Patient selection for laparoscopic excision of adrenal metastases: a multicenter cohort study

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Keywords: laparoscopy; adrenal; metastasis; adrenalectomy

Manuscript word count: 2334

Running title: Laparoscopic excision of adrenal metastases

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ABSTRACT:

Introduction: The use of laparoscopy for the excision of adrenal metastasis remains controversial. We aimed to report oncological and perioperative outcomes of laparoscopic excision of adrenal metastases and to seek for predictive factors of unfavourable oncological outcomes.

Methods: A retrospective chart review was conducted and all consecutive patients who underwent laparoscopic adrenalectomy (LA) in the setting of metastatic cancer in two academic urology departments from November 2006 through January 2014 were included. Primary tumors were categorized as pulmonary, renal or "other primary" tumors to allow statistical comparison. Unfavourable surgical outcomes were defined as the occurrence of either postoperative complications and/or positive surgical margins.

Results: Forty-three patients who underwent a total of 45 LA were included for analysis. There were 8 complications (17.8%). Positive surgical margins were found in 12 specimens (26.7%). After a median follow-up of 37 months, estimated overall survival rates were 89.5% and 51.5% at 1 year and 5 years, respectively. In multivariable analysis the only predictor of unfavourable surgical outcomes was a tumor size > 5 cm (OR= 20.5; p=0.001). In multivariate analysis the pulmonary (OR=0.3; p=0.008) or "other" (OR= 0.1; p=0.0006) origin of the primary tumor was the only prognostic factor of shorter cancer specific survival.

Conclusion: Laparoscopic resection of adrenal metastasis can be safely performed in most patients but is associated with an increased risk of positive surgical margins and postoperative complications in larger tumors (> 5 cm). Adrenalectomy provides better oncological outcomes in metastases from renal cell carcinoma compared to other primary tumors.

1. Introduction

Despite a low level of evidence, adrenalectomy is now recommended in case of isolated adrenal metastasis [1-2], as many retrospective series have shown the oncological benefit of surgical excision in this situation [3].

Firstly reported by Gagner et al. in 1992 [4], laparoscopic adrenalectomy (LA) has become the gold-standard treatment of benign adrenal tumors. Several series have proven the lower morbidity of this approach in adrenal surgery (notably decreased complication rate and blood loss, shorter length of stay) [5-6]. Although most of the series of LA have shown similar surgical and oncological outcomes to those reported in the open era [7-8], the role of laparoscopy in the treatment of malignant adrenal tumors remains controversial. In recent years, two series have raised concern about the laparoscopic approach for resection of adrenal metastases. In a single center cohort of 16 patients, Sebag et al. noted high rates of positive surgical margins, complications and conversion to open surgery [9]. In their single-center series of 13 patients, Crenn et al reported similar findings [10].

In this work, we therefore hypothesized that both the adrenal resection in itself and the laparoscopic approach could not be beneficial for every patient with isolated adrenal metastasis. We aimed to report oncological and perioperative outcomes of laparoscopic excision of adrenal metastases and to look for predictive factors of unfavourable surgical outcomes in order to determine which patients could benefit of laparoscopic resection of adrenal metastases.

2. Patients and methods

a. Study design

A retrospective chart review was conducted to include all consecutive patients treated by LA in the setting of metastatic cancer in two academic urology departments, from November 2006 through January 2014. Adrenalectomies performed as part of radical nephrectomy or for extra adrenal tumor with local extension to the adrenal gland were excluded. All patients were treated with curative intent. The study received approval of the local ethics committees (Unique Identifying Number (UIN) from the Research Registry: 538).

