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European Association of Urology

Platinum Priority – Review – Kidney Cancer
Editorial by XXX on pp. x–y of this issue

Systematic Review of Surgical Management of Nonmetastatic Renal Cell Carcinoma with Vena Caval Thrombus

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Article info

Article history:
Accepted November 30, 2015

Associate Editor:
James Catto

Keywords:
Nonmetastatic renal cell carcinoma
Vena caval thrombus
Surgical management of tumour thrombus
Thrombectomy
Circulatory bypass and preoperative embolisation
Systematic review

Abstract

Context: Overall, 4–10% of patients with renal cell carcinoma (RCC) present with venous tumour thrombus. It is uncertain which surgical technique is best for these patients. Appraisal of outcomes with differing techniques would guide practice.
Objective: To systematically review relevant literature comparing the outcomes of different surgical therapies and approaches in treating vena caval thrombus (VCT) from nonmetastatic RCC.
Evidence acquisition: Relevant databases (Medline, Embase, and the Cochrane Library) were searched to identify relevant comparative studies. Risk of bias and confounding assessments were performed. A narrative synthesis of the evidence was presented.
Evidence synthesis: The literature search identified 824 articles. Fourteen studies reporting on 2262 patients were included. No distinct surgical method was superior for the excision of VCT, although the method appeared to be dependent on tumour thrombus level. Minimal access techniques appeared to have better perioperative and recovery outcomes than traditional median sternotomy, but the impact on oncologic outcomes is unknown. Preoperative renal artery embolisation did not offer any oncologic benefits and instead resulted in significantly worse perioperative and recovery outcomes, including possibly higher perioperative mortality. The comparison of cardiopulmonary bypass versus no cardiopulmonary bypass showed no differences in oncologic outcomes. Overall, there were high risks of bias and confounding.
Conclusions: The evidence base, although derived from retrospective case series and complemented by expert opinion, suggests that patients with nonmetastatic RCC and VCT and acceptable performance status should be considered for surgical intervention.

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http://dx.doi.org/10.1016/j.eururo.2015.11.034

Despite a robust review, the findings were associated with uncertainty due to the poor quality of primary studies available. The most efficacious surgical technique remains unclear.

Patient summary: We examined the literature on the benefits of surgery to remove kidney cancers that have spread to neighbouring veins. The results suggest such surgery, although challenging and associated with high risk of complications, appears to be feasible and effective and should be contemplated for suitable patients if possible; however, many uncertainties remain due to the poor quality of the data.

1. Introduction

Renal cell carcinoma (RCC) accounts for approximately 2–3% of all malignant diseases in adults [1]. A feature of this malignancy is potential venous tumour thrombus (VTT) formation. At presentation, 4–10% of RCC patients have thrombus in the renal vein or inferior vena cava (IVC) [2]. The treatment of choice for RCC with VTT remains radical nephrectomy with thrombectomy [3]. Aggressive surgical resection is widely accepted as the default management option for these patients [4–7].

There is variation in how the surgery is undertaken in terms of preoperative strategies (eg, use of IVC filter [8] or embolisation of tumour [9]), surgical approach to access the IVC, special manoeuvres (eg, liver mobilisation, milking of thrombus, aortic cross-clamping, or Pringle's manoeuvre), circulatory bypass procedures to achieve vascular control (eg, venovenous bypass or cardiopulmonary bypass [CPB] and deep hypothermic circulatory arrest [DHCA] [10]), and perioperative strategies (eg, anticoagulation). In general, the IVC tumour is approached according to the VTT level [11,12].

Although several reviews regarding the management of vena caval thrombus (VCT) in nonmetastatic RCC have been published [13–16], most were narrative reviews using nonstandardised methodology. The primary objective of this systematic review was to determine the comparative effectiveness and harms of the different surgical therapies in treating patients with VCT from nonmetastatic RCC and to identify knowledge gaps.

2. Evidence acquisition

2.1. Search strategy

The review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [17] and Cochrane review principles [18] and was undertaken as part of the European Association of Urology (EAU) RCC guideline panel's forthcoming 2016 guideline update exercise. Highly sensitive electronic searches were undertaken to identify published and ongoing comparative studies and case series of surgical management of RCC with VCT. Searches were limited to studies published from the year 2000 onwards to reflect current clinical practice. No language restrictions were imposed. Searches conducted in bibliographical databases were complemented by additional sources, including the reference lists of included studies, which were hand searched to identify additional relevant studies, and reports identified by the guideline panel.

The databases searched were Medline, Medline In-Process, Embase, the Cochrane Controlled Trials Register, the Science Citation Index, and the Conference Proceedings Citation Index. Systematic reviews and other background information were identified by searching the Cochrane Database of Systematic Reviews. In addition, ClinicalTrials.gov and the World Health Organisation International Clinical Trials Registry were searched to identify ongoing trials. Full details of the search strategies used are described in Appendix 1.

Two reviewers screened all abstracts and full-text articles independently. Disagreement was resolved by discussion or reference to an independent third party.

2.2. Types of study design included

Randomised controlled trials (RCTs), quasi-RCTs, non-randomised comparative studies (NRCSs), and single-arm case series (with at least 50 patients) were eligible for inclusion.

2.3. Types of participants included

The study population was composed of patients diagnosed with nonmetastatic RCC with tumour extension into the IVC. Studies in which metastatic disease accounted for >10% of their participants were excluded. Previous surgery for VCT, recurrent tumours, and non-RCC malignancies were also grounds for exclusion.

2.4. Types of interventions included

Studies reporting any kind of surgery for VCT in at least one arm were included. For comparative studies, eligible comparators were either no intervention or any alternative surgery or treatment. Perioperative strategies were also included as long as thrombectomy was included in one arm.

2.5. Types of outcome measures included

The main outcome measures were specified a priori and included overall survival (OS) and cancer-specific survival (CSS). Other oncologic outcomes included incidence of recurrence, recurrence-free survival (RFS), and incidence of metastatic disease. Additional outcome measures included

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complications (including mortality), perioperative and recovery outcomes (eg, length of hospital stay, blood loss), and quality of life.

2.6. Assessment of risk of bias and confounding

For RCTs, risk of bias (RoB) assessment was undertaken using the Cochrane Collaboration RoB tool. For NRCSs, a modified RoB tool was adapted for use [19]. In addition, for NRCSs, the main confounders were identified a priori by the guideline panel for the primary outcome. A study was considered to be at high RoB if any of the confounders were imbalanced. The main confounders identified included age, tumour level, and presence of metastasis. Each confounder was assessed according to whether it had been considered by the authors (yes or no), whether the confounder was balanced across the groups (high risk, low risk, or unclear), and the degree to which adjustment had been made for the confounder (high risk, low risk, or unclear). Based on the available methodological research in the literature [20,21], RoB in the eligible case series reports was assessed according to four parameters:

- Selection bias (did study cohort include consecutive patients?)
- Attrition bias (were patients lost to follow-up accounted for?)
- Detection bias (were primary outcomes appropriately measured?)
- Use of a priori protocol

2.7. Data analysis

A data extraction form was developed a priori to collect information on study design, participant characteristics, characteristics of interventions, and outcome measures. Two reviewers independently extracted data relating to the prespecified outcomes. For data analysis, descriptive statistics were used to summarise baseline characteristic data. The main results were presented in a summary-of-findings table. Quantitative synthesis (meta-analysis) was planned only for RCTs. For all other studies, a narrative synthesis of the evidence was planned.

3. Evidence synthesis

3.1. Quantity of evidence identified

The literature searches identified 824 articles (Fig. 1). Of these, 71 were selected for full-text screening. Ten comparative studies [22–31] and four case series [7,32–34] were included.

3.2. Characteristics of the included studies

Data were included for 2262 patients from 14 studies (15 reports), all of which were retrospective studies (Table 1). No RCTs or prospective NRCSs were identified. Consequently, data were summarised narratively.

