



Adrenocortical carcinoma with venous tumor invasion: is there a role for mini-invasive surgery?

Alberto Olivero^{1,2} · Kan Liu³ · Enrico Checchucci⁴ · Lei Liu⁵ · Lulin Ma⁵ · Guoliang Wang⁵ · Guglielmo Mantica² · Stefano Tappero² · Daniele Amparore⁴ · Michele Sica⁴ · Cristian Fiori⁴ · Qingbo Huang³ · Shaoxi Niu³ · Baojun Wang³ · Xin Ma³ · Xiaofei Hou⁵ · Francesco Porpiglia⁴ · Carlo Terrone² · Xu Zhang³

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Abstract

Objective This study aims to investigate early oncologic outcomes in patients with adrenocortical carcinoma (ACC) with venous invasion (VI) treated using both open and mini-invasive approaches.

Patients and materials We conducted a retrospective analysis of 4 international referral center databases, including all the patients undergoing adrenalectomy for ACC with VI from January 2007 to March 2020. According to CT scan or MRI, the tumor thrombus was classified into four levels: (1) adrenal vein invasion; (2) renal vein invasion; (3) infra-hepatic Inferior vena cava (IVC); and (4) retro-hepatic IVC. In addition, we divided our patients into patients who had undergone open surgery and mini-invasive surgery.

Results We identified 20 patients with a median follow-up of 12 months. The median tumor size was 110mm. ENSAT stage was II in 4 patients, III in 13 patients, and IV in 3 patients. Tumor thrombus extended in the adrenal vein ($n=5$), renal vein ($n=1$), infra-hepatic IVC ($n=9$), or into the retro-hepatic IVC ($n=5$). Ten patients were treated with a mini-invasive approach. The patient treated with an open approach reported a more aggressive disease. The two groups did not differ in surgical margins, surgical time, blood losses, complications, and length of stay. The prognosis resulted worse in the patient undergoing open. Kaplan–Meier analysis indicated a difference in OS for the patients stratified by ENSAT stage (Log-rank $p=0.011$); we also reported a difference in DFS for patients stratified for thrombus extension ($p=0.004$) and ENSAT stage ($p<0.001$).

Conclusion The DFS of patients with VI from ACC is influenced by the staging and the extension of the venous invasion; the staging influences the OS. The mini-invasive approach seems feasible in selected patients; however, further studies investigating the oncological outcomes are needed.

Patient summary A mini-invasive approach for adrenal tumors with venous invasion is an explorable option in very selected patients.

Keywords Adrenocortical carcinoma · Tumor thrombectomy · Mini-invasive surgery · Laparoscopic surgery · Robotic surgery

Alberto Olivero, Kan Liu and Enrico Checchucci contributed equally to this work.

✉ Alberto Olivero
alberto.olivero@ospedaleniguarda.it

✉ Baojun Wang
baojun40009@126.com

¹ Department of Urology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

² Department of Urology, Policlinico San Martino Hospital, University of Genoa, Genoa, Italy

³ Department of Urology, Chinese PLA General Hospital, Beijing, China

⁴ Division of Urology, Department of Oncology, School of Medicine, University of Turin, San Luigi Hospital, Orbassano, Turin, Italy

⁵ Department of Urology, Peking University Third Hospital, Beijing, China

Introduction

Adrenocortical carcinoma (ACC) is a rare disease combined with a poor prognosis [1]. The increasing use of abdominal imaging decreases the percentage of metastatic tumors at the diagnosis to 25% [2]; the lesions are often extensive with possible extension into the venous system; controversially, the invasion of the venous system by the tumor is not well described, and only four case series are available [3–6].

The feasibility and the safety of ACC resection and venous tumor thrombectomy are poorly described, and its oncological outcomes have yet to be investigated. However, in recent years mini-invasive indications for ACC have been extended in referral centers, overtaking the 6-cm limit [7]. Simultaneously, a significant step has been made in the surgical management of locally advanced renal tumors with tumor thrombus, allowing a mini-invasive approach in IVC thrombus [8] and when the tumor infiltrates the vein walls [9].

Therefore, the current study aims to investigate early oncologic outcomes in patients with ACC with venous invasion and verify the feasibility and safety of a minimally invasive approach versus traditional open surgery in this rare clinical presentation.

Patients and methods

Patient selection and group formation

To identify the patients for this study, we conducted a retrospective analysis of the prospectively maintained institutional databases from four international referral centers for adrenal surgery (Chinese PLA General Hospital, Beijing; San Luigi Gonzaga Hospital, Orbassano; Peking University Third Hospital, Beijing; Ospedale Policlinico San Martino, Genova). We selected histologically proven ACC with tumor thrombus invasion undergone surgical treatment between January 2007 and March 2020.