Variables collected included patients' characteristics (age, gender, ASA score, Body Mass Index), tumor related data (primary tumor, size, laterality, synchronous or metachronous, isolated or oligometastatic disease, adjuvant treatments), surgeon's experience (categorized as: < 30 cases of LA or > 30 cases of LA), perioperative outcomes (operative time, intra and postoperative complications, blood loss, length of stay, surgical margins, conversion) and oncological outcomes (recurrence, date of recurrence and death, causes of death, recurrence location, date of last follow-up visit). Complications were graded according to Clavien-Dindo classification [11] and reported with full respect of the EAU guidelines on reporting complications [12]. Metastases were considered as synchronous if detected within 6 months after treatment of the primary tumor. Otherwise, they were defined as metachronous. Diseases were categorized as isolated (only one adrenal metastasis) or oligometastatic (other synchronous metastasis or history of previous metastasis). Unfavourable surgical outcomes were defined as the occurrence of either postoperative complications and/or positive surgical margins. Primary tumors were categorized as pulmonary, renal or "other primary" tumors to allow statistical comparison between groups. Tumors sizes were categorized as > 5cm or ≤ 5 cm.

Our main objective was to determine predictors of unfavourable surgical and oncological outcomes. Our secondary objective was to report outcomes of LA in a multicenter study.

b. Surgical techniques

All surgeries were performed laparoscopically. However, some procedures were performed through a transperitoneal approach whereas others were carried out by a retroperitoneal route. The choice of either the transperitoneal or retroperitoneal approach was left to surgeon's discretion. In one of the department all LA were performed through a transperitoneal approach while both approaches were used in the other department.

c. Patients follow-up

All patients were evaluated by their surgeon at an outpatient appointment 1 month after surgery. All complications occurring during the first post-operative month were collected and considered as postoperative complications. Further oncological follow-up was then left to the oncologist and involved a physical examination and imaging every six months during the first two years and then annually for a minimum of 5 years.

d. Statistical Analysis

Means and standard deviations were reported for continuous variables and proportions for qualitative and categorical variables. Comparisons between groups were performed using χ^2 test and Fisher exact test for discrete variables and student t test for continuous variables. To confirm the findings of univariate analysis, a logistic regression model was used to assess predictors of unfavourable surgical outcomes. Overall survival (OS), cancer-specific survival (CSS) and recurrence-free survival (RFS) were estimated using the Kaplan-Meier method and compared with the log-rank test. A Cox proportional hazards regression model was used to define the prognostic factors. Statistical analyzes were conducted using JMP v.10.0 software (SAS Institute Inc, Cary, NC, USA). All tests were two-sided with a significance level at $p< 0.05$.

3. Results

a. Patients' characteristics

Forty-three patients who underwent a total of 45 LA (2 cases of bilateral metastases: 1 renal carcinoma and 1 neuroendocrine tumor) were included for analysis. Mean age was 60.8 years (± 9.6) with 79.1% of male patients. Mean tumor size was 48.3 mm (±34.7). Primary tumors were renal carcinoma in 20 cases (44.4%), non-small cell lung cancer in 11 cases (24.4%), colorectal cancer in 3 cases (6.7%), bladder cancer in 3 cases (6.7%), melanoma in 3 cases (6.7%), neuroendocrine tumor in 2 cases (4.4%), glandular eye carcinoma in 1 case (2.2%) and breast cancer in 1 case (2.2%). All surgeries were performed laparoscopically, 14 (31.1%) through a retroperitoneal route and 31 (72.1%) via a transperitoneal approach, Twenty-four procedures (55.8%) were performed by highly experienced surgeons (≥ 30 cases) and 19 (44.2%) by less experienced surgeons (< 30 cases). Twenty-seven patients (62.8%) had isolated adrenal metastasis and 16 (37.2%) had a history of previous metastasis (oligometastatic disease). Eight metastases were considered as synchronous (17.8 %). A PET scan was requested in 15 patients (37.5%) and showed a localized hypermetabolic activity in 13 cases (86.7%) , which reinforced the hypothesis of an isolated adrenal metastasis.

