SURGICAL MANAGEMENT, STAGING AND OUTCOMES OF WILMS TUMOURS WITH INTRAVASCULAR EXTENSION – RESULTS OF THE IMPORT STUDY.

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List of abbreviations

WT	Wilms tumour
cenRR	Central radiology review
cenPR	Central pathology review
CT	Computed tomography
CRF	Case report form
CCLG	Children's Cancer and Leukemia group
IMPORT	Improving Population Outcomes for Renal Tumours of Childhood
SIOP	International Society of Pediatric Oncology
RTSG	Renal Tumour Study Group
COG	Children's Oncology Group
MDT	Multidisciplinary team
IC	Intracardiac
SH	Suprahepatic
RH	Retrohepatic
IH	Infrahepatic
IVC	Inferior vein cava
RV	Renal vein
EFS	Event free survival
OS	Overall survival
CPB	Cardiopulmonary bypass
A	Actinomycin

V	Vincristine
D	Doxorubicin
CI	Confidence interval

ABSTRACT

Purpose: to review surgical management, tumour stage and clinical outcomes in children with intravascular extension of Wilms tumour (WT) registered in a national clinical study (2012-19).

Methods: WTs with presence/suspicion of tumour thrombus in the renal vein (RV) or beyond on radiology, surgery or pathology case report forms were identified. Only cases where thrombus was confirmed by surgeon and/or reference pathologist were included. Surgical management, disease stage, overall (OS) and event free survival (EFS) were investigated.

Results: 69/583 (11.8%) patients met the inclusion criteria. Forty-six (67%) had abdominal stage III due to thrombus-related reasons: 11 had macroscopically incomplete resection, including 8 cases where cavotomy was not performed; 20 had piecemeal complete resection of thrombus; 15 had microscopically positive resection margins at the RV. 66% of tumour thrombi contained viable tumour. There were eight relapses and five deaths. EFS, but not OS, was significantly associated with completeness of surgical resection ($P<0.05$). OS and EFS were also significantly associated with histological risk group ($P<0.05$) but not with viability of tumour thrombus ($P=0.19$; $P=0.59$).

Conclusions: WTs with intravascular extension have a high risk of local stage III due to thrombus-related reasons. Controlled complete removal of the thrombus should be the aim of surgery

Keywords: Wilms tumor, thrombus, surgery, local stage, outcomes.

1. INTRODUCTION

Wilms tumour (WT) with intravascular extension to the renal vein (RV) and inferior vena cava (IVC) is reported in 10% of cases [1 - 3]. Further extension of the thrombus to the right atrium is rare (1% - 3%) [4 - 7]. To avoid radiotherapy with increased risks of long term sequelae, complete resection is required but may be challenging [8 - 10]. The Children's Cancer and Leukaemia Group (CCLG) and the International Society of Pediatric Oncology Renal Tumour Study Group (SIOP-RTSG) recommend pre-nephrectomy chemotherapy to facilitate shrinkage of the tumour thrombus and facilitate removal [1, 4]. However, prolonged pre-operative treatment, beyond 4 weeks, has not been shown to produce additional shrinkage [11]. The Children's Oncology Group (COG), who generally advocate an immediate surgery approach to WT, recommend use of pre-operative chemotherapy in cases with intravascular extension (intra-hepatic level and above), in order to reduce the known higher rate of surgical complications [12, 13, 14].

Surgical options for removing thrombus include en-bloc resection with the tumour, cavotomy/cavectomy with or without cardio-pulmonary bypass (CPB), especially when the tumour extends to the atrium [4, 6, 14 – 19]. However, removal of thrombus is often piecemeal due its adherence to the vascular endothelium [12], which by the current SIOP staging system results in a local stage III [20] demanding subsequent flank radiotherapy.

The aim of our study was to review reasons for local stage in relation to surgical management in children with WT and intravascular extension beyond the kidney in the Improving Population Outcomes for Renal Tumours of Childhood (IMPORT) study. We also investigated how completeness of surgical resection, histological risk and viability of tumour thrombus correlate with clinical outcomes.

2. PATIENTS AND METHODS

The IMPORT study is a prospective clinical study of imaging and molecular biomarkers in children treated according to current standards of care defined by the results of the SIOP Renal Tumour Study Group. It aims to maintain the success of first line therapy whilst improving risk stratification to reduce the burden of therapy for the overall population of children with WT.

It opened in Sept 2012 and registered 687 paediatric patients (0-18 years) with a renal tumour from the 20 paediatric oncology centers in the UK and Ireland until December 2019, the cut-

off for inclusion in this analysis. Among these, 583 were patients with a newly diagnosed WT. Ninety-eight were non-WT and 6 were patients registered at relapse only and therefore were excluded (Figure 1). Patients with presence or suspicion of thrombus in RV, IVC at infrahepatic (IH), retrohepatic (RH) and suprahepatic (SH) levels and intracardiac (IC) thrombus were identified from the Case Report Forms (CRFs) for the central radiology review (CenRR), central pathology review (CenPR), local pathology and surgical findings. Cases eligible for inclusion were those where the presence of tumour thrombus was confirmed by the surgeon and/or the reference pathologist. Cases where thrombus was suspected on CenRR but not found by the surgeon or pathologist were excluded.

