Author’s response to reviews

Title: Prognostic benefit of surgical management in patients with renal cell carcinoma extending to renal vein and inferior vena cava: 17-year experience at a single center

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Author’s response to reviews:

Dr. Philippe Spiess
Editor
BMC Urology

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Re: MS: 1155916256103276

Dear Dr. Spiess,

We would like to thank the editors and reviewers of our manuscript, which is now entitled “Prognostic benefit of surgical management in renal cell carcinoma patients with thrombus extending to the renal vein and inferior vena cava: 17-year experience at a single center”, for their extensive and thoughtful comments. We have extensively revised our manuscript based on these comments.

The manuscript has also been revised by a native English speaking editor to improve the clarity of the language. Our point-by-point responses to the comments of the reviewers, and details of the revisions made to the manuscript, are attached.

We appreciate your consideration of our revised manuscript for publication in
Responses to the comments of Reviewer #1 (Gaetano Ciancio)

1. Could the authors describe “multiple organ metastases” for RCC in renal vein, I, II, III and IV groups?

We have included detailed information about “multiple organ metastases” for RCC in renal vein, I, II, III and IV groups in our revised manuscript and Table1, as follows (page 9, lines 4-7).

“The prevalence of multiple organ metastases in surgical and non-surgical treatment group was 6% and 57% in renal vein, 14% and 50% in level I, 15% and 100% in level II, 25% and 50% in level III, 0% and 67% in level IV, respectively.”

We have included detailed information about the 14 patients with multiple organ metastases in our revised manuscript, as follows (page 9, lines 15-19).

“The reason for non-surgical management was multiple organ or unresectable metastasis in 14 patients (lung and lymph nodes, \(n = 6\); lung and bone, \(n = 2\); lung, \(n = 2\); lung, bone, and brain, \(n = 1\); lung and liver in a patient with duodenal invasion, \(n = 1\); brain, \(n = 1\); lymph nodes, \(n = 1\)”

2. Could the authors report the cause of death of the non-surgical group? What type of morbidity did the non-surgical group have? Could any be prevented by surgery?

The reasons for non-surgical management were documented previous part (on page 9, lines 15-20). The type of main cause of death is described in the revised manuscript, as follows (page 9, lines 24 to page 10, line 2).

“In all patients who did not receive surgical management, the main cause of death was cachexia.”

3. Why the authors consider multiorgan metastases a contraindication for surgery?

Patients with multiple organ metastases were thought to have a limited life expectancy in spite of challenging surgery. Other factors were also taken into account when deciding whether to perform surgery. The reasons for non-surgical management are described in the revised manuscript, as follows (on page 6, line
The basic treatment strategy for RCC with tumor thrombus was surgical extirpation of the tumor, with the aim of prolonging survival. Patients received non-surgical management if they refused surgery or if they had worsening systemic comorbidities, ECOG-PS >3, extremely advanced metastatic disease that would be difficult to control, or severe complications.

4. Figure 2 needs to be fixed

We apologize for the typographical error. We corrected “Surgery not performed 30 cases” to “Surgery performed 30 cases”.

5. In reality the authors have few patients to make any conclusions. Level III and IV are the type of RRC that can have more impact for outcome in comparison of RV, level I and II, therefore they have only 10 patients in the surgical group and 7 in the non-surgical group.

We agree with this comment, and have mentioned the small number of patients in the limitations section. Additional studies with larger numbers of patients are needed to clarify the benefits of surgical management in various patient groups.

6. Did the authors note differences in blood loss, transfusions, and surgical techniques depending of the level of the tumor thrombus?

The details of surgical techniques, blood loss, and transfusion are discussed in the revised manuscript, as follows.

Methods section (page 7, lines 3-13).

