Raised pre-operative INR identifies patients at high risk of peri-operative death after simultaneous renal and cardiac surgery for tumours involving the peri-diaphragmatic inferior vena cava (IVC) and right atrium.

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Abstract

Background The ability to predict and therefore avoid surgery in those patients likely to die from simultaneous renal and cardiac surgery for urological tumours involving the peri-diaphragmatic vena cava and right atrium would be valuable.

Objective To identify pre-operative factors that predict thirty-day mortality (TDM) in patients undergoing this type of surgery.

Design setting and participants Retrospective review of peri-operative outcomes in patients managed between December 2007 and January 2016 by a single team.

Outcome measurements and statistical analysis: Relationships with outcome analysed using Fisher's Exact and Mann Whitney U tests.

Results and Limitations: 46 patients of whom 41/46 (89%) underwent surgery

20 males; 21 females . Median age 65 yrs (range 17-95). 37 renal cell cancer, 1 adrenal cancer, 2 primitive neuroectodermal tumours and 1 leiomyosarcoma.

Overall TDM 3/41 patients (7%). INR, age and eGFR correlated significantly with TDM.

Mortality if INR >1.5, 3/5 (60%) compared to 0/36 (0%) if INR <1.5.

Mortality if INR >1.5 and age >70 years 3/3 (100%)

INR correlated with serious complications (≥Clavien 3) (INR>1.5: 5/5 (100%) vs INR<1.5: 12/36 (33%); p<0.002).

Median eGFR in those that died was 36 (range 26-37) compared to 52 (range 24-154) in those that survived (p=0.018).

Limitations include retrospective design

Conclusions: Combined cardiac and renal surgery is associated with high risk of TDM when the preoperative INR is abnormal and the patient is elderly. Surgery in patients with a normal INR is challenging but safer.

Patient summary: When kidney tumours invade the inferior vena cava and the heart, blood coagulation may become very abnormal (raised INR). Simultaneous cardiac and renal surgery appears very high risk if the pre-operative INR is raised, particularly in the elderly. The surgery appears much safer if the pre-operative INR is normal.

Introduction

Growth of renal cancer into the retro-hepatic IVC and onwards into the right atrium presents a considerable circulatory and oncological challenge. Patients may be very short of breath due to the circulatory compromise; venous return may be reduced; right atrial function sub-optimal; embolism of tumour may further impair cardio-pulmonary function; there may be very marked swelling of the abdomen and lower limbs limiting mobility; the mass of tumour itself may be enormous; and metastasis at the time of presentation is common. Nevertheless the situation is not hopeless and since the first reports of successful surgery in the 1970's [1,2] there has been steady progress in our understanding of how best to manage the various challenges associated with intra-caval and intra-cardiac renal cancer. When the tumour is in the right atrium the combination of radical nephrectomy with intra-cardiac and retro-hepatic intravenous tumour extraction under conditions of hypothermic total circulatory arrest on cardiopulmonary bypass is one approach [3-6]. There does however continue to be debate about the necessity for hypothermic arrest and even bypass in these situations, particularly when the cephalad extent of venous invasion is supra-hepatic but not atrial [7]. Expert multidisciplinary intra-operative care from cardiothoracic surgeons, cardiothoracic anaesthetists, and urologists combined with post-operative intensive care allows the surgery to be performed with acceptable morbidity and mortality [8]. Nevertheless this combination remains one of the highest risk procedures in urological surgery with contemporary series reporting thirty-day mortality (TDM) of approximately 11% [6].

Understanding who is most at risk of TDM would be a major step forward in the management of this condition. The surgery could then be offered selectively to those most likely to gain benefit from it. Other patients who were considered unlikely to survive the surgery or its

aftermath might be better managed with drugs or palliative approaches. This would also mean that this very expensive care could be concentrated on those likely to derive benefit from it. The question of who to offer surgery to has been made more pertinent by the introduction of drugs which are active in renal cancer [9]. This is for two reasons viz, firstly, the drugs may be an alternative to surgery altogether; and secondly, the drugs make control of metastatic disease a possibility thus opening up the whole field of complex intra-cardiac surgery in more advanced oncological situations or even cytoreductive settings.