Clinical data were extracted from the IMPORT study CRFs, including central pathology review letters as well as the full operative notes. CenPR was performed according to the SIOP 2001 classification and staging criteria [20] and was achieved in 100% of cases. Stage III for the WT with intravascular extension was assigned when tumour thrombi presented at resection margins of extra-renal vessels, transected or removed piecemeal by the surgeon. CenRR was performed by the central radiology review panel with an expertise in paediatric renal tumours and where possible in “real time”.

Patients were treated according to the national clinical guidelines of the CCLG. These are based on the results of the SIOP WT 2001 trial and study [21, 22], and were updated to also include tumour volume after pre-operative chemotherapy in the risk stratification of July 2019 [22]. Tumour histology, local, overall tumour stage and later volume dictated the postoperative chemotherapy regimen.

Event-free survival (EFS) was defined as time from diagnosis to first relapse/tumour progression, or death for any reason. Overall survival (OS) was defined as time to death from any cause. Patients were censored at the time of the last follow-up record. OS and EFS rates were plotted on Kaplan-Meier curves, and the log-rank test was used for comparison. The nominal significance level was set at $P < 0.05$. The association with EFS and OS was evaluated for: viability of tumour thrombus (viable versus nonviable), tumour histological risk group (high versus low and intermediate), completeness of thrombus surgical resection (complete versus incomplete). The multivariable EFS analysis using the Cox Proportional Hazards Model was done for the mentioned above three variables. Jamovi statistical package, version 1.6.1, with R version 3.6 was used for statistical analysis.

3. RESULTS

3.1.Patients' characteristics and radiological presentation

Sixty-nine/583 (11.8%) patients with a newly diagnosed WT had intravascular extension of WT beyond the kidney. Median age at diagnosis was 4.1 years (range 1.8-17.1 years) with 33 males and 36 females. Presenting clinical and radiological features are described in Table 1. In 10/69 (14.5%) cases thrombus was not identified on the cenRR (7 – RV and 3 - IH) due to RV and IVC compression by tumour or suboptimal image quality, making it difficult to comment on patency of the IVC.

3.2.Pre-operative treatment

Sixty-eight patients received neo-adjuvant chemotherapy. Thirty-eight patients with localized tumour at diagnosis were treated with Actinomycin and Vincristine (AV), 29 patients who presented with metastatic WT were treated with additional of Doxorubicin (AVD) and one had an alternative chemotherapy regimen due to suspicion of a non-WT diagnosis on initial biopsy (later revised to WT). Four patients had intra-abdominal haemorrhage requiring arterial embolization of the renal vessels with immediate (n = 1) or early (n = 3) nephrectomy and thus received no or shorter pre-operative chemotherapy duration. Shrinkage of the tumour thrombus was demonstrated in 13/59 (22%) cases for whom tumour thrombus was identified during the cenRR. In 44/59 (75%) cases the level of thrombus remained the same after neo-adjuvant chemotherapy and in two cases thrombus progressed cranially.

3.3.Surgical management

First definitive surgical treatment consisted of total unilateral nephrectomy in 62 patients (including 1 laparoscopic) and total nephrectomy on one side with contra-lateral nephron sparing surgery in 7 patients. Two patients with bilateral WT did not have surgery to the least affected kidney after chemotherapy. Details of the thrombectomy procedure according to the thrombus location are given in Table 2. Fifty-eight patients had complete macroscopic removal of thrombus. In 11 of these cases, reconstruction of IVC with artificial bovine patch was performed to achieve macroscopic clearance. In 15 cases thrombectomy was performed on were on CPB. There was no CPB associated mortality or morbidity in our series.

3.4.Tumour staging

In 55/69 (80%) patients, the abdominal tumour stage was classified as stage III (46 due to thrombus-related reasons, with these being the sole reason in 36 patients) (Table 3). Thrombus-

related reasons were macroscopic incomplete resection of the thrombus (n = 11), piecemeal complete resection of the thrombus (n = 20) and microscopic positive resection margins in the renal vein (n = 15). Other, thrombus-unrelated reasons, include lymph node metastasis, tumour capsular rupture, peritoneal deposits and positive tumour resection margins at another site (Table 3). Eight patients, whose tumours were classified as stage III due to macroscopic residual, had extensive thrombus adherent to the intimal vein layer and a surgical decision not to attempt complete removal. There were three cases where thrombus was left in the IVC, with no attempt to remove it. One patient had an emergency laparotomy and was in cardiac arrest, the other two were surgical decisions, one for thrombus being an unexpected operative finding and another for unknown reasons.

In 10/46 (22%) patients who had stage III due to the thrombus-related reasons, additional reasons for stage III were present (nonviable lymph nodes metastasis - 4, viable lymph node metastasis - 4, intraoperative tumour rupture – 1, positive tumour resection margins - 1).

There was one case with RH thrombus, which was considered to be local stage II as thrombus was completely although piecemeal excised with negative renal vein resection margins.

One case with radiologically reported intravascular extension and confirmed by the surgeon during the operation was not reported by the local or central pathologist. The patient was treated as a stage III by the local multidisciplinary team decision.

In 45/68 (66%) patients with tumour thrombus reported by the pathologist, it contained viable tumour cells. The primary tumour histology was low-risk in eight cases, intermediate-risk in 54 cases, and high-risk in seven.