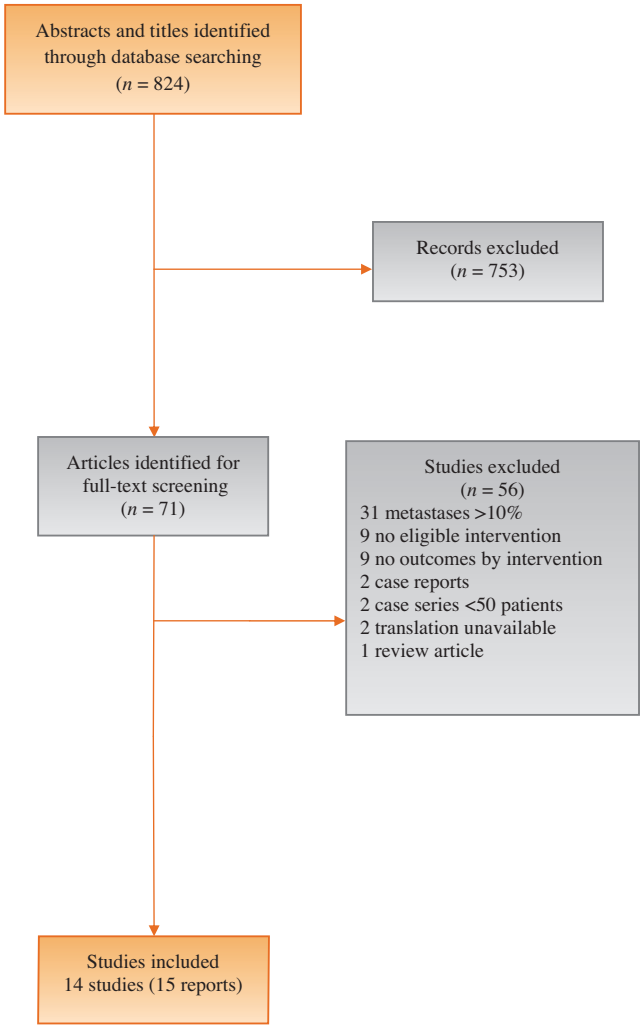

Fig. 1 – PRISMA flow diagram.

3.3. Risk of bias and quality assessment of the included studies

Figures 2 and 3 summarise the RoB and confounding assessment for all included studies. Due to the retrospective design of the included studies, there was high or unclear RoB across most domains. All studies were underpowered. The issue of confounding was also poorly addressed by most studies.

3.4. Comparisons of intervention results

3.4.1. Data from comparative studies

Table 2 summarises the outcome results for all 10 comparative studies [22–31].

3.4.1.1. Minimal access versus traditional median sternotomy. Two studies [23,29] compared minimal access (MA) techniques with traditional median sternotomy (TMS), but data were too heterogeneous for data pooling. In both studies, the median operating time was significantly shorter with MA techniques than with TMS. The MA group had numerically longer but not statistically significant RFS [23] and OS [29]

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Table 1 – Characteristics of included studies

Study, year, country, design, recruitment period	Interventions	Thrombus level	*n*	Age, yr, mean (SD) or median (range)	Follow-up, mo, median	Primary tumour size, cm, median (range)	Primary tumour stage	Outcomes
Chan 2011 [22], USA, retrospective, 1993–2009, NRCS	Preoperative renal artery embolisation	NR	48	NR	43.2	10.4 (2–28)	T3bN0M0 and T3cN0M0	Perioperative mortality, operating time, blood loss, hospital stay
	No preoperative renal artery embolisation	NR	205	NR	22.6			
Faust 2013 [23], USA, retrospective, 1986–2012, NRCS	Minimal access with circulatory arrest	NR	49	NR	NR	NR	NR	Disease-free survival, operating time, wound infection, sepsis; differences between groups in hospital stay and postoperative mechanical ventilation
	Traditional median sternotomy	NR	21	NR	NR	NR	NR	
Klink 2013 [24], USA, database review, 2000–2011, NRCS	IVC thrombus removed en bloc	II	37	NR	NR	NR	NR	Operating time, need for blood transfusion, intraoperative tumour thrombus embolisation, overall rate of intra- and postoperative complications
		III	17					
		IV	6					
	IVC thrombus transected	II	16					
		III	35					
		IV	41					
Krishnamurthi 2011 [25], USA, database review, 1990–2010, NRCS	Deep hypothermic circulatory arrest	NR	53	NR	NR	NR	NR	Operating time, bypass time, perioperative mortality, major postoperative complications
	Cardiopulmonary bypass without circulatory arrest	NR	44					
	Venovenous bypass	NR	10					
Nguyen et al., 2014 [26], USA and Europe, database review, 1971–2012, NRCS	No cardiopulmonary bypass with circulatory arrest	III-IV	305	NR	14.8 (NR)	NR	NR	Overall survival, cancer-specific survival; differences between groups in CPB and number of complications
	Cardiopulmonary bypass with circulatory arrest		150					
Orihashi et al., 2008 [27], Japan, retrospective case series, 1985–2008, NRCS	Single caval clamp without circulatory support	I	9	63.8	Range 5–276	9.8	NR	Operative deaths, 5-yr survival, local recurrence, operating time, blood loss, blood transfusion, circulatory arrest
		II	3					
		III	1					
		IV	0					
	Partial bypass	I	3	66.5		7.5		
		II	4					
		III	1					
		IV	0					
	Circulatory arrest	I	0	60.8		9.3		
		II	3					
		III	9					
		IV	3					
Tang et al., 2014 [28], China, database review, 2000–2011, NRCS	Preoperative renal artery embolisation	NR	46	NR	NR	8.06 (NR)	NR	Overall survival, operating time, blood loss, blood loss in patients with VCT above hepatic vein, amount of blood transfused in patients with VCT above hepatic vein
	No preoperative renal artery embolisation		94			9.94 (NR)		
Wotkowicz et al., 2006 [29], USA, retrospective database review, 1986–2005, NRCS	Minimal access (with chevron incision, IVC mobilised along anterior surface with 'no-touch' technique)	NR	28	60 (44–83)	Up to 192 mo	NR	T3b and T3c: 92% (46); T4: 8% (4)	Overall survival, operating time, need for blood transfusion, hospital stay, CPB (minutes), DHCA (minutes), ventilation support (minutes), perioperative complications
	Traditional median sternotomy	NR	22	61 (47–80)				

Yugisawa et al., 2013 [30], Japan, retrospective case series, 1986–2012, NRCS	Radical nephrectomy and IVC thrombectomy without IVC filter	I-III	29	NR	NR	NR	NR	Intraoperative pulmonary embolism
	Radical nephrectomy and IVC thrombectomy with IVC filter	I-III	25					
Zhang et al., 2013 [31], China, retrospective matched pair, 2003–2007, NRCS	Traditional nephrectomy plus IVC thrombectomy	NR	36	NR	60 (NR)	NR	NR	Overall survival, operating time, blood loss, need for blood transfusion, pneumonia, metastasis incidence
	Placement of IVC filter and application of liver mobilisation technique: tumour thrombus <2 cm above renal vein		11	60 (NR)		9.5 (NR)		
	Placement of IVC filter and application of liver mobilisation technique: tumour thrombus below hepatic vein		19	63 (NR)		10.1 (NR)		
	Placement of IVC filter and application of liver mobilisation technique: tumour thrombus above hepatic vein but below the diaphragm		12	58 (NR)		12.6 (NR)		
Al Otaibi et al., 2009 [32], Canada, case series, database review, 1985–2005	Radical nephrectomy and thrombectomy	I	7	59 (11)	28 (range 2–136)	NR	NR	Overall 5-yr survival, disease-free 5-yr survival, local recurrence, time to local/distant recurrence, perioperative complications, 30-d mortality
		II	26					
		III	10					
		IV	7					
Kim et al., 2012 [33], USA, case series, database review, 1980–2009	Radical nephrectomy and thrombectomy (only nononcologic outcomes extracted from this study)	0	357	NR	5.9 yr (0–30 yr)	NR	NR	Blood loss, 30- and 90-d morbidity, hospital stay
		I	78					
		II	113					
		III	47					
		IV	45					
Kulkarni et al., 2012 [34] and 2007 [35], India, case series, database review, 1991–2008	Midline abdominal incision only	NR	72	71 (23–90)	60 (NR)	NR	Unclear	Overall survival, 30- and 90-d mortality, operating time, need for blood transfusion, hospital stay, disease-free rate, death due to metastasis
	Midline abdominal and additional sternotomy	NR	20					
	Midline abdominal, sternotomy and cardiopulmonary bypass	NR	8					
Moinzadeh and Libertino, 2004 [7], USA, case series, database review, 1970–2000	Cavotomy and reconstruction	I	46	62.1 (39–82)	60 (12–221)	7.2 (2.5–20)	Unclear	5- and 10-yr cancer-specific survival
	Circulatory arrest with cardiopulmonary bypass	II	14	64.5 (47–82)		9.9 (4–13)		
	Circulatory arrest with cardiopulmonary bypass	III	17	63.6 (48.78)		9.8 (4.7–18.0)		

CPB = cardiopulmonary bypass; DHCA = deep hypothermic circulatory arrest; IVC = inferior vena cava; NR = not reported; NRCS = nonrandomised comparative study; VCT = Vena caval thrombus.