Abel et al [6] in a recent multicentre collaborative review of outcomes from several centres in the USA highlighted performance status and serum albumin as key determinants of peri-operative outcomes although neither could absolutely discriminate between those destined to die from complications arising from surgery and those destined to do well. Other recent reports suggest that the surgical Apgar score [10] may help identify patients at high risk of complications post-nephrectomy. The ideal test would be one that could be applied pre-operatively and would be both highly sensitive and specific for predicting adverse peri-operative outcomes.

In 2007 we established a programme in our hospitals for the management of these complex intra-cardiac renal tumours. Two urological surgeons and one cardiothoracic surgeon and one cardiothoracic anaesthetist have been part of the core surgical team. Our approach since inception of the programme has been inclusive, i.e. to err on the side of offering surgery rather than selecting out only lower risk candidates, often because surgery seemed to represent a patients only hope and because patients were often so symptomatic from the disease burden. In that time 46 patients have been referred to our team; 41 patients have undergone surgery,

and only 5 patients have been managed in other ways. Now in 2016 we report the key lessons we have learned over that 8 year period regarding peri-operative risk.

Methods

This study is a review of peri-operative outcomes and TDM in all patients who have undergone simultaneous cardiac and renal tumour surgery between December 2007 and May 2015 at our centre. A full review of electronic and paper records was undertaken. All operative records had been filed prospectively.

The surgery was performed in the cardiothoracic units of St Thomas Hospital or London Bridge Hospital. The core team has comprised two urological surgeons, one cardiothoracic surgeon and one cardiothoracic anaesthetist. Patients underwent general anaesthesia; position was supine; incision median sternotomy with Mercedes Benz extension to the abdomen; early ligation of renal artery; full renal mobilisation; full mobilisation of right hepatic lobe; IVC mobilisation with division of caudate lobe branches; heparinisation and establishment of cardiopulmonary bypass with cooling to 22C and circulatory arrest for ~20minutes (if required); complete removal of tumour; IVC repair/grafting (if required); re-establishment of circulation; warming to 37C; wound closure. Patients were admitted either to overnight theatre recovery or intensive care at the discretion of the team.

A number of potentially important pre and peri-operative variables were studied. These were then compared between patients who survived and patients who died in the perioperative period (30 days). Significance was determined using the Fisher's Exact or Mann Whitney U-test. As there were only three peri-operative deaths, non-parametric logistic regression was used to identify which of these variables were statistically significantly associated with TDM. With respect to INR, no further stratification or adjustments were made due to the occurrence of quasi-complete and complete separation.

Complications were categorised according to the Clavien Dindo classification [11]. A secondary univariate analysis was performed to identify potential risk factors for serious complications (Clavien ≥3). Multivariate models were not possible due to the occurrence of quasi-complete and complete separation.

Results

46 patients were assessed. 41/46(89%) underwent simultaneous urological and cardiac surgery. 5 patients did not undergo surgery (1 refused, 3 overwhelming metastatic load, 1 extreme frailty). 34/41 (83%) operations were performed with curative intent in the absence of radiological evidence of metastases. 7/41 (17%) cytoreductive. 3/41(7%) patients died in the perioperative period. Histology: 35 clear cell RCC; 2 papillary RCC; 1 adrenocortical carcinoma; 2 primitive neuroectodermal tumour; 1 leiomyosarcoma.

Operative details are outlined in table 1. Post-operative complications are detailed by Clavien-Dindo classification in table 2. Overall, 30/41 (73%) patients had complications. 17 of these were ≥Clavien 3 complications including 4 returns to theatre for bleeding and 1 for gastric perforation; 4 patients developed pulmonary emboli in the post-operative period and 4 developed fast atrial fibrillation.