b. Surgical outcomes

Surgical outcomes are summarized in table 1. Mean operative time was 162.2 minutes (± 75.1). Eight complications occurred (17.8%): 4 blood transfusions due to intraoperative blood loss (Clavien grade 2); 1 pulmonary infection (Clavien grade 2); 1 reoperation due to bleeding of the adrenal resection bed (Clavien grade 3B); 1 septic shock due to gallbladder perforation unnoticed intraoperatively (Clavien grade 4A) and 1 mesenteric ischemia resulting in a fatal outcome on postoperative day 4 (Clavien 5). Positive surgical margins were found in 12 specimens (26.7%). Conversion to open surgery was needed in 7 procedures (15.6%): because of important bleeding in 4 cases, of caval invasion in 2 patients and due to gastric perforation in another patient.

c. Oncological outcomes

After a median follow-up of 37 months (range: 1-94), estimated overall survival rates following adrenalectomy were 89.5% and 51.5% at 1 year and 5 years, respectively (see figure 1 a). Estimated cancer specific survival (CSS) rates were 89.5% and 53.3% respectively 1 year and 5 years after surgery (see figure 1b). Thirteen patients passed away during follow-up: eleven from disease, one from post-operative complications (mesenteric ischemia) and one from acute heart failure 21 months after surgery. This latter patient had a history of valvular disease and had no evidence of disease recurrence at the time of death. In the subgroup of 15 patients who had a minimum follow up of 5 years: 8 were alive with no evidence of disease (53.3%) while 7 died from disease (47.7%) 1 to 5 years following adrenalectomy.

During follow-up, 24 patients had recurrence of disease (55.8%). The median recurrence-free survival was 17 months. Estimated recurrence free survival (RFS) rate was 65.4% and 26.4% at 1 year and 5 years after surgery, respectively (see figure 1c).

Recurrence consisted in distant metastasis in 22 cases (mostly lung, bone and brain metastases), in local recurrence in the adrenal resection bed in one case and in retroperitoneal carcinomatosis in one case. The latter two patients had large adrenal metastasis (79 and 120 mm respectively). They underwent conversion to open surgery due to intraoperative bleeding and both had positive surgical margins on final pathology.

d. Predictive factors of unfavourable surgical outcomes

Positive surgical margins and/or post-operative complications occurred in 15 patients (34.9%) who were considered to have unfavourable surgical outcomes. Patients with unfavourable surgical outcomes had larger tumors (69.4 vs. 36.6 mm; p=0.002) and were more likely to have “other primary” tumors (53.3% vs. 14.3%; 0.02). There was a trend towards a higher risk of unfavourable surgical outcomes in patients operated via a retroperitoneal route (50% vs. 29%; p=0.2) or when

adrenalectomy was performed by a less-experienced surgeon (47.4% vs. 25%; p= 0.13). In univariate analysis, only "other primary tumors" (pulmonary cancer: OR= 0.2, p=0.04; renal cancer: OR=0.1, p=0.01) and tumor size > 5 cm (OR= 16; p=0.0002) were predictive factors of a negative surgical outcome (see table 2). In multivariable analysis that adjusted for age, ASA score, surgeon's experience, laparoscopic route, and types of primary tumor, the only predictor of negative surgical outcomes was a tumor size > 5 cm (OR= 20.5; p=0.001) but there was still a tendency towards better surgical outcomes in patients whose primary tumor was a pulmonary cancer (OR= 0.1; p=0.06) or renal cancer (OR=0.2; p=0.1) compared to patients with other primary tumors (see table 2).

e. Prognostic factors of survival

Patients with negative surgical margins (p=0.04), those with metastasis size ≤ 5cm (p=0.03), and those with a renal origin of the primary tumor (p=0.002) had longer CSS (see figure 1 d). In multivariate analysis the pulmonary (OR=0.3; p=0.008) or "other" (OR= 0.1; p=0.0006) origin of the primary tumor was the only prognostic factor of shorter CSS (see table 3). No prognostic factors of recurrence free survival (RFS) were found in either univariate or multivariate analysis. In the subgroup of adrenal metastasis from renal carcinoma (19 Patients, 20 metastasis), estimated 5-year CSS and RFS were 100% and 21.3% respectively.