3.5.Radiotherapy

Fifty-three of 55 patients with abdominal stage III disease received abdominal/flank radiotherapy with a total dose of a 14.4 Gr for the flank and 25.0 Gr for the whole abdomen. Two patients had no radiotherapy - one with RH extension and piecemeal complete excision of nonviable thrombus, for whom stage III was also attributed to nonviable lymph node metastasis and another one with microscopically positive resection margins of the renal vein and nonviable histology.

3.6.Clinical outcomes

Median follow-up was 20 months (range 6 – 80 months). There were 8/69 (12%) relapses, within a median time of 34 months (range 7 – 80 months) and 5/69 (7%) deaths (Table 4).

All five deaths occurred in the group with viable tumour thrombus and abdominal stage III. Of these, 3 were overall stage IV disease and death occurred after relapse/tumour progression in the lungs/liver with high risk (n = 2) and intermediate risk (n = 1) WT. One patient had a metachronous relapse requiring contralateral nephrectomy and subsequent renal transplantation. Death was due to post-transplant lymphoproliferative disease. One patient had localised disease at diagnosis but died of recurrent disease from thrombus residual in the IVC.

Two relapses (both distant metastases) occurred in the group with nonviable tumour thrombus (RH – 1, IVC - 1). Both patients had local stage III due to incomplete surgical resection. One patient with intermediate risk histology had a relapse in the lungs treated by metastatectomy and lung radiotherapy; the other patient had a high risk histology tumour and relapsed in mediastinal lymph nodes and was treated by chemotherapy and radiotherapy. Both patients are still alive.

Two year overall and event-free survival of all 69 patients was 90.2% (95% CI: 81.5-99.8) and 88.1% (95% CI: 79.5-97.7), respectively. EFS, but not OS, was significantly associated with completeness of surgical resection of the thrombus (complete versus incomplete $P<0.05$) (Figure 2A). OS and EFS were also significantly associated with tumour histological risk (high risk versus intermediate and low $P<0.05$) (Figure 2B) but not with viability of tumour thrombus ($P=0.19$; $P=0.59$) (Figure 2C). In multivariable analysis including histology, viability and completeness of surgical resection of tumour thrombus, a significant association of EFS was found with incomplete surgical resection ($P=0.007$). High histological risk and viable tumour thrombus were not associated with worse EFS ($P = 0.1$, $P = 0.3$) (Table 5).

4. DISCUSSION

Intravascular extension of WT must be considered in all patients, as it occurs in about 1/10 of patients. Our findings of 11.8% WT thrombus are in keeping with other large published series from SIOP and COG [1, 4, 11, 23].

The limitations of our study are small numbers of events (8 relapses and 5 deaths) in this cohort and hence limit statistical power for a multivariable overall survival analysis. There was also no data collected on short- and long-term surgical morbidity.

The strength of our study is that we were able to look in detail at the factors that contributed to clinical and pathological staging of the abdominal tumour in conjunction with the surgical approach and outcomes in a national study. We found a high proportion (46/69, 67%) of patients with WT thrombus were local stage III due to reasons related to thrombus, with over half (31 cases) due to incomplete surgical resection or piecemeal excision of the thrombus.

We found macroscopically incomplete surgical resection of the thrombus to be an adverse prognostic factor for EFS in both univariable and multivariable analysis. Moreover, all tumour related deaths and 75% of relapses occurred in the group with macroscopically incomplete surgical resection and viable tumour thrombus. Six out of eight children who experienced a relapse had an initially localised tumour, but 5/6 of these relapses were distant metastases or a metachronous tumour. It should be noted that only one of five deaths could be attributed to recurrence within residual tumour thrombus. The previous literature is conflicting regarding the importance of complete thrombus resection. Loh et al. has shown that for 12 WT patients completeness of surgical thrombectomy was not associated with worse OS [24]. Shamberger et al. reported only two relapses out of 18 cases of incomplete resection [12]. Xu et al. described one peritoneal relapse out of six with residual vascular disease [25]. Szavay et al. had 1 pulmonary relapse out of 5 patients with residual disease, although there were 2 other deaths in this groups due to advanced disease at operation [26]. While Akyuz et al. reported that 6/10 died of progressive disease after incomplete thrombectomy [5].

Currently, the recommended surgical technique is thrombectomy using curettage in a manner similar to that used for carotid endarterectomy but not partial cavectomy with its replacement [23, 26]. In our series there were 11 patients with extensive vena cava resection and artificial bovine patch reconstruction on CPB. Complete surgical clearance was achieved without surgical mortality and good outcomes (no relapse or death). Murthi et al. also have performed gross resection of thrombus as opposed to intimal dissection, and found no vascular relapses, but lung metastases developed in 4/13 patients [18].

A further consideration in balancing of risks between extensive surgery and reliance on postoperative radiotherapy for tumour control is the viability of tumour thrombus. Our study showed 66% of tumour thrombus contained viable tumour cells after pre-operative chemotherapy and a significantly elevated risk of relapse (HR 3.48) in multivariable analysis. This is comparable to the 52% (22/44) prevalence of viable thrombus in the series reported by Shamberger et al. [12]. Hence, even though most of these cases receive local radiotherapy, this suggests that every effort should be made to achieve complete resection.

To summarize, our data suggest that extensive surgery to achieve complete surgical clearance may improve event free survival. In addition, our experience suggests that artificial IVC replacement is a safe and reliable method to achieve complete resection of tumour thrombi. However, further studies are needed to evaluate long term patency [27 - 29].