Baseline characteristics of those that died and those that survived are compared in Table 3. INR, age and estimated glomerular filtration rate (eGFR) were the only pre-operative variables that were statistically significantly associated with TDM. When conducting non-parametric logistic regression for INR (INR ≥1.5 vs <1.5) and perioperative death, we found an odds ratio (OR) of +∞ (95%CI: 4.04 - +∞) with a p-value of 0.001. Even though the occurrence of quasi-complete separation did not allow us to estimate the actual OR or the upper limit of the 95% CI, the lower limit of 4.04 indicates a strong positive association between an INR≥1.5 and risk of TDM. As a result, no further adjustments for age or eGFR could be made.

Despite preoperative correction of INR, all 5 patients (100%) who had raised pre-operative INR had serious complications (≥ Clavien 3) (1 Clavien 3b, 1 Clavien 4b, 3 Clavien V), compared to 12/36(33%) of patients with normal INR ($p<0.002$; table 2). The mortality for those with a raised INR ≥1.5 was 3/5(60%) compared to 0/36 (0%) if the INR was normal. All 3 patients with a raised INR who died were aged ≥70 years. 5/8(62%) patients aged ≥70 years survived; all five had a normal INR.

A similar non-parametric logistic regression model was conducted for serious complications as INR was the only risk factor showing an association in a multivariate analysis (table 4). When conducting a non-parametric logistic regression for INR (INR > 1.5 vs ≤ 1.5) and Clavien ≥3, we found an OR of $+\infty$ (95%CI: 1.51 - $+\infty$), with a P-value of 0.008. Even though the occurrence of quasi-complete separation did not allow us to estimate the actual OR or the upper limit of the 95%CI, the lower limit of 1.51 indicates a positive association between an INR≥1.5 and risk of serious complications.

The positive predictive value (PPV) of raised INR alone for death is 3/5 (60%). PPV of age ≥70 years is 3/8 (37.5%). PPV for combination of age ≥70 years and INR ≥1.5 was 3/3 (100%). None of the 36 patients with a normal INR died. Negative predictive value (NPV) of normal INR 100%

Bloods loss; the use of cardiac bypass with or without arrest and cooling; whether the tumour was above or below the diaphragm; abnormal liver profiles and albumin level; and performance status were not statistically significantly associated with TDM.

Discussion

Surgery for patients with renal tumours invading the peri-diaphragmatic IVC and/or right atrium is high risk. This study suggests that surgery of this type is potentially dangerous if a patient's pre-operative INR is abnormal. All 3 patients who died had an abnormal INR, despite the INR being corrected prior to surgery. The overall thirty-day mortality (TDM) in patients with INR ≥1.5 was 3/5(60%). The two patients with INR ≥1.5 who survived had serious complications (Clavien 3b and 4b) and prolonged lengths of stay (62 and 70 days). Furthermore, this study has shown that this surgery can be performed relatively safely in patients with normal INR. No patients with a normal INR died in the post-operative period (TDM 0%).

It is of interest that the three patients who died in this series not only had an abnormal INR, but were also aged over 70, whereas the two patients with an abnormal INR who survived surgery were aged under 70 (aged 63 and 54 years). No patient over the age of 70 with an abnormal pre-operative INR >1.5 has survived. Put another way, the PPV for TDM of the combination of raised INR and age over 70 is 100%. This is important as it would suggest that elderly patients who are already showing signs of metabolic compromise by virtue of raised INR do not have the physiological reserve to survive the peri-operative challenge. The scale of the physiological challenge must be the same in younger patients, but they may have more physiological reserve to withstand it.