All the centers involved have at least a dedicated radiologist and an expert pathologist in adrenal malignancy. The surgical approach choice was based on the patient's clinical and oncological characteristics and the single-center surgical experience. All the patients performed at least a total-body axial imaging exam within the first 6 months after the surgery. The absence of a proper follow-up was the only exclusion criterion from the study.

The following parameters of each case were collected:

- Patients' baseline characteristics: age, gender, race, body mass index (BMI), and comorbidities profile, including diabetes mellitus and hypertension. A detailed hormonal

workup was performed for each patient, including aldosterone, cortisol, and plasmatic catecholamines.

- Oncological and pathology characteristics: side, size, stage according to tumor–node–metastasis (TNM) classification and European Network for the Study of Adrenal Tumors (ENSAT) staging system [10]. According to the co-axial imaging performed during the preoperative tests (contrast-enhanced computer tomography (CT) or magnetic resonance imaging (MRI), we classified the tumor thrombus invasion into four levels: level 1, thrombus reach the main adrenal vein; level 2, thrombus reach the renal vein; level 3, thrombus inside the infra-hepatic Inferior vena cava (IVC); and level 4, tumor thrombus reach the retro-hepatic IVC (Fig. 1). We also evaluated margin status and adjacent organ invasion.
- Perioperative variables: surgical approach (open, laparoscopic, or robot-assisted laparoscopic surgery; transperitoneal vs. retroperitoneal approach), operative time, estimated blood losses (EBL), intraoperative complications, conversions to a different approach, concurrent ipsilateral nephrectomy, postoperative complication (classified according to the modified Clavien–Dindo classification) [11], and length of stay.
- Follow-up data: adjuvant chemotherapy administration, length of follow-up, tumor recurrence, tumor metastasis, disease-free survival (DFS), and overall survival (OS).

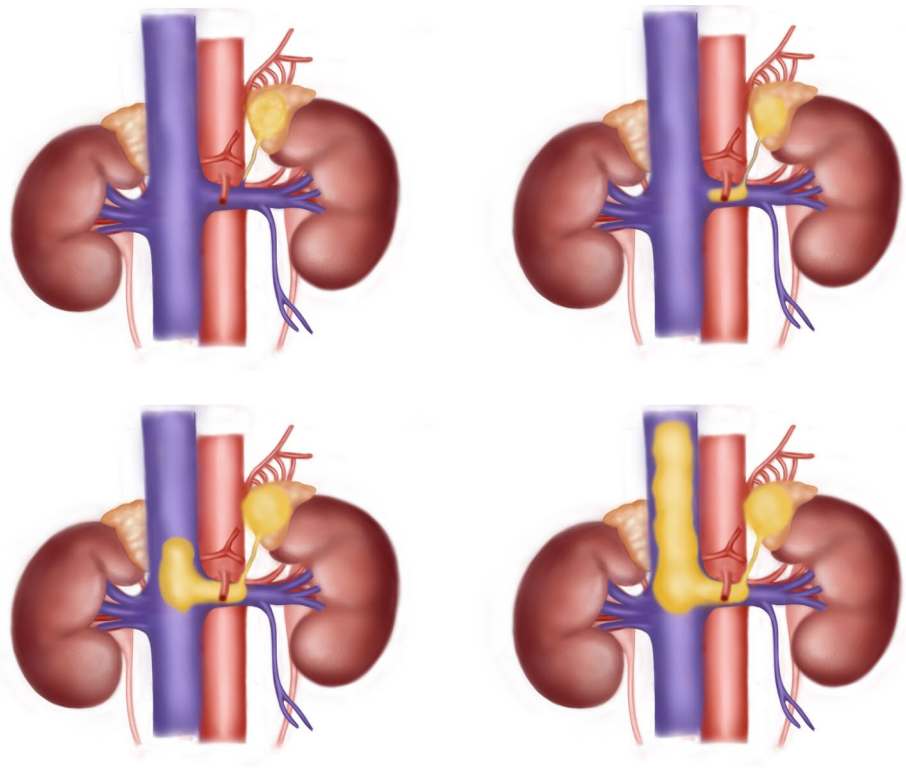
We divided patients into two groups: patients who underwent open surgery and a mini-invasive approach (both laparoscopic and robotic surgery).