Even when thrombus resection was complete, current staging systems classify piecemeal resection as stage III [20]. In our series, there was no relapse or death among 20 patients in this category, 6 of whom had non-viable thrombus. With the proviso that our series is small, and all but two of these patients had postoperative radiotherapy (the two exceptions had piecemeal complete removal of nonviable thrombi), we recommend that a future clinical trial should explore the possibility of omitting radiotherapy where there is complete removal of tumour thrombus that is completely non-viable on histology.

Our study showed that more than half (15/29) of patients with RV thrombus were assigned local pathological stage III due to the presence of thrombus at the renal vein resection margin, whereas in the operative notes the transection of the renal vein was documented to have been beyond the thrombus. Since the renal vein contracts after the transection, the thrombus may artificially appear to be at the resection margin. This emphasises the importance of good communication between the operating surgeon and reporting pathologist to avoid upstaging, and hence reducing the need for radiotherapy and its long-term sequelae.

To enable appropriate surgical planning, radiological preoperative detection of the tumour thrombus and its extent is essential. Our study has shown 15% of tumour thrombi were not seen on cross-sectional imaging, which is similar to the literature [30, 31]. In cases where pre-surgical uncertainty persists, it is prudent to perform a pre-operative or an intra-operative doppler US to define the extent of thrombus ‘on-table’ [32]. It may be necessary to plan for an

extensive vena cava resection. If the surgical team does not have the relevant services on site, onward referral to a centre that does should be considered.

5. CONCLUSIONS

WTs with intravascular extension comprised 12% in our series and had a high rate of being local stage III (67%) due to reasons related to the thrombus. Incomplete surgical resection of IVC thrombus is significantly associated with a worse EFS in both univariable and multivariable analysis, suggesting that sufficiently extensive surgery should be planned. Complete thrombectomy was not associated with survival disadvantage and consideration could be given to avoiding radiotherapy if the thrombus is completely necrotic. The small size of our study cohort and lack of detailed information on surgical morbidity are limitations. Prospective clinical studies are needed to address these points.

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LEGENDS

Table 1. Clinical and radiological features reported at presentation of WT with intravascular extension.

Table 2. Summary of surgical management of tumour thrombus in relation to its level.

Table 3. Reasons for abdominal tumour stage, split by viability of the tumour thrombus.

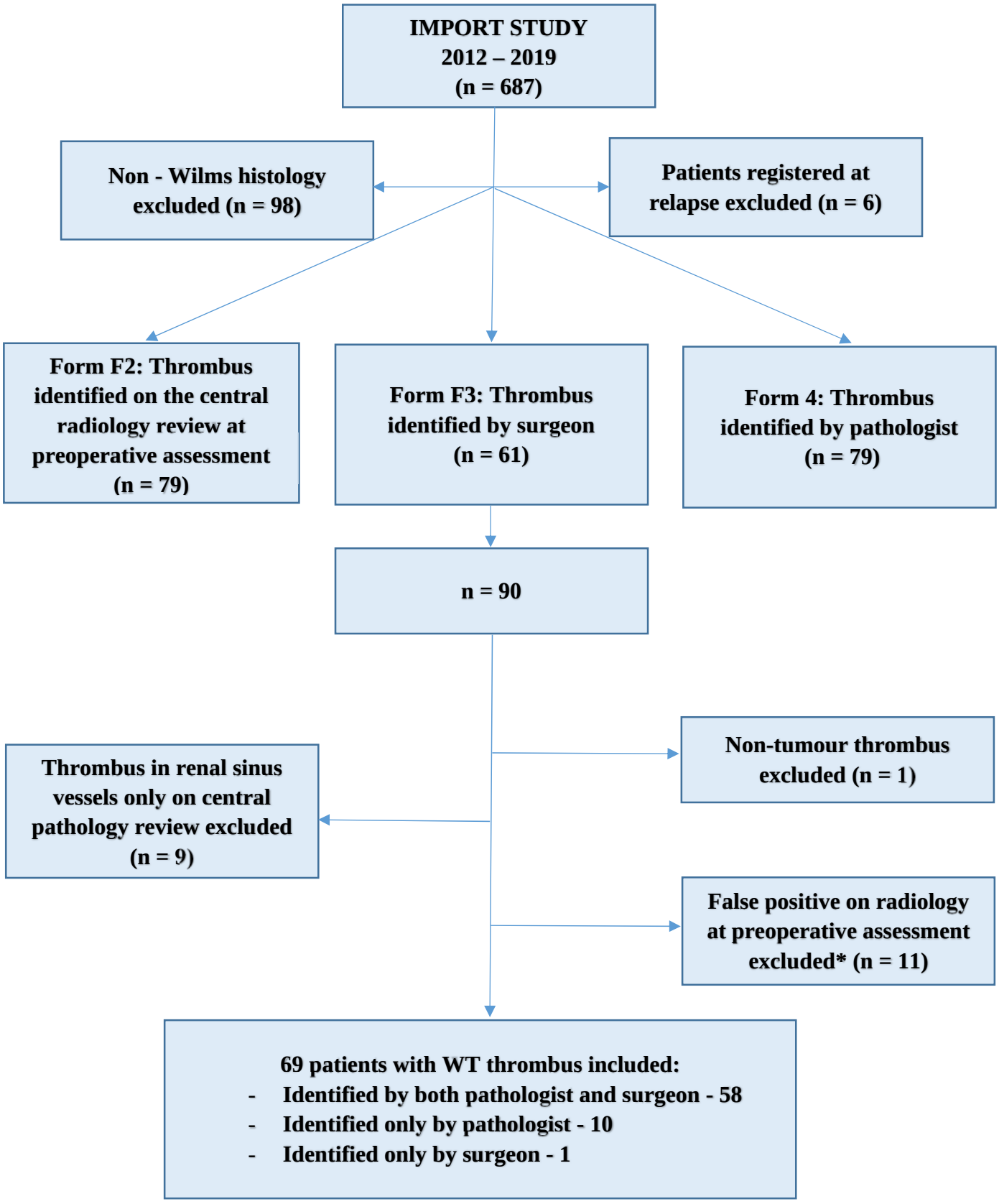
Table 4. Outcomes for patients with viable versus nonviable tumour thrombus histology.