“Surgical management
All patients who received surgical management underwent radical nephrectomy, thrombectomy, and lymph node dissection. Surgery was performed via a flank or midline abdominal incision, depending on surgeon preference and the characteristics of the tumor and associated thrombus. In patients with supradiaphragmatic IVC thrombus, the liver was mobilized to expose the retrohepatic vena cava by incision of the falciform, triangular, and coronary ligaments, in cooperation with the Department of Gastroenterological Surgery. In patients with right atrium thrombus, sternotomy and extracorporeal circulation with cardiopulmonary bypass were performed in cooperation with the Department of Cardiothoracic Surgery.”

Results section (page 11, lines 1-3).

“In patients who received surgical management, the median blood loss was 744 g (range 10–3,221 g). Five patients with blood loss >1,500 g received blood transfusions.”

Results section (page 12, lines 9–13).

“In patients with thrombus level I, II, and III/IV who received surgical management, the median blood loss was 620 g (range 80–953 g), 1,255 g (range
810–5,100 g), and 3,397 g (range 2,454–13,800 g), respectively. Eighteen patients underwent blood transfusion because of blood loss >1,000 g or hypotension.”

7. Given that the patient outcome data in this study are pretty limited, in order for this report to add meaningfully to the literature, I think there should be a much more detailed literature review and comparison of outcomes.

In accordance with this comment, we have added the following discussions to the revised manuscript.

Page 14, lines 16–22.
“The largest reported series of RCC patients with renal vein and IVC thrombus, which included 1,122 patients with a median follow-up period of 24.7 months, found a median overall survival time of 33.8 months [19]. However, the role of surgical management in that series is unclear because outcomes were not compared between RCC patients with tumor thrombus who underwent surgery and those who did not.”

Page 16, line 24 to page 17, line 7
“The relationship between the level of IVC thrombus and prognosis is currently unclear [10,19-21]. Kim et al. reported that the level of tumor thrombus was not a predictor of cancer-specific survival on multivariate analysis (HR 0.95, P = 0.872) [20]. In contrast, Martinez-Salamanca et al. reported that tumor thrombus extending above the diaphragm (HR 2.10, P = 0.00), tumor diameter >7 cm, Furman grade, fat invasion, lymph node metastasis, and presence of distant metastasis were independent predictors of cancer-specific survival [19].”

Page 17, lines 14–17.
“Lambert et al. studied RCC patients with venous tumor thrombus, and found a 5-year cancer-specific survival rate of 10.0% in patients with distant metastasis and 60.3% in those without distant metastasis [22].”

8. Quality of written English: Needs some language corrections before being published.

The entire manuscript has been revised by a native English speaking editor to ensure accuracy and increase the clarity of the language.

Responses to the comments of Reviewer #2 (Yasushi Yoshino)

1. The authors did not describe how many patients underwent surgical treatment (so called metastasectomy) for patient with lymph node disease and distant metastases and how many failed in the insufficient resection (positive surgical margin disease or remaining tumor) in surgery group. If most patients had untreated metastatic disease in surgery group, the significance of nephrectomy with tumor thrombus would be equaled to the cytoreductive surgery.

These details are described in the revised manuscript, as follows.
For patients with thrombus extending to the renal vein: page 10, lines 19-20.
“None of these patients underwent metastasectomy, except for lymph node dissection.”

For patients with thrombus extending to the IVC: page 11, lines 24 to page 12, line 4.
“Ten of these patients underwent metastasectomy (adrenal, n = 1; bone, n = 1; lymph nodes, n = 2; liver, n = 1; liver, n = 2; IVC, n = 4) at the time of radical nephrectomy with thrombectomy. Four of these patients had positive surgical tumor margins, and these four all died within 3 years of surgery (median overall survival time: 26 months).”

2. Cardiopulmonary bypass was required in some patients. However, it is uncertain how many patients received renal artery embolization prior to the surgery. Subramanian VS et al reported increased risk of perioperative death in embolization group [Subramanian VS et al. Urol 74: 154, 2009].