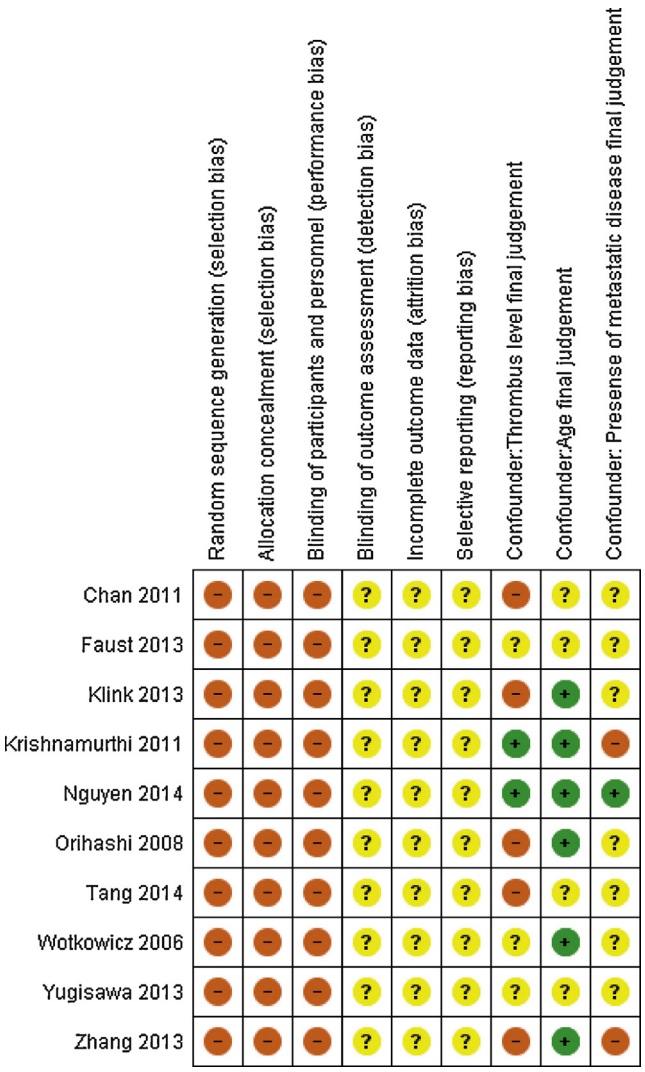

Fig. 2 – Risk of bias and confounder assessment for nonrandomised comparative studies only. Key: Red = high RoB; Yellow = uncertain RoB; Green = low RoB.

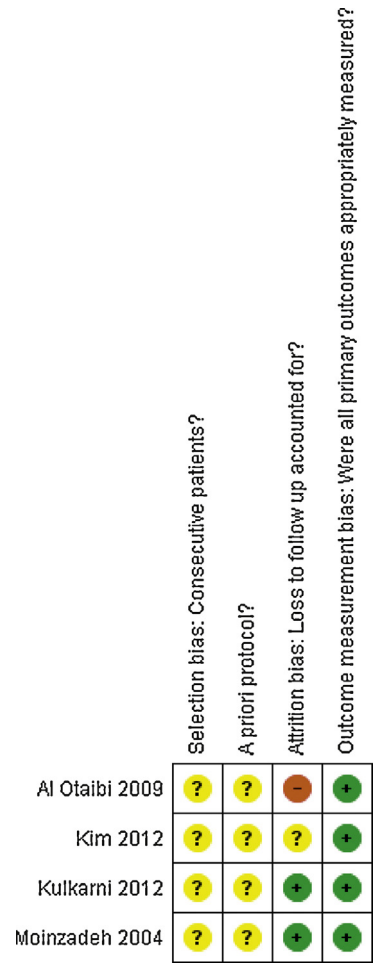

Fig. 3 – Risk of bias for case series. Key: Red = high RoB; Yellow = uncertain RoB; Green = low RoB.

than the TMS group. The study by Wotkowicz et al [29] was conducted in patients with T3 and T4 RCC, whereas Faust et al [23] did not report primary tumour stage. Faust et al [23] also found statistically significant differences in favour of MA for wound infection, sepsis, hospital stay, and ventilatory requirements. Similarly, Wotkowicz et al [29] found statistically significant differences in favour of MA for transfusion, hospital stay, and ventilator requirements.

3.4.1.2. Preoperative renal artery embolisation versus no preoperative renal artery embolisation. Chan et al [22] compared preoperative renal artery embolisation (PRAE) with no PRAE in patients with T3 RCC and found that PRAE was associated with increases in operating time, blood loss, and hospital stay (all statistically significant) and higher perioperative mortality (8.4% vs 3.4% for PRAE vs no PRAE respectively, p value not stated). PRAE, however, appeared to be associated with a nonsignificant trend towards a lower risk of death from any cause. Tang et al [28] found that PRAE may be more appropriate for patients with advanced tumour thrombus because of its benefit in reducing intraoperative blood loss and blood transfusion ($p = 0.043$ and $p = 0.028$, respectively), but otherwise the authors did not find a measurable advantage in terms of long-term prognosis for patients in the PRAE group.

3.4.1.3. Cardiopulmonary bypass versus no cardiopulmonary bypass. Nguyen et al [26] compared 455 patients with level III–IV thrombus who underwent nephrectomy and IVC thrombectomy with and without CPB. OS did not differ significantly between both groups ($p = 0.18$). Orihashi et al [27] compared three interventions (single caval clamp without circulatory support, partial bypass, and circulatory arrest) for patients with level I–IV thrombus. They found no significant differences in operative deaths, 5-yr OS, local recurrence, blood loss, or blood transfusion requirements. Finally, in the study by Krishnamurthi et al [25], CPB was associated with significantly less bypass time ($p < 0.001$) and total operative time ($p = 0.004$) compared with DHCA for patients with thrombus extending to the right atrium. Fewer major complications were reported with CPB, although the differences were not statistically significant ($p = 0.17$).