Table 5. Event free survival association with completeness of surgical resection, histological risk and viability of tumour thrombus in multivariable Cox proportional hazards model.

Figure 1. Methodology flow-chart.

Figure 2. Overall (OS) and event free survival (EFS) associations with completeness of surgical resection (A), histological risk (B) and viability of tumour thrombus (C).

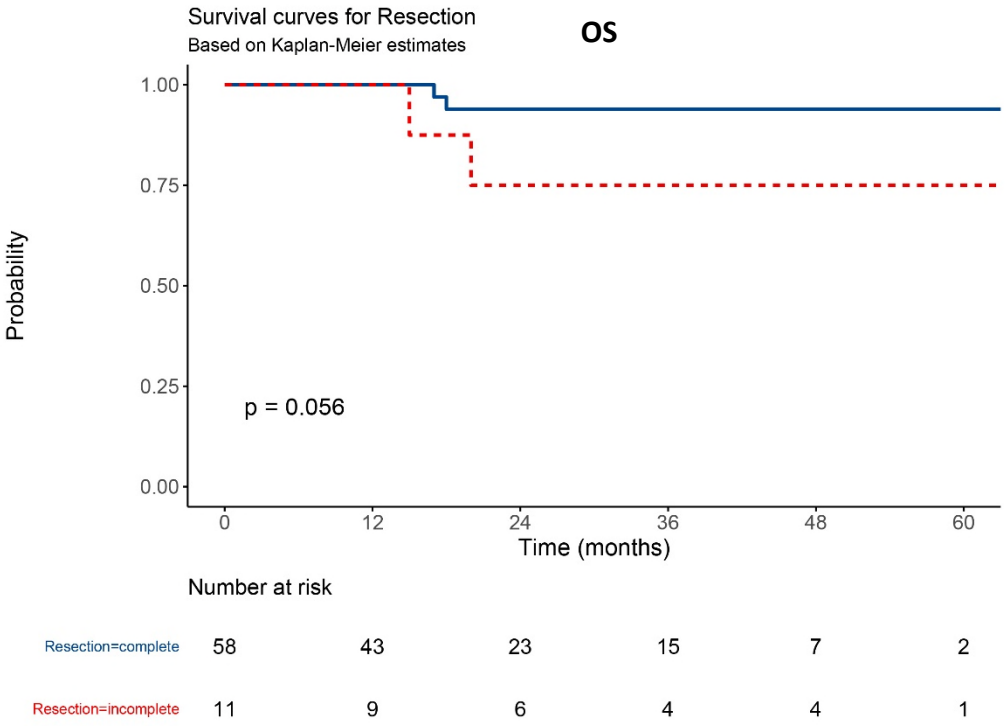
Figure 1. Methodology flow-chart.

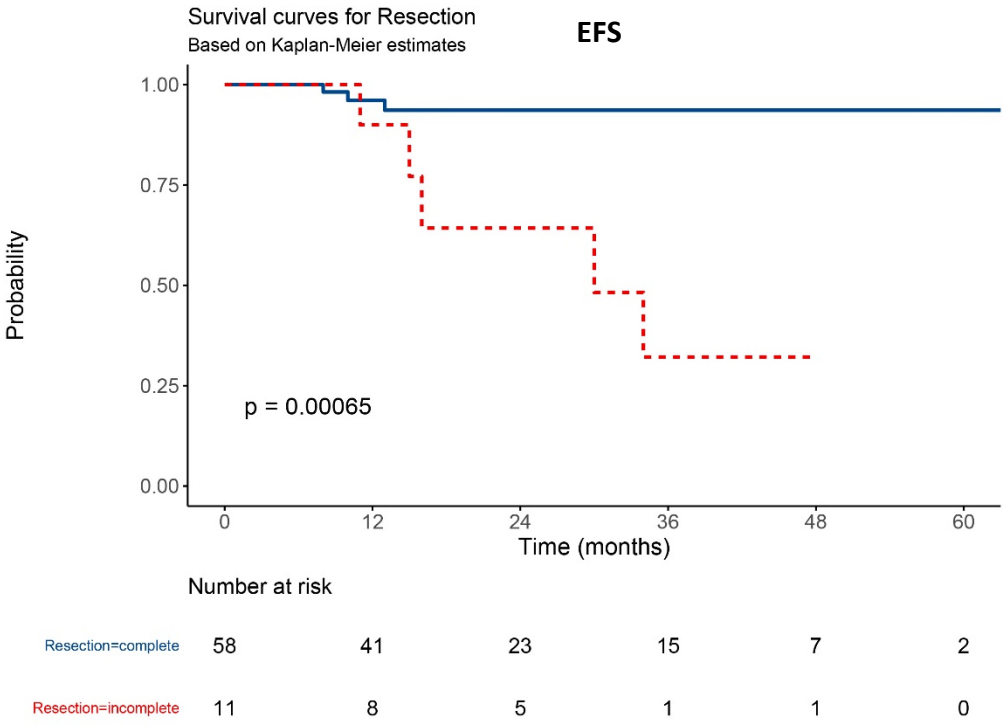


*thrombus suspected on the radiology but not identified by either surgeon or pathologist.