Age and eGFR were also shown to be important determinants of risk. An obvious question to ask is, which is the most important risk factor– the INR, the eGFR or the age? Our data would suggest very strongly the INR. All five patients over the age of 70 who had normal INR survived. Furthermore, both younger patients with abnormal INR had very stormy post-operative periods. With respect to eGFR, the median eGFR of those who survived was 52 compared to 36

in those who died. All three patients who died had an eGFR <40 and overall the mortality in patients with an eGFR <40 was 3/8 (37.5%). Patients with a low GFR may be at increased risk of peri-operative death. Constraints of time in the pre-operative period precluded formal measurement of GFR (e.g. with chromium 51 labelled EDTA GFR) but might be of interest to investigate this association further.

The reason the INR becomes abnormal in these patients is likely to be complex but probably due to hepatocellular dysfunction arising as a consequence of congestion as a result of partial hepatic venous obstruction. This in turn leads to ischaemia of parenchymal cells and deranged production of clotting factors [12}. Alterations to coagulation parameters in these patients seem to be a sign of advancing liver disease. Approximately 50% of our patients have abnormal pre-operative liver enzymes (AST, ALT, Alkaline phosphatise) presumably indicating mild liver dysfunction, but only 12% of these patients had progressed to have abnormal INR. It is also interesting that despite all the patients with abnormal pre-operative coagulation having aggressive pre-procedure corrective measures with vitamin K and fresh frozen plasma infusions, major complications still transpired. The abnormalities signalled by a raised INR are probably far more complex than those simply of coagulation; and rather indicate a metabolic disorder which remains largely uncorrected despite the normalisation of coagulation. Equally interestingly, the hepatic venous obstruction leading to the abnormal INR is not always associated with clinical manifestations of the Budd-Chiari syndrome [12,13]. Only two of the five patients with an abnormal INR had a clinical Budd-Chiari syndrome as evidenced by ascites. None of the patients were jaundiced or encephalopathic.

Should patients with an abnormal INR not be offered this type of surgery? Based on this study we would exercise caution if the patient is elderly - as all three patients who had a raised INR and were aged over 70 years died (mortality 100%). In younger patients with an abnormal INR, we would still consider surgery if their background health was good prior to the tumour presentation, and particularly if the patient was very symptomatic from the circulatory disturbance; serious complications and a challenging post-operative period might be expected. Furthermore, our work should not be viewed in isolation. Abel et al [6] suggested performance status and serum albumin were also important factors associated with peri-operative complications and TDM. In our series performance status (PS) was not statistically significantly associated with TDM and deranged INR was a far more accurate predictor of mortality. We speculate that reverse causation might explain why PS is not significantly associated with death – rather than a reflection of underlying co-morbidity, poor PS may be a direct consequence of circulatory obstruction or tumour volume, and therefore reversible with surgical correction. It should also be noted that in the Abel series albumin levels were only available on 50% of the patients making it difficult to be certain of the significance of the effect. One strength of our study is that INR is available on all our patients.

This study is also very encouraging in demonstrating that combined cardiac and renal surgery can be performed in patients with a normal INR with a low risk of TDM. None of our 36 patients died. This may be valuable for optimising multidisciplinary clinical decision-making and for counselling patients pre-procedure. The majority of patients despite feeling ill, having compromised circulation and dyspnoea on exertion, and a large volume of tumour can be steered through surgery successfully and have much to gain symptomatically from correction of the circulatory problem. Nonetheless, the surgical and anaesthetic challenges are considerable

and success is only possible with a well-organised highly committed skillful team. In the context of this disease this is also a high volume team.

Despite overall TDM being low, complications are common in this group. Overall complications occurred in 30/41(73%) with 17/41(42%) having ≥Clavien 3 complications. Even in the group we would now consider relatively low risk for peri-operative death (normal INR, <70yrs), the complication rate was still 20/31(64%). INR appears to be a risk factor for predicting serious complications (Clavien ≥3) as well as TDM.