Minimal invasive surgical technique

Robotic approach for level III thrombi Patients were positioned in the left lateral decubitus position. In this position, right adrenalectomy and thrombectomy can be performed.

Four robotic and two or three assistant ports were used and positioned as described for inferior vena cava thrombectomy [12]. After the hepatocolic ligament incision, the assistant retracted the liver cephalically. The ascending colon was reflected medially, and the IVC was exposed. Then the ventral surfaces of the right and left renal veins were isolated. The IVC was dissected above and below the insertion of the renal and adrenal veins. The right adrenal vein was also isolated. The left renal vein was dissected circumferentially in the interaortocaval space. Cross-clamping of the IVC was performed by vessel loops. The right adrenal and renal veins are closed using an Endo GIA device. The caudal IVC, the left renal vein, and the cephalic IVC were sequentially clamped. After clamping, the IVC wall was open, and the thrombus was removed. The thrombus was placed in an endoscopic bag to avoid tumor dissemination. After the IVC

Fig. 1 The tumor thrombus classification proposed: level 1, thrombus reach the main adrenal vein; level 2, thrombus reach the renal vein; level 3, thrombus inside the infra-hepatic Inferior vena cava [IVC]; and level 4, tumor thrombus reach the retro-hepatic IVC



lumen was irrigated with heparinized saline, a 5-0 polypropylene suture was used to close the IVC.

Right adrenalectomy and nephrectomy were completed in a transperitoneal fashion in the same position.

For left-side disease, after thrombectomy, the operative room staff converted the patient's position to a right lateral decubitus position to perform the left adrenalectomy and nephrectomy.

Robotic approach for level IV thrombi For retro-hepatic thrombi, complete liver mobilization is needed. After the robot docking, the perihepatic ligaments were resected, including the round and falciform ligaments and the right and left triangular and coronary ligaments. Additional hepatic veins were ligated. Both the right and left liver lobes were mobilized away from the IVC. Vessel tourniquets were placed in the sovra-hepatic and infra-diaphragmatic IVC above the thrombus under intraoperative ultrasound guidance. In this fashion, the surgeon could achieve control of retro-hepatic and IVC.

Statistical analysis

Continuous variables were reported using medians and interquartile ranges (IQR). Frequencies and proportions were used for categorical variables. A Kaplan–Meier plot was used to describe the DFS between the groups, and the log-rank test was used to test the effect of the variables of

interest (ENSAT Stage and Thrombus extension). All the statistical analyses were performed using SPSS v.23 (IBM Corp., Armonk, NY, USA), and significance was considered for two-tailed $p < 0.05$.

Results

Twenty patients who underwent adrenalectomy for ACC with venous invasion were included in the study. During the study period, other 281 ACC without venous invasion were treated. Patients' baseline characteristics are reported in Table 1. The median age was 51 years (IQR= 28–58). Nine patients (45%) presented a right-side disease. The median tumor size was 110 mm (IQR= 78–137). ENSAT stage was classified as II in 4 patients, III in 13 patients, and IV in 3 patients. Tumor thrombus extended in the adrenal vein in 5 patients, in the renal vein in one, in the infra-hepatic IVC in 9, and into the retro-hepatic IVC in five.

Ten patients were treated with a mini-invasive approach (5 robotic-assisted and five laparoscopic); consequently, ten underwent open surgery. All the patients treated with open surgery underwent transperitoneal surgery. In the mini-invasive group, four patients (40%) were treated with the retroperitoneal approach while six (60%) with the transperitoneal approach. The characteristics and results of the two groups are summarized in Table 2. Briefly, the two groups did not differ in the demographic characteristics except for

Table 1 Baseline characteristics of the patients

Variable	All cases N = 20 (100%)
Age, median [IQR]	51 [38–58]
Male (%)	9 (45)
Ethnicity	
Asian (%)	12 (60)
Caucasian (%)	8 (40)
BMI, median [IQR]	24.8 [21.3–27.5]
Laterality	
Right (%)	9 (45)
Left (%)	11 (55)
Symptoms at diagnosis (%)	9 (45)
Hormonally active (%)	6 (30)
Tumor size, mm, median [IQR]	110 [78–137]
pT stage	
T2 (%)	4 (20)
T3 (%)	1 (5)
T4 (%)	15 (75)
Tumor thrombus extension	
Adrenal vein (%)	5 (25)
Renal vein (%)	1 (5)
Infra-hepatic IVC (%)	9 (45)
Retro-hepatic IVC (%)	5 (25)
Other organs' involvement	
Liver (%)	2 (10)
Kidney (%)	5 (25)
ENSAT stage	
II (%)	4 (20)
III (%)	13 (65)
IV (%)	3 (15)

IQR, interquartile range; BMI, body mass index; IVC, inferior vena cava; ENSAT, European Network for the Study of Adrenal Tumors

Asian ethnicity (3 in open approach vs. 9 in mini-invasive). However, patients treated with an open approach presented a more aggressive disease with significant differences in the T stage, ENSAT stage, and thrombus extension.