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Table 2 – Summary of results for comparative studies

Study and year	Intervention	Comparator		Outcome	Baseline, *n*			Value			Reported *p* values	Notes
					Int		Com	Int	Com			
Chan et al., 2011 [22]	Preoperative renal artery embolisation	No preoperative renal artery embolisation		Overall survival	48		205	NR	NR		NR	14% lower risk of death in intervention group but did not reach statistical significance (HR 0.86, 95% CI 0.57–1.19)
				Operating time, min, median	48		205	350	250		0.008	
				Blood loss, ml, median	48		205	3000	1500		0.003	
				Perioperative mortality, %	48		205	8.4	3.4		NR	
				Hospital stay, d, median	48		205	11.5	8		<0.001	
Faust et al., 2013 [23]	Minimal access with circulatory arrest	Traditional median sternotomy		Operating time, min, median	49		21	478	540		0.056	Statistically significant differences in favour of intervention (no values reported) for hospital stay and post-operative mechanical ventilation
				Recurrence-free survival, yr*	49		21	1.2	0.59		0.06	
				Time to local recurrence, yr*	49		21	1.2	0.59		0.06	
				Wound infection, %	49		21	12.5	37.9		0.0135	
				Sepsis, %	49		21	0	14.3		0.0137	
				Hospital stay, d	49		21	NR	NR		<0.05	
				Postoperative mechanical ventilation, *n*	49		21	NR	NR		<0.05	
Klink et al., 2013 [24]	IVC thrombus removed en bloc	Resection of IVC thrombus		Operating time, min, mean	Level II	37	16	300	300		0.2	
					Level III	17	35	312	360		0.1	
					Level IV	6	41	325	402		0.7	
				Blood transfusion, units of blood	Level II	37	16	3	5		0.3	
					Level III	17	35	5	9		0.06	
					Level IV	6	41	6	14		0.4	
				Intraoperative tumour thrombus embolisation, n	Level II	37	16	0	3		NR	
					Level III	17	35					
					Level IV	6	41					
				Overall rate of intra- and postoperative complications	Level II	37	16	8	6		>0.2	
					Level III	17	35	7	15			
					Level IV	6	41	2	25			
Krishnamurthi et al., 2011 [25]	DHCA	CPB without CA	v-v bypass	Operating time, min, mean	DHCA	CPB no CA	v-v bypass	DHCA	CPB no CA	v-v bypass		
					53	44	10	480	420	NR	0.004	
				Bypass time, min	53	44	10	NR	NR	NR	<0.001	
				Perioperative mortality, *n* (%)	53	44	10	11 (21)	4 (8)	0 (0)	NR	
				Major postoperative complications, *n* (%)	53	44	10	17 (32)	8 (19)	NR	0.7	

Table 2 (*Continued*)

Study and year	Intervention	Comparator		Outcome	Baseline, *n*			Value			Reported *p* values	Notes
					Int	Com		Int	Com			
Nguyen et al., 2014 [26]	CA without CPB	CA with CPB		Overall survival, mo, median (95% CI)	305	150		24.6 (18.9–33.2)	26.6 (12.2–34.4)		0.180 (univariate analysis), 0.734 (multivariate analysis)	
				Cancer-specific survival, mo, median (95% CI)	305	150		29.1 (21.2–48.3)	39.4 (29.3–80.0)		0.704 (univariate analysis), 0.888 (multivariate analysis)	
				Operating time	305	150		NR	NR		26% longer in CPB patients; 0.002 (univariate analysis), 0.439 (multivariate analysis)	
				Complications	305	150		NR (fewer complications in CPB patients)	NR (fewer complications in CPB patients)		0.053 (univariate analysis), 0.457 (multivariate analysis)	
Orihashi et al., 2008 [27]	Single caval clamp without circulatory support	Partial bypass	CA	Operative deaths	13	8	15	1	1	0	NR	
				5-yr survival, %	13	8	15	52.9	58.3	51.6	NR	
				Local recurrence, *n* (%)	13	8	15	2 (15.4)	1 (12.5)	2 (13.3)	NR	
				Operating time, min*	13	8	15	335.2	429.4	545.7	0.0003	
				Blood loss, ml*	13	8	15	1796.2	2682.5	2170.9	NS	
				Blood transfusion, ml*	13	8	15				NS	
				Circulatory arrest, min, mean (range)	13	8	15	0	0	16.2 (3–40)	<0.0001	
Tang et al., 2014 [28]	PRAE	No PRAE		Overall survival, mo	46	94		43	57		0.666	
				Operating time, h*	46	94		4.5	3.5		0.001	
				Blood loss, ml	46	94		1000	475		0.002	
				Blood loss (patients with VCC above hepatic vein), ml	46	94		2000	5100		0.043	
				Blood transfusion (patients with VCC above hepatic vein), ml	46	94		1900	4425		0.028	

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Wotkowicz et al., 2006 [29]	Minimal access	Traditional median sternotomy	Operating time, median (range)	28	22	450 (270–761)	600 (285–995)	<0.001	
			Overall survival, yr, median	28	22	2.84	0.62	0.06; HR 2.02 (95% CI 0.97–4.72)	
			Blood transfusions, median (range)	28	22	5 (2–15)	11 (4–50)	0.002	
			Hospital stay, d, median (range)	28	22	5 (2–15)	26 (2–114)	0.007	
			CPB, min, median (range),	28	22	148 (86–265)	135 (50–217)	0.527	
			DHCA, min, median (range)	28	22	34 (17–62)	33 (12–90)	0.880	
			Ventilation support, min, median (range)	28	22	4 (1–46)	7 (1–110)	0.032	
			Perioperative complications (*n*)	22	28				
			• Respiratory			12	7	0.264	
			• Cardiac			12	13	0.741	
			• Renal			6	4	0.311	
			• Infectious			10	7	0.210	
			• Hepatic			7	5	0.331	
Yugisawa et al., 2013 [30]	Radical nephrectomy and IVC thrombectomy without IVC filter	Radical nephrectomy and IVC thrombectomy with IVC filter	Intraoperative pulmonary embolism, *n* (%)	29	25	3 (10.3)	0	NR	
Zhang et al., 2013 [31]	Traditional nephrectomy and IVC thrombectomy	Placement of IVC filter and application of liver mobilisation technique for tumour thrombus <2 cm above renal vein	1) Overall survival 2) Operating time (mins, mean) 3) Blood loss (ml, mean) 4) Need for blood transfusion (*n*) 5) Pneumonia 6) Metastasis incidence	36	11	NR	1) NR, 2) 170, 3) 400, 4) 2, 5) 0	0.0055 (overall survival)	6) Metastasis incidence: 15/37 in three comparator groups
		Placement of IVC filter and application of liver mobilisation technique for tumour thrombus below hepatic vein			19		1) NR, 2) 230, 3) 800, 4) 5, 5) 1		
		Placement of IVC filter and application of liver mobilisation technique for tumour thrombus above hepatic vein but below the diaphragm			12		1) NR, 2) 250, 3) 1000, 4) 5, 5) 0		

CA = circulatory arrest; CI = confidence interval; Com = Comparator; CPB = cardiopulmonary bypass; DHCA = deep hypothermic circulatory arrest; HR = hazard ratio; Int = Intervention; IVC = inferior vena cava; NR = not reported; NS = not significant; PRAE = preoperative renal artery embolisation; v-v = venovenous.

* Unclear if median or mean.

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Table 3 – Summary of results for case series

Study and year	Intervention	Outcome	Baseline, *n*		Value	Reported *p* values	Notes
Al Otaibi et al., 2009 [32]	Radical nephrectomy and thrombectomy	Overall 5-yr survival (%)	50		47	NA	
		Disease-free 5-yr survival, %			35		
		Local recurrence			5 (3 with level IV, 2 with level II thrombus)		
		Time to local/distant recurrence, mo, median			10		
		Perioperative complications, *n*			8		
		30-d mortality			2 (1 had level II, 1 had level III)		
Kim et al., 2012 [33]	Radical nephrectomy and thrombectomy	Blood loss, ml, median	Level 0	357	500	<0.001	The *p* values refer to different thrombus levels
			Level I	78	1050		
			Level II	113	1500		
			Level III	47	2000		
			Level IV	45	3200		
		30-d morbidity, *n*	Level 0	357	19 (5%)	<0.001	
			Level I	78	11 (14%)		
			Level II	113	26 (23%)		
			Level III	47	17 (36%)		
			Level IV	45	21 (47%)		
		90-d morbidity, *n*	Level 0	357	117 (33%)	0.26	
			Level I	78	27 (35%)		
			Level II	113	45 (40%)		
			Level III	47	21 (45%)		
			Level IV	45	20 (44%)		
		Hospital stay, d, median	Level 0	357	7	<0.001	
			Level I	78	7		
			Level II	113	7		
			Level III	47	8		
			Level IV	45	10		
Kulkarni et al., 2012 [34] and 2007 [35]	Radical nephrectomy and thrombectomy	Overall 5-yr survival, %	100		63	NA	
		30-d mortality, *n*	100		2		
		90-d mortality, n	100		2		
		Operating time, min, mean	Abdominal incision	72	246		
			Plus sternotomy	20	318		
			Plus sternotomy and CBP	8	408		
		Need for blood transfusion, U, mean	Abdominal incision	72	3.1		
			Plus sternotomy	20	3.8		
			Plus sternotomy and CBP	8	5.6		
		Hospital stay, d, median	Abdominal incision	72	8.2		
			Plus sternotomy	20	10.6		
			Plus sternotomy and CBP	8	12.2		
		Disease-free rate, %	100		55		
		Death due to metastasis within 5 yr, *n*	100		30		
Moinzadeh and Libertino, 2004 [7]	Radical nephrectomy and thrombectomy	5-yr cancer-specific survival, % (SE)	Level I	46	52.7 (8.5)	0.4874	The *p* values refer to different thrombus levels (for level I cavotomy and reconstruction was performed and for level II–III CA with CPB)
			Level II	14	38.9 (17.3)		
			Level III	17	29.0 (16.2)		
		10-yr cancer-specific survival, % (SE)	Level I	46	30.4 (8.7)	0.4874	
			Level II	14	19.4 (16.3)		
			Level III	17	29.0 (16.2)		

CA = circulatory arrest; CPB = cardiopulmonary bypass; NA = not applicable; SE = standard error.