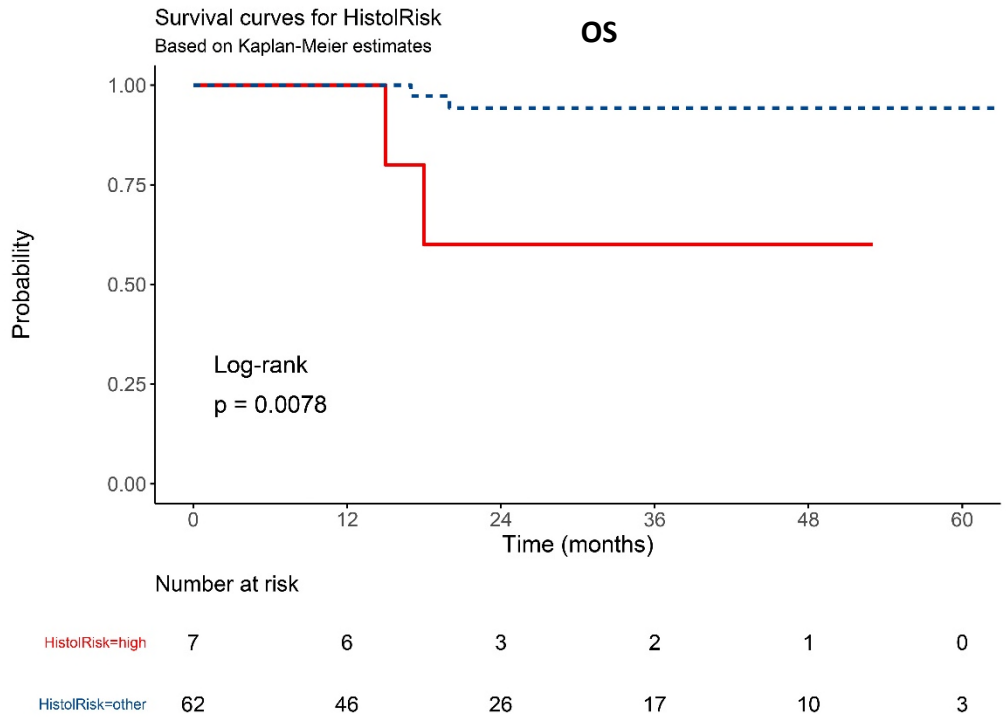
Figure 2. Overall (OS) and event free survival (EFS) associations with completeness of surgical resection (A), histological risk (B) and viability of tumour thrombus (C).

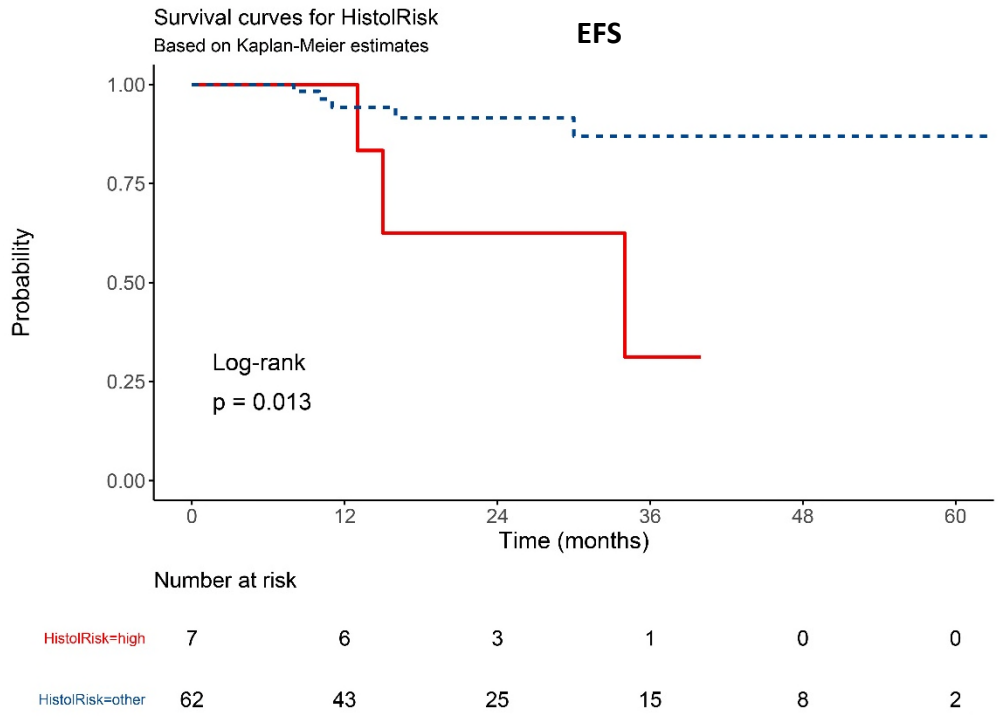
A.