This report is not considering the long-term oncological outcomes in this group of patients, but it is known that the majority of patients with locally advanced renal cancer of this type will develop systemic relapse [14,15]. The advent of multiple new medications for the control of metastatic disease does, however, offer hope to patients if their heavily symptomatic loco-regional disease can be controlled [16]. A particularly difficult scenario is to know whether this type of surgery should be offered in cytoreductive settings [17,18]. A heavy burden of metastatic disease would in most instances disqualify a patient, but a low volume of metastatic disease in a younger patient, who has a normal INR and who is symptomatic from the circulatory disturbance, might be considered a reasonable candidate for cytoreductive surgery.

The main limitation of this study is size making it difficult to draw stronger conclusions. However given the frequency of this tumour our single institution data is still clinically informative. Future study of the association between INR and TDM across wider groups of patients, and particularly in national audits of nephrectomy [19], may provide a larger number of events allowing for the calculation of multivariate logistic regression models. Moreover, our data can now inform sample size calculations for these future studies.

297 **Conclusion**

298 In patients undergoing simultaneous renal and cardiac surgery for renal cancer, a raised pre-
299 operative INR appears to be a predictor of thirty-day mortality in elderly patients (≥70 years)
300 and of significant post-operative complications in younger patients (<70 years). The surgery can
301 be offered with more confidence to patients with a normal INR.

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Tables

Table 1. Operative details (n=41)

Cardiac bypass	31 (76%)
Arrest + cooling	27 (66%)
Median blood loss in mls (min-max)	2250 (300-20000)
Median Operation time in hours (min-max)	5 (2.25-7.5)
Median length of stay in days (min-max)	16 (7-97)

Table 2. Complications by INR

	INR < 1.5 (n=36)	INR ≥ 1.5 (n=5)	P value
Clavien-Dindo Classification			0.002
0	11 (31)	0 (0)	
1	2 (6)	0 (0)	
2	11(31)	0 (0)	
3a	6 (17)	0 (0)	
3b	2 (6)	1 (20)	
4a	3 (8)	0 (0)	
4b	1 (3)	1 (20)	
5	0 (0)	3 (60)	

Table 3. Risk factors for serious complications

	Clavien <3 (n=24)	**Clavien ≥3 (n=17)**	**P-value**
Median age (min-max)	64.73 (31.00-95.00)	68.00 (17.00-76.00)	0.584
Sex			0.086

Male	9 (37.50)	11 (64.71)	
Female	15 (62.50)	6 (35.29)	
Karnofsky performance status			0.258
20	0 (0.00)	2 (11.76)	
30	0 (0.00)	1 (5.88)	
40	0 (0.00)	1 (5.88)	
50	2 (8.33)	2 (11.76)	
60	3 (12.50)	0 (0.00)	
70	6 (25.00)	5 (29.41)	
80	8 (33.33)	3 (17.65)	
90			0.258
Symptomatic	11 (45.83)	10 (58.82)	0.412
Curative	18 (75.00)	16 (94.12)	0.109
Above diaphragm	21 (91.30)	15 (88.24)	0.749
Bypass	16 (66.67)	15 (88.24)	0.113
Cooling	14 (58.33)	13 (76.47)	0.228
Median EBL (min-max)	2000 (100-5000)	3000 (30-2000)	0.157
Median Hb (min-max)	10.90 (10.00-87.00)	12.00 (9.00-13.00)	0.357
Median CRP (min-max)	35.50 (26.00-49.00)	37.00 (5.00-312.00)	0.598
Median INR (min-max)	1.00 (0.90-1.30)	1.00 (1.00-3.00)	0.033
Abnormal LFTs	8 (33.33)	10 (58.82)	0.105
Median albumin (min-max)	35.50 (26.00-49.00)	40.00 (26.00-50.00)	0.255
Median creatinine (min-max)	95.00 (54.00-180.00)	111.00 (17.00-	0.235
Median GFR (min-max)	52.50 (54.00-180.00)	46.00 (24.00-150.00)	0.910