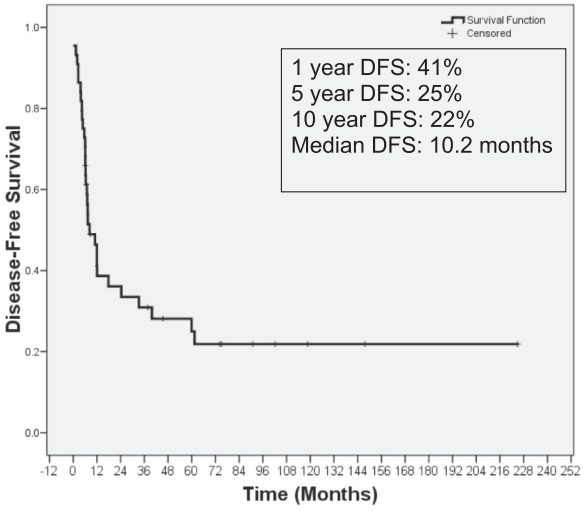

Fig. 1 Kaplan–Meier curve: DFS.

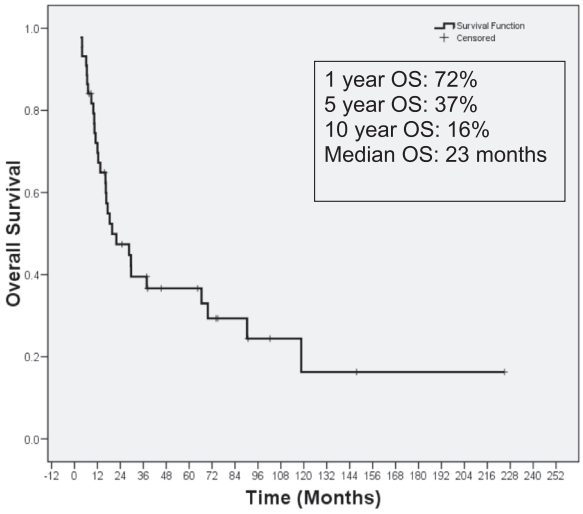

Fig. 2 Kaplan–Meier curve: OS.

Table 4 Cox regression analysis of factors influencing DFS and OS.

Variable	DFS, *P*	OS, *P*
Age	0.050	0.361
Anaemia (preoperative)	0.462	0.889
IVC tumour level	0.609	0.919
Circulatory arrest time	0.271	0.026
Pathological tumour size	0.364	0.549
Fuhrman grade	0.269	0.305
Necrosis	0.689	0.609
Perinephric fat invasion	0.029	0.327
Tumour diameter	0.204	0.837

showed that HCA times of >35 min conferred a significantly poorer OS ($P = 0.011$; log-rank Mantel-Cox), reducing OS at 5 years from 60% to 20% (Fig. 4).

Discussion

Patients with locally advanced renal cancer with tumour thrombus extending into the IVC have limited treatment options, with complete surgical excision providing the only chance of cure. Improvements in operative technique and postoperative intensive care have minimised the mortality rates associated with this type of surgery.

A multidisciplinary team approach to the management of these patients is essential. Expert radiological input is required to determine the proximal extent of the tumour and to perform embolisation of the kidney if required. We are fortunate to have outstanding input from cardiothoracic surgeons, anaesthetic and intensive care colleagues. Preoperative cardiological evaluation assesses both fitness for surgery and the need for any additional cardiac interventions during the same CPB procedure. Anaesthetic expertise in CPB and HCA ensures adequate body cooling and correction of bleeding diatheses associated with bypass surgery. Cooperation between the urological and cardiac surgeons ensures that the kidney and IVC tumour are removed in a safe and timely fashion, minimising the risks of uncontrolled haemorrhage, tumour embolus, and any myocardial or cerebrovascular impairment. Postoperative intensive care serves to minimise complications.

Selected level III tumours are amenable to excision via a thoraco-abdominal approach, where they can be manipulated below the hepatic veins allowing proximal clamp placement.

The tumours in the present series were deemed too extensive for this approach, instead requiring excision utilising CPB and HCA, which allows the surgeon to

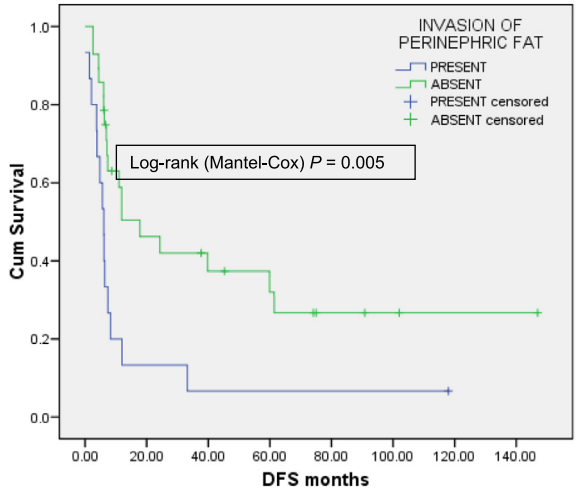

Fig. 3 Kaplan–Meier curve: DFS with and without perinephric fat invasion.