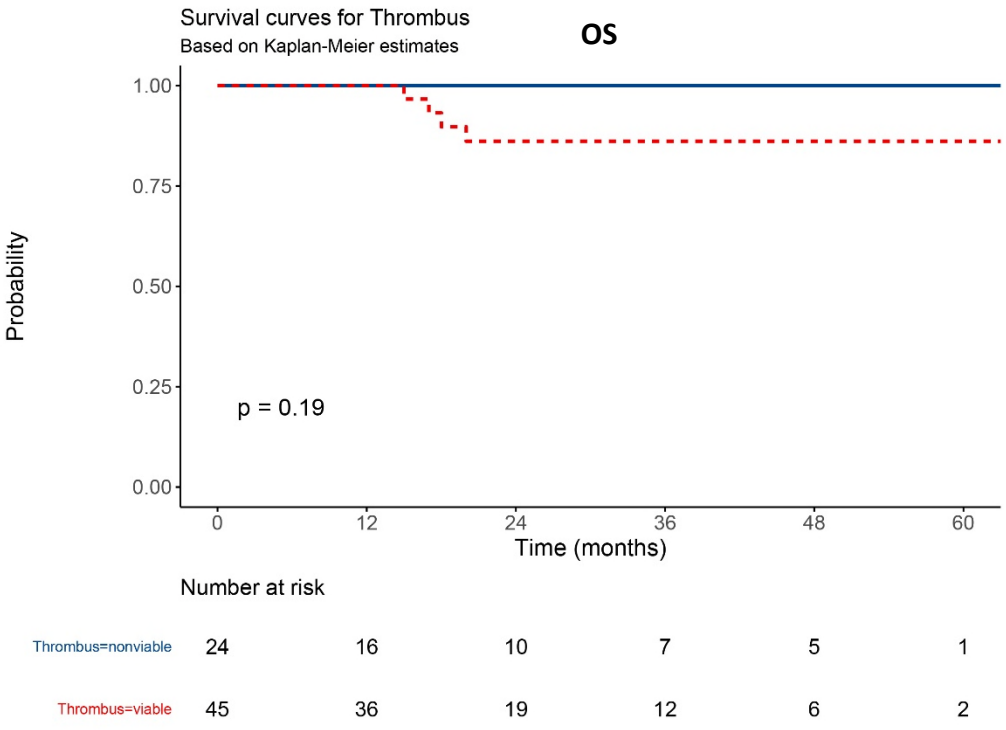


B.


Survival curves for HistolRisk
Based on Kaplan-Meier estimates
OS
Probability
1.00
0.75
0.50
0.25
0.00
Log-rank
p = 0.0078
0
12
24
36
48
60
Time (months)
Number at risk
HistolRisk=high 7 6 3 2 1 0
HistolRisk=other 62 46 26 17 10 3


Survival curves for HistolRisk
Based on Kaplan-Meier estimates
EFS
Probability
1.00
0.75
0.50
0.25
0.00
Log-rank
p = 0.013
0
12
24
36
48
60
Time (months)
Number at risk
HistolRisk=high 7 6 3 1 0 0
HistolRisk=other 62 43 25 15 8 2

C.


Survival curves for Thrombus
Based on Kaplan-Meier estimates
OS
Probability
1.00
0.75
0.50
0.25
0.00
p = 0.19
0
12
24
36
48
60
Time (months)
Number at risk
Thrombus=nonviable 24 16 10 7 5 1
Thrombus=viable 45 36 19 12 6 2