This is clarified in the revised manuscript as follows. (Page 9, lines 9-10).

“None of the patients who received surgical management underwent preoperative renal artery embolization.”

3. Section of Background, Page 5, and Line 3: Another article should be considered to add the reference list which describes 4 to 15% of patients with RCC demonstrate direct tumor extension into the IVC [O’Donohoe MK et al. Br J Urol 60: 492, 1987].

We have cited this reference in the revised manuscript, as follows (page 5, lines 2–3).

“In renal cell carcinoma (RCC), thrombus extends to the inferior vena cava (IVC) in 4–15% of patients [1,2].”

4. Section of Background: The first appearance in references was the surgery that Berg AA reported in 1913 [5]. It is only for author’s reference and recommendations for improvement but which the author can choose to ignore.

We have deleted this reference from the manuscript.

5. Section of Background, Page 5, and Line 6: Perioperative mortality rates ranged from 2 to 9% with my knowledge. Please consider to show the incidence of surgical mortalities to compare your intuitive experiences with early death caused by surgeries.

At our institute, we experienced only three cases of perioperative death after urological surgery from 2005 to 2012, giving a perioperative mortality rate of <0.1%. In the literature, the reported perioperative mortality rate for general surgery is 0.1% and for radical nephrectomy with IVC thrombectomy is 5–10%. In the current series, the perioperative mortality rate in patients with thrombus
extending to the IVC was 6.7% (2/30 cases). The following changes were made to the revised manuscript.

Page 5, lines 5–9.

“However, surgery carries significant risks of perioperative morbidity and mortality [4]. Previous studies reported perioperative mortality rates of 0.1% for general surgery patients overall and 5–10% for patients undergoing radical nephrectomy with IVC thrombectomy [5-7].”

For patients with thrombus extending to the renal vein: page 11, line 5.

“there were no deaths within 1 month of surgery”

For patients with thrombus extending to the IVC: page 12, line 15.

“two patients (6.7%) died within 1 month of surgery”

Page 14, lines 6-9.

“In this study, the perioperative mortality rate in patients with IVC thrombus was 6.7%, which is significantly higher than the overall perioperative mortality rate of <0.1% in patients who undergo urological surgery at our institute.”

6. Section of Follow-up schedule, Page 8, and Line 2: Did post-operative CT scan include chest and brain or only for abdominal check-up? Did you check chest X-ray for follow-up examinations?

7. Section of Follow-up schedule: Did further treatment start from the first appearance of new metastatic regions or just after surgery as adjuvant therapy?

The follow-up details are clarified in the revised manuscript, as follows (page 7, lines 16–23).

“Patients were evaluated for postoperative recurrence and general condition by blood count, blood biochemistry analysis, and chest and abdominal CT every 3 months for the first year, and every 6 months thereafter. Chest CT was used instead of chest X-ray in consideration of the relative risks and benefits of these examinations. Brain CT was performed when any new metastatic lesions or neurological symptoms were observed. Patients did not receive routine postoperative adjuvant therapy, but additional treatment was given when new metastatic lesions were identified.”

8. Section of Statistical analysis and Discussion: The level of tumor thrombus had no impact on overall survival in this study. Where the thrombus levels were divided? Between RV thrombus and IVC thrombus or any other partition between suprahepatic thrombus and infrahepatic?

In this study, patients were divided into a group with thrombus extending to the renal vein only and a group with thrombus extending to the IVC. We also compared overall survival between patients with infrahepatic and suprahepatic thrombus, and obtained similar results. This is discussed in the revised manuscript, as follows.
“Patients in the RV thrombus group and IVC thrombus group were analyzed separately.”

“In this study, thrombus level of IVC was not identified as a significant predictor of overall survival. There was also no significant difference in overall survival between patients with suprahepatic IVC thrombus and those with infrahepatic IVC thrombus only (data not shown). This lack of association between thrombus level and survival may be due to the relatively small sample size.”