3.4.1.4. Inferior vena cava filter versus no inferior vena cava filter. Yagisawa et al [30] compared radical nephrectomy and IVC thrombectomy with and without IVC filter and measured the number of intraoperative pulmonary embolisms (IPEs). Three IPEs occurred in the no IVC filter group, and none occurred in the filter group (10.3% vs 0%, respectively); however, the p value was not stated. Similarly, in another study [31], patients implanted with IVC filter did not show any symptoms of tumour embolism perioperatively, but the p value was not stated.

3.4.1.5. Liver mobilisation technique versus traditional radical nephrectomy and inferior vena cava thrombectomy. Zhang et al [31] compared traditional radical nephrectomy and IVC thrombectomy with a liver mobilisation technique and temporary IVC filter placement and concluded that OS was higher with liver mobilisation ($p = 0.0055$). It must be also noted that the authors found that tumour thrombus size and position was associated with OS ($p = 0.0185$).

3.4.1.6. En bloc versus transected techniques for inferior vena cava thrombus. Klink et al [24] compared patients in whom the thrombus was purposely transected with those in whom the IVC thrombus was removed en bloc with the kidney. The overall rate of complications was not statistically significantly different ($p > 0.2$) between the en bloc and transected groups.

3.4.2. Data from case series

Table 3 summarises the outcome results for all four case series [7,32–34].

3.4.2.1. Evaluation of surgical management of renal cell carcinoma with vena caval thrombus. Four case series [7,32–34] evaluated the surgical management of RCC with VCT. Kulkarni et al [34] reported that 5-yr OS and disease-free survival (DFS) were 63% and 55%, respectively. The authors also noted that pathologic factors such as stage and grade of tumour, rather than clinical factors such as level of thrombus, influenced survival, confirming another study [7] that reported that cephalad extension of tumour thrombus does not affect CSS ($p = 0.4874$ for 5- and 10-yr CSS). Al Otaibi et al [32] reported that 5-yr OS and DFS were 47% and 35%, respectively, and suggested that although the level of the thrombus might affect the recurrence rate, it had no impact on OS. Finally, in another study with 640 patients [33], patients with higher levels of VTT were more likely to experience early complications ($p < 0.001$), but there was no statistically significant difference in late complications.

3.5. Discussion

3.5.1. Principal findings

The main objective of the review was to synthesise evidence regarding the benefits of the different surgical techniques in treating VCT from nonmetastatic RCC. Eligible studies mainly reported on preoperative strategies, surgical access, and circulatory bypass procedures; apart from four case series, no comparative studies assessed the benefits or harms of surgical excision of VCT.

In terms of surgical access, MA techniques appeared to have better perioperative and recovery outcomes than TMS, but it is not known if these differences are important oncologically. In addition, whether IVC thrombectomy is performed simultaneously with the kidney removal (en bloc) or after it does not appear to influence perioperative outcomes [24]; however, there was clinical heterogeneity between the groups, with the thrombus level and clinical stage lower in the en bloc group.

In considering data on circulatory bypass procedures, one study [27] found no significant difference in outcomes between CPB with DHCA or partial bypass under normothermia or single caval clamp without circulatory support; however, results from this study should be interpreted with caution due to clinical heterogeneity. CPB with DHCA was performed in patients with significantly higher levels of tumour extension, introducing a high risk of indication bias. When the effect of use of CPB was evaluated in patients with level III–IV tumour thrombus, it did not significantly affect CSS or OS [26], and in patients with thrombus extending to the right atrium, CPB resulted in improved perioperative outcomes compared with DHCA [25].

Regarding PRAE, data from two studies [22,28] showed that it had no oncologic benefits and resulted in significantly worse perioperative and recovery outcomes, including possibly higher perioperative mortality shown in one study [22]. In the study by Tang et al [28], however, PRAE demonstrated a benefit for patients with advanced tumour thrombus (above the hepatic vein) in reducing intraoperative blood loss and blood transfusion. These results coincide with those of a previous study [36] that found no measurable advantage with PRAE in patients with nonmetastatic and metastatic RCC with VCT, but PRAE was associated with increased complications. Consequently, the available data suggest that PRAE does not appear to have an adjunct role prior to surgery, although it might be considered for patients with advanced tumour thrombus.

With regard to the use of an IVC filter in reducing IPE, the findings from one study [30]—available only as an abstract and involving cohorts from different time periods—are of doubtful clinical and statistical significance. Moreover, in 8% of patients in the IVC filter group, the filter could not be removed from the sheath because of tumour thrombus incorporation requiring intervention with cavotomy to extract the filter. For this reason, other authors have recommended avoiding the insertion of IVC filters [8,15,16]. Conversely, another study [31] suggested that temporary IVC filter placement is a feasible method of avoiding tumour thrombus embolism. These results have unclear clinical and statistical significance because no data are available for the control cohort, and in the experimental cohort, a different surgical technique for IVC thrombectomy was used. In summary, there was no strong evidence to support the use of IVC filters, although data from better designed prospective studies would be required to either confirm or refute this assertion.

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Last, data from several large case series ($n > 50$ patients) concerning surgical management of RCC with VCT suggest that surgical treatment can be associated with meaningful oncologic benefits, although it is technically complex and challenging; however, the quality of the evidence was poor.

3.5.2. *Do patients with nonmetastatic renal cell carcinoma and vena caval thrombus derive benefit from surgical excision of the thrombus? If so, how does surgery influence prognosis?*

This systematic review revealed several important knowledge gaps in the evidence base. We were unable to identify any high-quality evidence that addresses the question of whether patients with nonmetastatic RCC and VCT derive a benefit from surgery to remove the thrombus and how thrombectomy influences prognosis from an oncologic perspective. Currently, aggressive surgical treatment is acknowledged as the only potentially curative treatment [2,3,10,37], provided that complete tumour thrombus removal can be achieved [38,39]. The justification for such an approach is based on relatively low levels of evidence; single-arm case series of patients who underwent surgery for VCT often showed comparable survival outcomes with corresponding TNM-stage patients without VCT. In a matched-pair analysis of patients with RCC and VCT and patients with RCC without VCT, Kuczyk et al [40] concluded that a radical surgical approach is essential as standard therapy for the treatment of patients with RCC and VCT.

Nevertheless, in the absence of any reliable comparative data, it remains unclear to what extent surgical treatment of VCT influences prognosis. In addition, there appear to be contradictory data regarding the extent of thrombus removal, with some studies showing that complete removal of IVC tumour thrombus did not affect patient prognosis [7,37]. These conflicting data demonstrate the need for better quality prospective studies involving different tumour stages, appropriate stratification of patients based on relevant confounding factors, and various surgical approaches with long-term follow-up to answer these questions more definitively.