4. Discussion

Surgical resection of adrenal metastasis has gained wide acceptance over the past decade in case of isolated or oligometastatic disease and is now considered as the standard treatment in this situation [1-3]. However there is a paucity of data to support this management and no randomized evidence to suggest that local therapy of adrenal metastases alters the natural course of the disease [13]. In the only large case-control study to date, Vazquez et al compared survivals of their patients treated with

adrenalectomy for adrenal metastasis to those of SEER-database stage-matched patients with no resection of adrenal metastases. They found a survival benefit in favour of surgical resection for metastases arising from lung, kidney, pancreas and sarcoma but their findings are debatable due to their study design [14]. Our results reinforce those previously reported in the literature by showing that resection of adrenal metastases may be associated with prolonged survival (5-year CSS and RFS rates: 53.3% and 26.4%, respectively) [3, 7-10, 13-14]. However, our 5-year CSS rate exceeds those reported in other series (from 30 to 40%) [3, 7-10, 13-14]. This may be due to the larger proportion in our series of patients with renal cell carcinoma who have been shown to have a significantly better prognosis compared with other primary tumors [8, 15-16].

To date, only 5 series analyzed prognostic factors for resected adrenal metastases using a Cox regression model [8, 15-18]. Out of these studies, three showed a better prognosis in multivariate analysis for metastases from renal carcinoma [8, 15-16]. Our results confirm that a primary renal tumour is the main prognostic factor in surgical excision of adrenal metastases. Conversely, we did not find a prognostic impact for factors such as tumor size, type of treatment of the primary tumor (surgery, radiotherapy, …) or status of margins, which have ever been reported by others [8, 15-18]. This could be due to the relatively small sample size of our study.

The present study is the first to report complications of surgery of adrenal metastases in a standardized way (i.e. using Clavien score [11], with respect of the EAU guidelines [12]). We report a complication rate similar to those previously published in the literature: 17.8% in our series versus 4 to 20% in other laparoscopic series [7, 9, 15, 18-19]. These complications rates seem overall comparable to the complication rates of open surgical adrenalectomies (6 to 20% [13,18]) but no firm conclusions can be established due to the lack of standardization of the complications report in most studies.

In our study we used the concept of an unfavourable surgical outcome in the presence of post-operative complications and/or positive surgical margins. Postoperative complications are indeed the most frequently used surrogate marker of quality in surgery [20] and on the other hand, positive

surgical margins have been show to negatively impact the oncological outcome in case adrenalectomy for metastasis [15,17]

We found that a metastasis size > 5 cm was the only predictor of an unfavourable surgical outcome in multivariate analysis. Most authors advocate an open surgical approach for the excision of bigger lesions however the upper limit proposed for a laparoscopic approach varies in different studies [21-22]. While it is quite obvious that excision of bigger lesions will involve a higher risk of complications and positive surgical margins, there is no firm evidence that an open approach would obtain a better surgical outcome. Our series similarly to most other published series did not have a control group and could not answer this question [3]. Due to the non-controlled design of our study we could not bring new evidence concerning the potential survival benefits of resection of adrenal metastasis compared to a non-surgical management. Another limitation of the present study is its retrospective nature, which can introduce selection and ascertainment bias. Finally, systemic therapies that have been shown to impact prognosis in other studies [17] were not taken into account in our series.

5. Conclusion

Laparoscopic resection of adrenal metastasis can be safely performed in most patients but is associated with an increased risk of positive surgical margins and of postoperative complications in larger tumors (size ≥ 5 cm). Adrenalectomy for metastasis can be associated with a prolonged survival in selected patients and provide better oncological outcomes in metastases from renal cell carcinoma compared to other primary tumors.