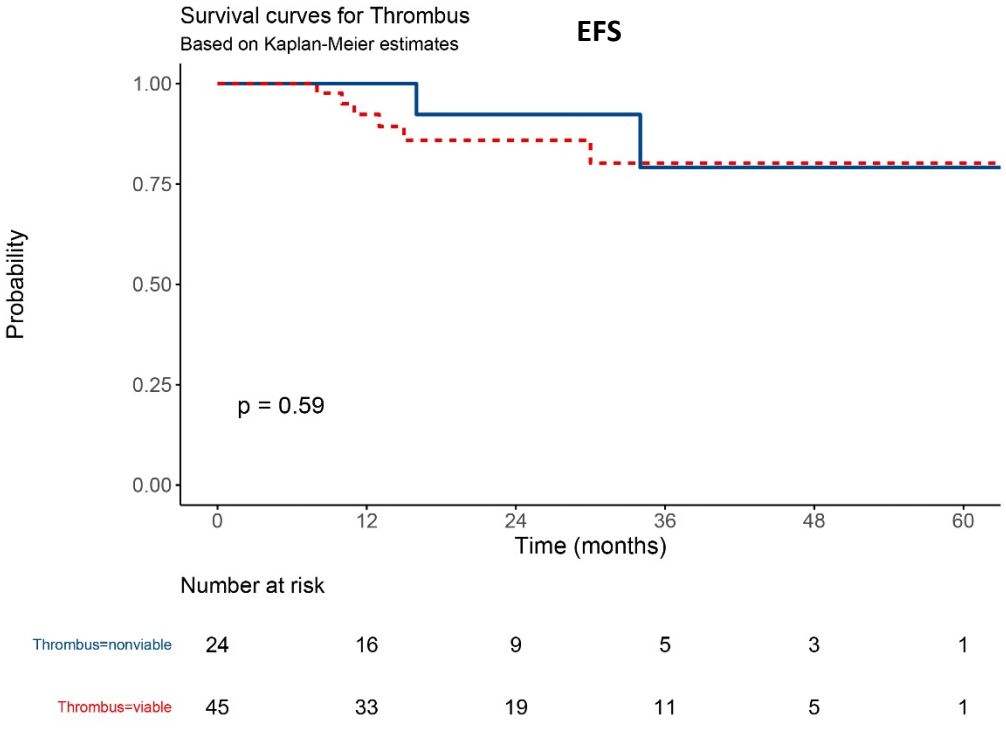

Survival curves for Thrombus
Based on Kaplan-Meier estimates
EFS
Probability
1.00
0.75
0.50
0.25
0.00
p = 0.59
0
12
24
36
48
60
Time (months)
Number at risk
Thrombus=nonviable 24 16 9 5 3 1
Thrombus=viable 45 33 19 11 5 1

Table 1. Clinical and radiological features reported at presentation of WT with intravascular extension

Feature	**No. patients**	**%**
Unilateral tumour	60	87
Bilateral tumours	9	13
Localised tumour	40	58
Metastatic tumour	29	42
Level of thrombus seen on CenRR		
Renal vein (RV)	14	20
Infra-hepatic (IH)	21	30
Retro-hepatic (RH)	10	15
Supra-hepatic (SH)	6	9
Intra-cardiac (IC)	8	12
No thrombus reported	10	15
Tumour volume (ml)	593	median
	92 - 2659	range

Table 2. Summary of surgical management of tumour thrombus in relation to its level

Surgical approach	**Level of the thrombus after preoperative chemotherapy**					
	RV (n = 27)	IH (n =18)	RH (n = 14)	SH (n = 2)	IC (n =8)	n = 69
Only biopsy of the IVC thrombus	0	0	2*	0	0	**2**
Thrombus resection together with RV without IVC opening	16	6	0	0	0	**22**
Cavotomy with thrombectomy after vascular control	1	9	7	1	1**	**19**
Cavotomy with thrombectomy on CPB	0	1	6	1	7	**15**
No mention of thrombus in operative notes	10	2	0	0	0	**12**

RV – renal vein, IVC – inferior vena cava, IH – infrahepatic, RH – retrohepatic, SH – suprahepatic, IC – intracardiac, CPB – cardiopulmonary bypass, CRR – central radiology review

* In one patient thrombectomy on CPB was performed 15 months later

** Thrombus mobile enough to pull down into the IVC

Table 3. Reasons for abdominal tumour stage, split by viability of the tumour thrombus

Thrombus level after preoperative chemotherapy	Reasons for abdominal tumour stage									
	Stage II		**Stage III**							
	Negative RV resection margin*		Positive RV resection margin*		Piecemeal complete thrombus resection		Macroscopic incomplete thrombus resection		Other reasons**	
	V	N	V	N	V	N	V	N	V	N
RV (n = 27)	7	4	4	4	1	0	0	0	6	1
IH (n = 18)	2	0	3	2	3	3	2	2	1	0
RH (n = 14)	0	1	1	0	5	1	4	2	0	0
SH (n = 2)	0	0	0	0	1	0	0	1	0	0
IC (n = 8)	0	0	1	0	4	2	0	0	0	1
Total (n = 69)	**14 (20%)**		15 (27%)		20 (37%)		11 (20%)		9 (16%)	
			55 (80%)							

RV – renal vein, IH – infrahepatic, RH – retrohepatic, SH – suprahepatic, IC – intracardiac, N - nonviable, V – viable.

* Microscopically.

** Lymph nodes metastasis, peritoneal deposits, positive resection margins at non-RV sites, tumour rupture.

Table 4. Outcomes for patients with viable versus nonviable tumour thrombus histology.

	Viable (n = 45)	**Nonviable (n = 24)**
Overall tumour stage (no. patients)		
Stage II/III (localised)	28 (62%)	7 (29%)
Stage IV (metastatic)	12 (27%)	17 (71%)
Stage V (bilateral)	7 (16%)	2 (8%)
Abdominal tumour stage III (no. patients)	36 (80%)	19 (80%)
Number and site of relapse	6 (14.6%) - IVC thrombus residual -1 (L) - Lungs – 2 (L) - Liver – 1 (L) - Kidney -1 (L) - LN – 1 (M)	2 (10.5%) - Lungs – 1 (M) - LN – 1 (L)
Number of deaths Reason for stage III	5 (13%) Incomplete thrombus surgical resection - 4, LN metastasis - 1	0 -
Median time of follow-up	22 months (range 8 – 80 months)	18 months (range 6 – 64 months)

IVC – inferior vena cava, LN – lymph nodes, L – localised tumour at diagnoses, M – metastatic tumour at diagnosis

Table 5. Table 5. Event free survival association with completeness of surgical resection, histological risk and viability of tumour thrombus in multivariable Cox proportional hazards model

	P	*Hazard ratio*
Risk (high/other)	0.10087	3.4876
Thrombus (viable/nonviable)	0.30169	2.4148
Resection (incomplete/complete)	**0.00751**	7.5333