3.5.3. *Is there a strategy that optimises patient selection for surgery to remove inferior vena cava vena caval thrombus?*

No eligible study addressed this question. The prognostic value of IVC involvement has been a controversial topic, and although it has been extensively evaluated, there is still a considerable degree of uncertainty. In many studies, there is little or no correlation between the level of tumour thrombus within the IVC and OS or DSS [7,11,41–43], whereas other studies identified IVC thrombus as a negative prognostic factor [5,31,37,44,45]. In the context of nonmetastatic disease with isolated VTT, the 5-yr CSS ranged between 18% and 68% after surgical resection [2,4]. Although surgery for IVC tumour thrombus can be curative in many patients, a large proportion of patients develop recurrence and progressive disease [6,32]. In this regard, a prognostication system that combines the various independent prognostic factors, such as the University of California Los Angeles Integrated Staging System [46], may better predict the outcomes following surgery and thereby facilitate patient selection for surgery.

3.5.4. *What is the most appropriate surgical approach or strategy relevant to each thrombus level?*

The objectives of surgery include complete resection of the primary tumour and VTT while averting tumour embolism, maintaining haemodynamic stability, minimising blood loss, and circumventing organ ischaemia. Data from included studies suggest that the surgical method appears to be dependent on the level of the tumour thrombus and the grade of occlusion of the IVC [23,27,29,32,34]; however, the question of which approach is best for each thrombus level was not appropriately addressed by any of the included studies.

Based on conventional wisdom and traditional dicta, for level I tumour thrombus, minimal modifications of the standard surgical approach are usually required [11]. Level II thrombus can be managed with occlusion of the IVC below and above the thrombus in the IVC and the contralateral renal vein including occlusion of lumbar veins entering the IVC and can generally be resected without bypass [11]. For level III thrombus, the surgery is more demanding, with more complex dissections of IVC and the liver. For level IV thrombus, the optimal management is still debatable; traditionally, CPB with or without DHCA has been used in those patients [47,48] but seems to be associated with a high risk of blood loss, coagulopathy, and longer operating times [39,49]. In our review, however, one study [26] found no evidence that CPB was associated with higher surgical complications or longer hospital stay and concluded that, from an oncologic perspective, use of CPB is safe for the treatment of patients with RCC and level III–IV tumour thrombus. Studies suggesting that non-CPB approaches are feasible [39,50–52] have also been reported. Venovenous bypass is another alternative method that has been used in selected cases and has been associated with decreased intraoperative blood loss and operating times compared with CPB [53].

In summary, although data representing low levels of evidence exist, it must be acknowledged that due to the paucity of comparative data, the relative benefits and harms of these different techniques and approaches and how they vary according to different thrombus levels remain unclear.

3.5.5. *Strengths and limitations of the review*

The strengths of this review are the systematic, transparent, and robust approach taken to examine the evidence base; the use of Cochrane review methodology throughout, including the assessment of RoB and confounding, which are essential to any review involving NRCSs and case series; and adherence to PRISMA guidelines. The search strategy was complemented by additional sources for potentially important articles, including an expert panel (EAU RCC guideline panel) because the work was undertaken as part of the panel's guideline update for 2016. This approach ensured a comprehensive review of the literature while maintaining methodological rigour and enabled the authors

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to put into clinical context the relevance and implications of the review findings.

The major limitation of this review is that all studies were retrospective and had high risks of bias and confounding. This review highlights the lack of high-quality and reliable evidence for the management of VCT in patients with nonmetastatic RCC.

3.5.6. How does this systematic review compare with other recent systematic reviews?

The EAU has issued some guidance on the management of patients with RCC and VCT, based on the present systematic review findings [54].

A host of literature surrounds surgical techniques relating to the resection of RCC with VCT, but the vast majority of published reviews are narrative in nature and use unspecified or nonstandardised methodology. In a narrative review article by Pouliot et al [15], the authors reviewed a multitude of aspects, including surgical treatment options, to create an algorithm for deciding on the type of surgical treatment for VCT. One of their conclusions suggested that PRAE should be used only as a palliative procedure in poor surgical candidates or when the renal hilum is full of disease. The authors also advised against preoperative IVC filters except in cases in which the IVC is completely and chronically occluded.

Woodruff et al [16] established a multidisciplinary perioperative protocol for patients with RCC and VCT. One of their conclusions was that such patients should not be offered IVC filters as much as possible because there is the potential for caval thrombosis, which can make surgical resection more challenging. These conclusions are similar to those of Lawindy et al [13], who also did not support preoperative IVC placement. In addition, Lawindy et al suggested that the surgical approach should be tailored to the individual patient as well as the level of the IVC tumour thrombus. Based on a narrative review, Margulis et al [14] recommended that routine renal artery embolisation prior to radical nephrectomy should not be advocated.

Recently, the results of the International Renal Cell Carcinoma–Venous Thrombus Consortium [45] were published. The authors concluded that tumour thrombus level is an independent survival predictive factor and that for patients with level III–IV tumour thrombus, surgical treatments with or without CPB are equally effective oncologically. There was no reliable conclusion about the role of PRAE.

4. Conclusions

The surgical management of patients with nonmetastatic RCC and VCT is complex, yet complete surgical resection appears to be the only potentially curative intervention. This systematic review set out to determine the evidence base with regard to the comparative effectiveness and harms of the multitude of surgical techniques and approaches in dealing with this condition. Traditional surgical dicta concerning the management of VCT indicate that patients with nonmetastatic RCC and VCT and acceptable performance status should be considered for surgical intervention, regardless of VCT level. Although the most appropriate or efficacious surgical technique remains unclear, it should be selected judiciously for each case based on the level of tumour thrombus. The review findings reveal an evidence base derived from retrospective studies and case series with significant risks of bias and confounding, and there was a serious lack of prospective comparative studies. Future research must endeavour to carefully design prospective comparative studies with experimental designs and use of appropriate controls to ascertain which surgical technique offers the best outcomes. Even in the absence of RCTs, the field can benefit from well-designed, prospective NRCSs based on sound methodological principles [55]. Until then, it seems prudent to make treatment decisions on a case-by-case basis, relying on a combination of likely prognostic variables within the context of a multidisciplinary team.

Author contributions: Thomas B.L. Lam had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lam, Ljungberg, Bex.
Acquisition of data: Lardas, Stewart, Scimgeour, Lam.
Analysis and interpretation of data: Lardas, Stewart, Scimgeour, Lam, Ljungberg.
Drafting of the manuscript: Lardas, Lam.
Critical revision of the manuscript for important intellectual content: Lardas, Stewart, Scimgeour, Lam, Ljungberg, Bex, Volpe, Canfield, Staehler, Hora, Powel, Merseburger, Kuczyk, Bensalah, Mulders, Hofmann, Marconi, Dabestani.
Statistical analysis: Lardas, Lam.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Lam, Ljungberg, Bex.
Other (specify): None.

Financial disclosures: Thomas B.L. Lam certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: A. Bex has received company speaker honoraria and grants/research support from Pfizer, has participated in trials for Pfizer Europe, has participated on advisory boards for GSK and Novartis, and has been a company consultant for Pfizer and Novartis. S. Canfield has received company speaker honoraria from Amgen, Genomic Health, Algeta, and Bayer. M. Staehler has been a company consultant for Pfizer, Novartis, GSK, Roche, Astellas, and Bayer; has received company speaker honoraria from Pfizer, Novartis, GSK, Roche, Astellas, Bayer, and Aveo; has participated in trials for Pfizer, Novartis, GSK, Roche, Bayer, Aveo, Wilex, and Immatics; has received fellowship and travel grants from Pfizer, Novartis, GSK, Roche, and Bayer; and has received grants/research support from Pfizer, Novartis, GSK, Roche, Bayer, and Aveo. M. Hora has received company speaker honoraria from Covidien, Olympus, Janssen, and Astellas; has participated in trials for Janssen; and has received grants/research support from Ipsen. T. Powles has been a company consultant for and has received grants/research support fromt Novartis, Pfizer, and GSK; has received company speaker honoraria from Novartis, Pfizer, GSK, and Genentech; and has participated in trials for GSK, Pfizer, BMS, Genentech, and Genetech. A. Merseburger has been a company consultant for Ipsen Pharma, Bayer, Astellas, Janssen Cilag, Novartis, and Pfizer; has received company speaker honoraria from