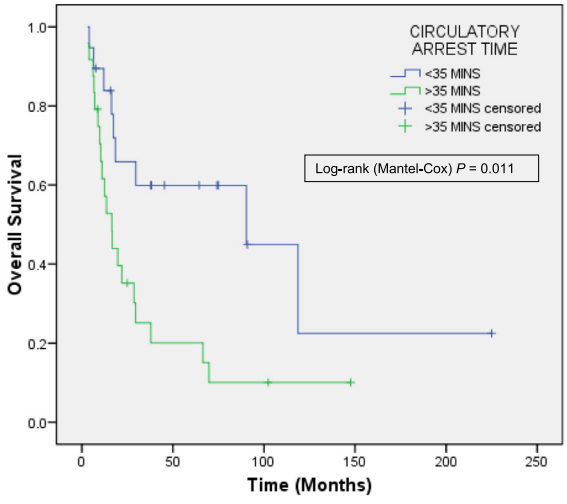

Fig. 4 Kaplan–Meier curve: OS by HCA time.

operate in a bloodless field for up to 60 min. The improved visibility afforded by this approach facilitates complete removal of these bulkier tumours that are often adherent to the IVC wall.

Currently, we have changed this technique for level III tumours (above hepatic veins and below diaphragm), we have stopped using a thoraco-abdominal approach and we aim to mobilise the liver with help of liver surgeons, use a Pringle manoeuvre soft clamp and a clamp on IVC just under the diaphragm and above the tumour thrombus, manipulate the thrombus below the hepatic veins, then apply a second clamp across the IVC below the hepatic veins to avoid using CPB, and the number of cases on CPB has decreased over years.

Despite the involved nature of this type of surgery our postoperative mortality rate was only 6.3%, with all three patients dying of MOF. This operative mortality rate is comparable to other reported series and supports our rigorous preoperative assessment of suitability for surgery [11,12]. Linear regression analysis revealed that ASA grade and blood transfusion requirement within 24 h were factors associated with perioperative death. The known association between large volume blood transfusions and MOF may partially account for these deaths. None of the eight patients who underwent preoperative embolisation died in the perioperative period, although they demonstrated no significant reduction in transfusion requirements. There are also logistic challenges as perioperative embolisation will add an extra hour or two under anaesthetic before the start of an already long surgery, if patients are embolised the day before surgery they can often suffer from post-embolisation syndrome and become acutely unwell before major surgery. In our experience preoperative embolisation is not helpful and we no longer use this technique.

Morbidity rates in our present series were relatively high, reflecting the extensive nature of this surgery, although in most cases were short-lived.

A high rate of postoperative gastrointestinal bleeds (8%) was noted and has led us to introduce pharmacological peptic ulcer prophylaxis routinely for all patients undergoing these procedures.

Our initial experience of this procedure was reported in 1994 [3], but at that time DFS and OS data were not mature. Our present updated results confirm that long-term survival is possible with a 5-year OS rate of 37%, which is consistent with other published series (Table 5) [5–9,13–16].

Several papers have shown that IVC invasion carries a significantly poorer prognosis when compared to renal vein invasion [13,14]. However, controversy exists over whether or not the cephalad extent of IVC tumour thrombus has any impact on survival. Several recent series have reported poorer survival outcomes associated with higher levels of IVC involvement, especially with supradiaphragmatic involvement (Table 5) [5–9]. However, some of these studies focus more on the differences in outcomes of the T3b and T3c TNM staging categories. The results may therefore be skewed by cases with renal vein invasion in the T3b staging category and not represent a true difference in outcomes with level of IVC involvement [4,5,9].

In contrast, other series have concluded that cephalad extent of IVC involvement has no impact on survival (Table 5) [13–16]. The largest of these series included 259 patients with IVC involvement and showed no difference in median survival between subdiaphragmatic and supradiaphragmatic involvement [14]. Cox regression analysis of our present results also failed to show any difference in DFS or OS between level III and IV tumours (Table 4).