Conflicts of interest:

None

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Table 1: perioperative parameters (n=45)

Operative time (min)	162.2 (± 75.1)
Mean +/- SD	
Estimated Blood loss (ml)	288 (± 550)
Mean +/- SD	
Complications	
N (%)	
Clavien 2	5 (11.6%)
Clavien 3B	1 (2.3%)
Clavien 4A	1 (2.3%)
Clavien 5	1 (2.3%)
Surgical margins	
N (%)	
positive	12 (26.7%)
negative	33 (73.3%)
Length of stay (days)	4.6 (±3.2)
N (%)	
Open Conversion	7 (15.5%)
N (%)	
Negative surgical outcome	15 (34.9%)
N (%)	

Table 2: Predictive factors of unfavourable surgical outcome: univariate and multivariate analysis

Variables	Negative surgical outcome							
	Univariate analysis				Multivariate analysis			
	Odds-Ratio	Confidence Interval 95 %		P-value	Odds-ratio	Confidence Interval 95 %		P-value
		Lower	Upper			Lower	Upper	
Age (years)	2.5	0.2	36.8	0.47	1.9	0.05	79.3	0.71
Surgeon's experience *< 30 cases* *> 30 cases*	 1 [ref] 0.3	 - 0.1	 - 1.3	0.13	 1 [ref] 0.5	 - 0.1	 - 3.4	0.48
Laparoscopic route *Transperitoneal* *Retroperitoneal*	 1 [ref] 2.4	 - 0.6	 - 9.9	0.2	 1 [ref] 4.8	 - 0.6	 - 52.6	0.15
Primary tumor *Other* *Lung cancer* *Renal cancer*	 1 [ref] 0.2 0.1	 - 0.02 0.02	 - 0.9 0.6	 - **0.04*** **0.01***	 1 [ref] 0.1 0.2	 - 0.01 0.01	 - 1.1 1.4	 - 0.06 0.1
Tumor size *≤ 5 cm* *> 5cm*	 1 [ref] 16	 - 3.6	 - 94.7	 **0.0002***	 1 [ref] 20.5	 - 3.1	 - 237	 **0.001***
ASA score	1.4	0.2	12	0.71	0.7	0.02	14.6	0.79

Table 3: Prognostic factors of cancer-specific survival: multivariate analysis

	Cancer-specific survival			
	Hazard Ratio	Confidence Interval 95%		p-value
		Lower	Upper	
Age	0.9	0.1	12.6	0.93
Tumor size				
≤ 5cm	1[Ref]	-	-	0.4
> 5cm	0.4	0.1	3.5	
Surgical margins				
Negative	1[Ref]	-	-	0.74
positive	0.7	0.1	6.7	
Metastasis				
Synchronous	1[Ref]	-	-	0.95
Metachronous	0.9	0.1	18.6	
Status				
Isolated metastasis	1[Ref]	-	-	0.59
Oligometastatic	0.7	0.1	2.6	
Primary tumor				
Renal cancer	1[Ref]	-	-	
Lung cancer	0.3	0	0.4	**0.008***
Other	0.1	0	0.2	**0.0006***
Surgeon's experience				
< 30 cases	1[Ref]	-	-	0.08
≥ 30 cases	0.2	0.04	1.2	
Laparoscopic route				
Transperitoneal	1[Ref]	-	-	0.43
Retroperitoneal	2	0.4	12.3	