Ipsen Pharma, Wyeth, Astellas, Novartis, Pfizer, and SEP; has participated in trials for AstraZeneca, Bayer, Pfizer, TEVA, Novartis, and Astellas; has received grants/research support from Wyeth; and has participated in a company-sponsored speakers bureau for TEVA, Janssen, Pfizer, Astellas, Ferring, and Novartis. M.A. Kuczyk is a stock shareholder of Bayer Healthcare, Astellas, Storz, Pfizer, Wyeth, and Novartis; is a company consultant for Karl Storz, Coloplast, AstraZeneca, Astellas, Storz, and Hexal AG; has received company speaker honoraria from Pfizer, Astellas, Bayer, GSK, Pierre Fabre, and Jansen Cilag & Hexal; has participated in trials for the Protect study; Millenium Study C21004, Millenium Study C21005, Astellas, Ipsen, and Janssen; and has received grants/research support from Wyeth and Pfizer. K. Bensalah has received grants/research support from Pfizer and has received honoraria or consultation fees from Intuitive Surgical. P.F.A. Mulders has received company speaker honoraria from Astellas, Pfizer, Novartis, GSK, AstraZeneca, J&J, and Bayer; has participated in trials for Astellas, Pfizer, GlaxoSmithKline, J&J, Millenium, and Provenge; has received grants/research support from Astellas, Wilex, GlaxoSmithKline, Pfizer, and Bayer. B. Ljungberg has received company speaker honoraria from GlaxoSmithKline, Roche, Pfizer, and Novartis; has participated in trials for GlaxoSmithKline, Medivation, Pfizer, and Janssen R&D, Inc.; and has served on advisory boards for Pfizer and GSK. T. Lam is a company consultant for and has received company speaker honoraria from Pfizer, GSK, Astellas, and Ipsen. The other authors have nothing to disclose.

Funding/Support and role of the sponsor: None.

Appendix 1. Search strategies used

Databases
Medline 1946 to January 2015
Medline In-Process 20 January 2015
Embase 1974 to 2015 January week 3

Ovid multifile search
URL: http://shibboleth.ovid.com

1. ((thrombus or thrombi or tumo?r$ or neoplas$) adj2 (vena cava or IVC or caval or intravascular or venous)).tw.
2. exp thrombectomy/
3. (((surgery or surgical) adj3 (thrombus or thrombi)) or thrombectomy).tw.
4. or/1-3
5. kidney carcinoma/ use oemezd
6. renal cell carcinoma/ use prmz
7. ((kidney or renal) adj3 (carcinoma$ or cancer$ or tumo?r$ or neoplas$ or mass or masses)).tw.
8. or/5-7
9. comparative study/ use prmz
10. follow-up studies/ use prmz
11. major clinical study/ use oemezd
12. controlled study/ use oemezd
13. clinical trial/ use oemezd
14. (chang$ or evaluat$ or baseline).tw.
15. (prospective$ or retrospective$).tw.
16. (compara$ or compare$).tw.
17. exp clinical trial/
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomization/
21. randomi?ed.ab.
22. randomly.ab.
23. trial.ab.
24. groups.ab.
25. or/9-24
26. 4 and 8 and 25
27. exp animals/ not humans/
28. 26 not 27
29. 28 not (comment$ or letter or editorial or case report).pt.
30. limit 29 to yr="2000 -Current"
31. remove duplicates from 30

Cochrane Database of Systematic Reviews: Issue 1, January 2015
URL: www.thecochranelibrary.com

1. MeSH descriptor: [Carcinoma, Renal Cell] this term only
2. (kidney or renal) near/2 (cancer* or carcinoma* or neoplasm* or tumor* or tumour*)
3. #1 or #2
4. (thrombus or thrombi or tumor* or tumour* or neoplas*) near/2 (vena cava or IVC or caval or intravascular or venous)
5. MeSH descriptor: [Thrombectomy] this term only
6. (surgery or surgical) near/3 (thrombus or thrombi)
7. thrombectomy
8. #4 or #5 or #6 or #7
9. #3 and #8

Science Citation Index (1970 to 21st January 2015)
Conference Proceedings Citation Index – Science (1990 to 21st January 2015)
URL: www.isiknowledge.com

1. TS=((kidney or renal) near/3 (cancer or carcinoma or neoplasm* or tumor* or tumour*))
2. TS=((thrombus or thrombi or tumor* or tumour* or neoplas*) SAME (vena cava or IVC or caval or intravascular or venous))
3. TS=thrombectomy
4. TS=((surgery or surgical) near/3 (thrombus or thrombi))
5. #4 OR #3 OR #2
6. TS=(trial or compara* or random* or compare* or retrospectiv* or prospective*)
7. #1 and #5 and #6. Timespan=2000-2013

Trials registries (searched January 2015)
US National Institutes of Health
http://clinicaltrials.gov/
World Health Organisation
http://apps.who.int/trialsearch/AdvSearch.aspx

References

[1] Gupta K, Miller JD, Li JZ, et al. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev 2008;34:193–205.
[2] Bissada NK, Yakout HH, Babanouri A, et al. Long-term experience with management of renal cell carcinoma involving the inferior vena cava. Urology 2003;61:89–92.
[3] Kaplan S, Ekici S, Dogan R, et al. Surgical management of renal cell carcinoma with inferior vena cava tumor thrombus. Am J Surg 2002;183:292–9.