In terms of OS, HCA time was the only significant factor identified that affected outcomes. Longer HCA times may reflect the tumour thrombus volume and difficulty of the excision, which may act as a surrogate marker of future metastatic potential. Prolonged HCA could also have a deleterious effect on long-term cardiovascular reserves, which may account for reduced OS.

Several papers have identified perinephric fat invasion as an indicator of poor prognosis [4,5,9,14,17]. Our present regression analysis results are in agreement with these findings with 5-year DFS reducing from 32% to 7% in those with perinephric fat invasion.

Despite extensive preoperative investigations, many of these patients harbour occult metastases at the time of surgery. In our present series, 59% of patients developed metastatic disease within 1 year of surgery, similar to other published results [4,5,7,11,17]. Sites of recurrence in these patients were lung (11), liver (seven), bone (six), brain (six), local recurrence (three), lymph nodes (two), colon (one) and unknown site (six), with some patients having more than one site of recurrence. Patients with clinically evident metastatic disease at diagnosis have a much poorer outlook with 5-year survival rates of $<15\%$ [6,7,11,12,15].

Preoperative bone scanning and brain imaging were not routinely performed. However, given the high frequency of metastases to these sites, we have now instituted these as part of our standard staging protocol. Newer imaging modalities may have a future role in identifying those with metastatic disease that cannot be detected by current imaging technologies. Improved radiological staging investigations may help to guide prognosis and improve patient selection if the aim of surgery is curative, but should not necessarily preclude surgery in symptomatic patients with low-volume metastases or indeterminate lesions.

The use of tyrosine kinase inhibitors in a neoadjuvant setting has been reported in patients with locally advanced tumours, where the aim is to downstage the tumour preoperatively [18–20]. This would seem an

Table 5 Summary of available literature assessing the impact of the level of IVC invasion on DFS and OS.

Reference	Year	Survival	Difference in IVC levels, statistically significant Yes/No (*P* value)
Blute et al. [13]	2004	5-year CSS, % RVI (n = 349): 49.1 Level I (n = 66): 31.7 Level II (n = 77): 26.3 Level III (n = 28): 39.4 Level IV (n = 20): 37	No (0.868)
Moinzadeh et al. [16]	2004	5-year CSS, % Subdiaphragmatic (n = 68): 52.7 Supradiaphragmatic (n = 17): 38.9 Right atrium (n = 22): 29.0	No (0.48)
Lambert et al. [15]	2007	5-year DSS, % Subdiaphragmatic (n = 22) 57 Supradiaphragmatic (n = 9) 25	No (0.25)
Wagner et al. [14]	2009	Median survival, months RVI (n = 933): 52 Subdiaphragmatic (n = 196): 25.8 Supradiaphragmatic (n = 63): 18	No (0.613)
Present study	2018	5-year DFS, % Level III (n = 23): 33% Level IV (n = 25): 20% 5-year OS, % Level III (n = 23): 40% Level IV (n = 25): 32%	No (0.609) No (0.919)
Kim et al. [7]	2004	3-year DSS, % RVI (n = 114): 36 Subdiaphragmatic (n = 80): 35 Supradiaphragmatic (n = 22): 12	Yes (0.009)
Leibovich et al. [9]	2005	5-year CSS, % RVI/subdiaphragmatic (n = 422): 45.9 Supradiaphragmatic (n = 19): 34.4	Yes (0.082)
Ficarra et al. [5]	2007	5 year CSS, % RVI/subdiaphragmatic (n = 705): 46.2 Supradiaphragmatic (n = 27): 10	Yes ($<$0.001)
Haferkamp et al. [6]	2007	Median survival, months Level I and II (n = 65): 25.1 Level III and IV (n = 46): 13.2	Yes (0.032)
Klaver et al. [8]	2008	Median CSS, months Level I (n = 25): 69 Level II (n = 23): 26 Level III (n = 3): 21	Yes (0.003)

RVI, renal vein invasion; CSS, cancer-specific survival; DSS, disease-specific survival.

attractive proposition, as it could render the tumour amenable to less invasive surgery, thus reducing operative morbidity and would also treat any micrometastatic disease early.

A large proportion of these patients present with constitutional symptoms affecting their quality of life. The palliative effect of surgery in patients with debilitating effects of IVC obstruction has been previously reported [11,21,22]. In our experience, this extensive surgery is worthwhile, and morbidity and mortality are acceptable for such a fatal disease. Without intervention, survival beyond few months is uncommon with such extensive IVC involvement. Also patients often report resolution of many of these symptoms postoperatively, so would appear to derive some benefit from surgery even if they go on to develop early metastatic disease.

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Conflict of interest

None declared.

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