Figure 1: Survival curves

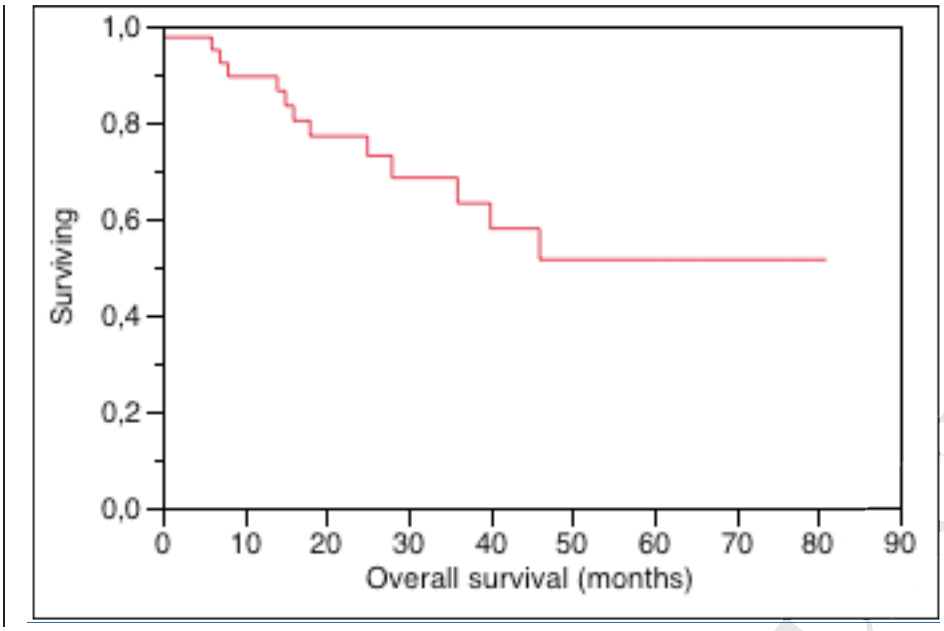

Fig 1a: Estimated overall survival

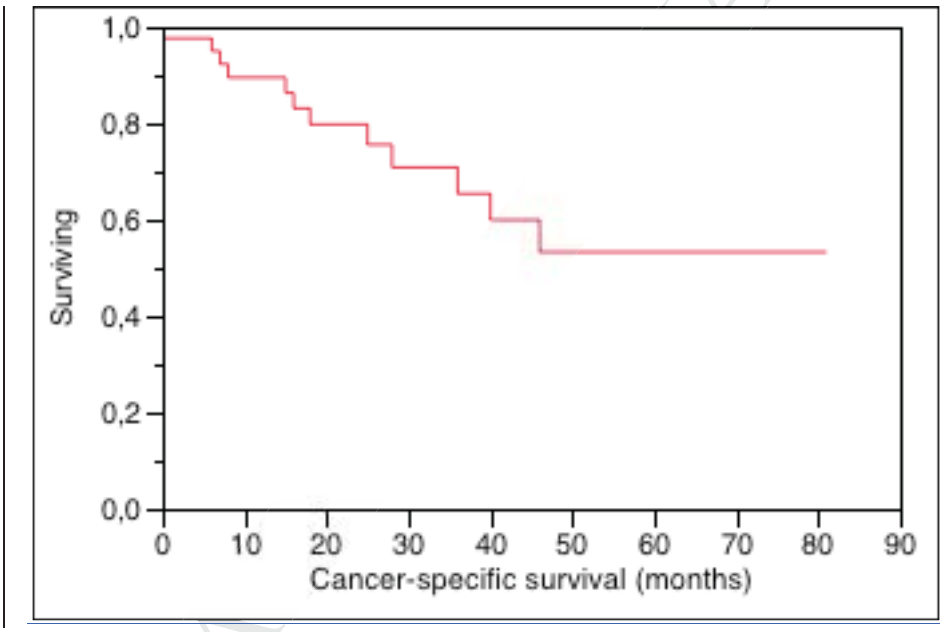

Fig 1b: Estimated cancer-specific survival

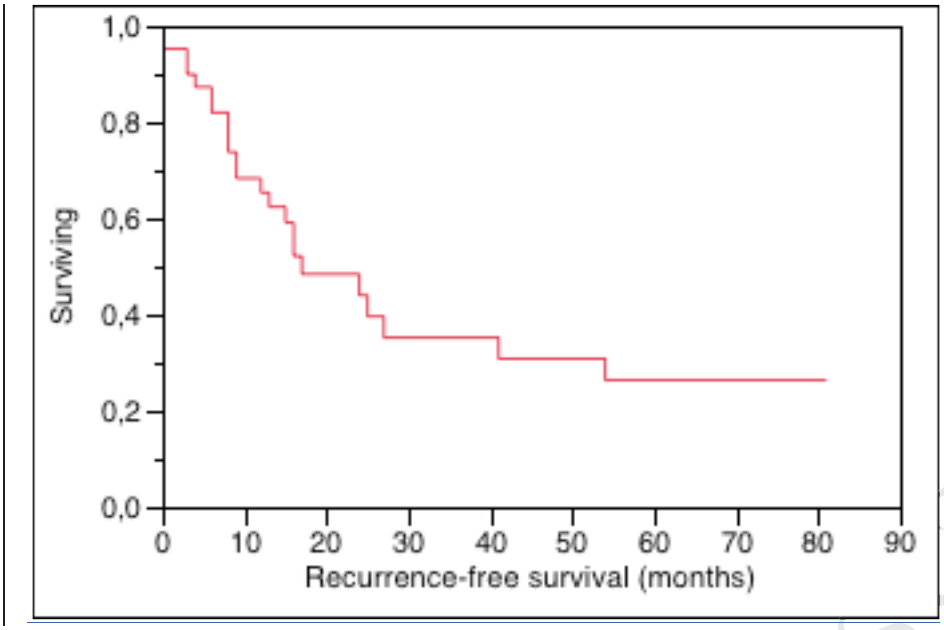

Fig 1 c: Estimated recurrence-free survival

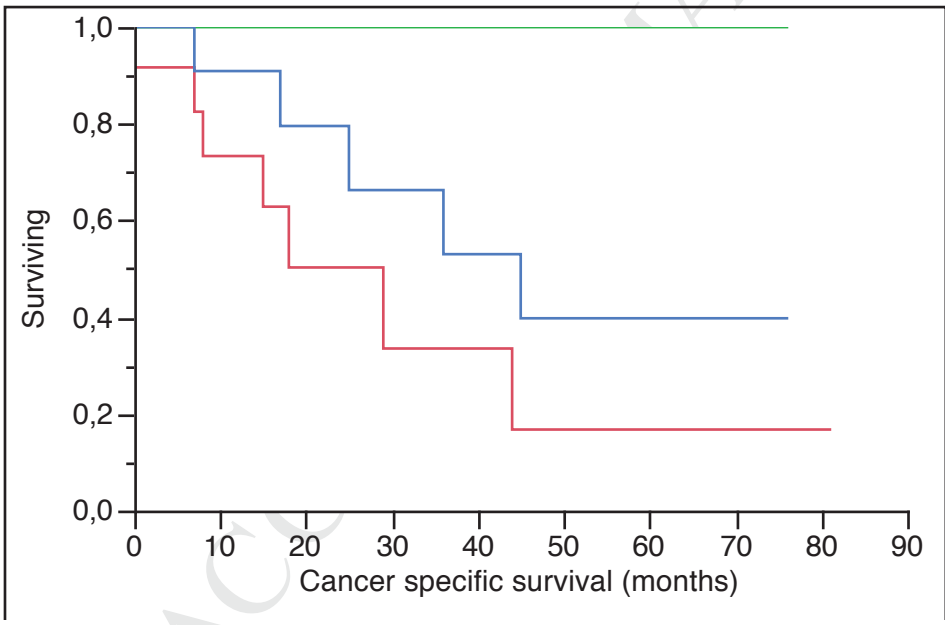

Figure 1 d: Cancer-specific survival according to the origin of primary tumor

1 : other primary tumors

2 : renal cancer
3 : pulmonary cancer

Highlights

- Positive surgical margins and complications rates were 26.7% and 17.8% respectively
- Tumor size >5 cm was the only predictor of positive margins and/or complication
- Non renal origin of the primary tumor was the only survival prognostic factor