[4] Neves RJ, Zincke H. Surgical treatment of renal cancer with vena cava extension. Br J Urol 1987;59:390–5.
[5] Haferkamp A, Bastian PJ, Jakobi H, et al. Renal cell carcinoma with tumor thrombus extension into the vena cava: prospective long-term followup. J Urol 2007;177:1703–8.
[6] Kirkali Z, Van Poppel H. A critical analysis of surgery for kidney cancer with vena cava invasion. Eur Urol 2007;52:658–62.
[7] Moinzadeh A, Libertino JA. Prognostic significance of tumor thrombus level in patients with renal cell carcinoma and venous tumor thrombus extension. Is all T3b the same? J Urol 2004;171:598–601.
[8] Blute ML, Boorjian SA, Leibovich BC, et al. Results of inferior vena caval interruption by greenfield filter, ligation or resection during radical nephrectomy and tumor thrombectomy. J Urol 2007;178:440–5.
[9] Craven WM, Redmond PL, Kumpe DA, et al. Planned delayed nephrectomy after ethanol embolization of renal carcinoma. J Urol 1991;146:704–8.
[10] Wein AJ, Kavoussi LR, Campbell MF. Campbell-Walsh Urology. Philadelphia, PA: Elsevier; 2012.
[11] Blute ML, Leibovich BC, Lohse CM, et al. The Mayo Clinic experience with surgical management, complications and outcome for patients with renal cell carcinoma and venous tumour thrombus. BJU Int 2004;94:33–41.
[12] Wotkowicz C, Wszolek MF, Libertino JA. Resection of renal tumors invading the vena cava. Urol Clin North Am 2008;35:657–71.
[13] Lawindy SM, Kurian T, Kim T, et al. Important surgical considerations in the management of renal cell carcinoma (RCC) with inferior vena cava (IVC) tumour thrombus. BJU Int 2012;110:926–39.
[14] Margulis V, Master VA, Cost NG, et al. International consultation on urologic diseases and the European association of urology international consultation on locally advanced renal cell carcinoma. Eur Urol 2011;60:673–83.
[15] Pouliot F, Shuch B, Larochelle JC, et al. Contemporary management of renal tumors with venous tumor thrombus. J Urol 2010;184:833–41.
[16] Woodruff DY, Van Veldhuizen P, Muehlebach G, et al. The perioperative management of an inferior vena caval tumor thrombus in patients with renal cell carcinoma. Urol Oncol 2013;31:517–21.
[17] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.
[18] Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions, version 5.0.2. Cochrane Collaboration Web site. http://www.cochrane-handbook.org/. Accessed April 2015.
[19] Reeves B, Deeks J, Higgins J, et al. Chapter 13: including non-randomised studies. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions version 5.0.2. Cochrane Col laboration Web site. http://www.cochrane-handbook.org/. Accessed February 2014.
[20] Viswanathan M, Ansari M, Berkman N, et al. Assessing the risk of bias of individual studies in systematic reviews of health care interventions. Agency for Healthcare Research and Quality Web site. http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=998&pageaction=display product. Accessed July 2015.
[21] Dalziel K, Round A, Stein K, et al. Do the findings of case series studies vary significantly according to methodological characteristics? Health Technol Assess 2005;9:1–146.
[22] Chan AA, Abel J, Carrasco A, et al. Impact of preoperative renal artery embolization on surgical outcomes and overall survival in patients with renal cell carcinoma and inferior vena cava thrombus. J Urol 2011;185(Suppl):e707–8.
[23] Faust W, Ruthazer R, Topjian L, et al. Minimal access versus median sternotomy for cardiopulmonary bypass in the management of renal cell carcinoma with vena caval and atrial involvment. J Urol 2013;189(Suppl.):e255.
[24] Klink JC, Westesson KE, Gao T, et al. Tumor thrombus transection in renal cell carcinoma. J Clin Oncol 2013;31:4090.
[25] Krishnamurthi V, Subramanian V, Berglund R, et al. Contemporary vascular bypass approach for treatment of retroperitoneal tumors with inferior vena cava and atrial extension: A 20-year single institution experience. Urology 2011;78:S71–2.
[26] Nguyen H, Tilki D, Dall'Era M, et al. Does the use of cardiopulmonary by-pass (CPB) impact survival in patients undergoing nephrectomy/level III-IV tumor thrombectomy? A multi-institutional analysis. J Urol 2014;191:e645–6.
[27] Orihashi K, Sueda T, Usui T, et al. Deep hypothermic circulatory arrest for resection of renal tumor in the inferior vena cava: beneficial or deleterious? Circ J 2008;72:1175–7.
[28] Tang Q, Li X, Song Y, et al. Application of preoperative renal artery embolization in patients with renal cell carcinoma and venous tumor thrombus: an effective preoperative adjuvant therapy for patients with advanced tumor thrombus. Eur Urol Suppl 2014;13:e938.
[29] Wotkowicz C, Libertino JA, Sorcini A, et al. Management of renal cell carcinoma with vena cava and atrial thrombus: minimal access vs median sternotomy with circulatory arrest. BJU Int 2006;98:289–97.
[30] Yagisawa T, Kondo T, Yoshida K, et al. Usefulness of temporary inferior vena cava filter in preventing intraoperative pulmonary embolism for patients with renal cell carcinoma extending into inferior vena cava thrombus. J Urol 2013;189(Suppl):e783–4.
[31] Zhang JP, Zhu Y, Liu YJ, et al. Temporary filters and liver mobilization technique improve the safety and prognosis of radical nephrectomy and inferior vena cava thrombectomy in renal cell carcinoma with subdiaphragmatic thrombosis. Urol Int 2013;91:279–84.
[32] Al Otaibi M, Youssif TA, Alkhaldi A, et al. Renal cell carcinoma with inferior vena caval extention: Impact of tumour extent on surgical outcome. BJU Int 2009;104:1467–70.
[33] Kim S, Boorjian S, Thompson RH, et al. Complications and outcomes for patients with renal cell carcinoma and venous tumor thrombus: results from the Mayo Clinic. J Urol 2012;187:e726–7.
[34] Kulkarni J, Jadhav Y, Valsangkar RS. IVC thrombectomy in renal cell carcinoma-analysis of out come data of 100 patients and review of literature. Indian J Surg Oncol 2012;3:107–13.
[35] Kulkarni JN, Acharya PU, Rizvi SJ, et al. Surgical management of renal cell carcinoma with inferior vena caval thrombus: a teaching hospital experience. Indian J Cancer 2007;44:45–50.
[36] Subramanian VS, Stephenson AJ, Goldfarb DA, et al. Utility of preoperative renal artery embolization for management of renal tumors with inferior vena caval thrombi. Urology 2009;74: 154–9.
[37] Skinner DG, Pritchett TR, Lieskovsky G, et al. Vena caval involvement by renal cell carcinoma: surgical resection provides meaningful long-term survival. Ann Surg 1989;210:387–94.
[38] Hatcher PA, Anderson EE, Paulson DF, et al. Surgical management and prognosis of renal cell carcinoma invading the vena cava. J Urol 1991;145:20–4.
[39] Nesbitt JC, Soltero ER, Dinney CPN, et al. Surgical management of renal cell carcinoma with inferior vena cava tumor thrombus. Ann Thorac Surg 1997;63:1592–600.
[40] Kuczyk MA. Prognostic relevance of intracaval neoplastic extension for patients with renal cell cancer. Br J Urol 1997;80:18–24.
[41] Lambert EH, Pierorazio PM, Shabsigh A, et al. Prognostic risk stratification and clinical outcomes in patients undergoing surgical treatment for renal cell carcinoma with vascular tumor thrombus. Urology 2007;69:1054–8.
[42] Wagner B, Patard JJ, Mejean A, et al. Prognostic value of renal vein and inferior vena cava involvement in renal cell carcinoma. Eur Urol 2009;55:452–60.
[43] Ljungberg B, Stenling R, Osterdahl B, et al. Vein invasion in renal cell carcinoma: impact on metastatic behavior and survival. J Urol 1995;154:1681–4.

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[44] Kim HL, Zisman A, Han KR, et al. Prognostic significance of venous thrombus in renal cell carcinoma. Are renal vein and inferior vena cava involvement different? J Urol 2004;171:588–91.
[45] Martinez-Salamanca JI, Linares E, Gonzalez J, et al. Lessons learned from the International Renal Cell Carcinoma-Venous Thrombus Consortium (IRCC-VTC). Curr Urol Rep 2014;15:404.
[46] Zisman A, Pantuck AJ, Dorey F, et al. Improved prognostication of renal cell carcinoma using an integrated staging system. J Clin Oncol 2001;19:1649–57.
[47] Novick AC, Kaye MC, Cosgrove DM, et al. Experience with cardiopulmonary bypass and deep hypothermic circulatory arrest in the management of retroperitoneal tumors with large vena caval thrombi. Ann Surg 1990;212:472–6.
[48] Stewart JR, Carey JA, McDougal WS, et al. Cavoatrial tumor thrombectomy using cardipulmonary bypass without circulatory arrest. Ann Thorac Surg 1991;51:717–22.
[49] Tsuji Y, Goto A, Hara I, et al. Renal cell carcinoma with extension of tumor thrombus into the vena cava: surgical strategy and prognosis. J Vasc Surg 2001;33:789–96.
[50] Kemmer H, Siemer S, Stockle M. Nephrectomy, work bench surgery, and autotransplantation: a case of a solitary left kidney with an extensive centrally located renal cell carcinoma and a tumour thrombus entering the vena cava. Eur Urol 2007;52:1518–20.
[51] Zini L, Koussa M, Haulon S, et al. Results of endoluminal occlusion of the inferior vena cava during radical nephrectomy and thrombectomy. Eur Urol 2008;54:778–84.
[52] Ciancio G, Gonzalez J, Shirodkar SP, et al. Liver transplantation techniques for the surgical management of renal cell carcinoma with tumor thrombus in the inferior vena cava: step-by-step description. Eur Urol 2011;59:401–6.
[53] Granberg CF, Boorjian SA, Schaff HV, et al. Surgical management, complications, and outcome of radical nephrectomy with inferior vena cava tumor thrombectomy facilitated by vascular bypass. Urology 2008;72:148–52.
[54] Ljungberg B, Bensalah K, Bex A, et al. Guidelines on renal cell carcinoma. European Association of Urology Web site. http://uroweb.org/wp-content/uploads/EAU-Guidelines-Renal-Cell-Cancer-2015-v2.pdf. Accessed August 2015.
[55] McCulloch M, Altman DG, Campbell WB, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet 2009;374:1105–12.

Please cite this article in press as: Lardas M, et al. Systematic Review of Surgical Management of Nonmetastatic Renal Cell Carcinoma with Vena Caval Thrombus. Eur Urol (2015), http://dx.doi.org/10.1016/j.eururo.2015.11.034