Surgical outcomes

We reported similar outcomes regarding surgical margins, operating times, blood losses, and intraoperative transfusion requirements. The post-operative complications rate was similar in the two groups. However, we reported a grade III complication (bleeding from the resection bed treated with surgical exploration) in the open group, while none were in the mini-invasive group. No postoperative complications regarding IVC patency have been reported. We found a trend toward the shorter length of stay in the minimally invasive group; however, it did not reach statistical significance (7 vs. 9 days).

Oncological outcomes

The median follow-up was similar in the two groups (11 months in open vs. 14 months in MI). An equal rate of patients (60%) underwent mitotane-based chemotherapy after the surgery in both groups. However, according to the more aggressive disease, the prognosis was worse in the patient undergoing an open approach: no patients were found disease-free at the last follow-up time, while six died from the disease (60%). In the mini-invasive patients, six patients (60%) were disease-free, one (10%) with local recurrence and one (10%) with distant metastasis, and two (20%) patients died of ACC progression.

Kaplan–Meier analyses have shown significant difference in OS for patients stratified by ENSAT stage (log-rank $p = 0.011$) (Fig. 2A) but not for thrombus extension ($p = 0.063$) (Fig. 2B). We reported a difference in DFS for patient stratified for thrombus extension ($p = 0.004$) and ENSAT stage ($p < 0.001$) (Fig. 2C and D).

Discussion

In this multicentric study, we compared the outcomes of patients with ACC with venous tumor thrombus extension treated with open surgery or a minimally invasive approach. We did not report differences in intraoperative and postoperative outcomes. However, mini-invasive surgery patients had favorable oncological features and reported better outcomes during the follow-up.

ACC is a rare malignancy with an estimated incidence of 0.72 cases/per million inhabitants, causing 0.2% of the cancer-related deaths in the USA [13]. Venous thrombus invasion is a rare presentation of ACC, and its incidence is unknown.

Historically, the laparoscopic approach has discouraged adrenal malignancies bigger than six centimeters in one dimension [14, 15]; in the last years, pure laparoscopic and robot-assisted laparoscopic surgeries have become an accepted option for adrenal tumors greater than 6 cm, in selected referral centers [7, 16].

Clinical presentation with tumor thrombus in the adrenal vein is still considered a contraindication for a mini-invasive approach [17]. Consequently, the treatment of adrenal masses with tumor thrombus is only reported as a case report [18]. Therefore, our study has clinical significance because it is the first case series of ACC with venous invasion treated with a mini-invasive approach.

Several demographics and clinical characteristics influence the prognosis of ACC patients: age is correlated with a reduction in OS. However, it is unclear if this is true for DFS [19]. Worse tumor staging, metastatic status at presentation, and the number of organs affected by metastasis determined

Table 2 Characteristics and surgical and oncological results of the two groups

Variable	Open approach N = 10	Mini-invasive approach n = 10
Age, median [IQR]	53 [44–65]	46 [35–57]
Male (%)	4 (40)	5 (50)
Ethnicity		
Asian (%)	3 (30)	9 (90)
Caucasian (%)	7 (70)	1 (10)
BMI, median [IQR]	23.9 [21.0–28.7]	25.7 [21.1–26.9]
Laterality		
Right (%)	4 (40)	5 (50)
Left (%)	6 (60)	5 (50)
Symptoms at diagnosis (%)	4 (40)	5 (50)
Hormonally active (%)	3	3
Tumor size, median [IQR]	110 [85–124]	84 [65–112]
pT stage		
T2 (%)	0	4 (40)
T3 (%)	0	1 (10)
T4 (%)	10 (100)	5 (50)
Tumor thrombus extension		
Adrenal vein (%)	0	5 (50)
Renal vein (%)	1 (10)	0
Infra-hepatic IVC (%)	7 (70)	2 (20)
Retro-hepatic IVC (%)	2 (90)	3 (30)
Other organs' involvement		
Liver (%)	1 (10)	1 (10)
Kidney (%)	4 (40)	1 (10)
ENSAT stage		
II (%)	0	4 (40)
III (%)	7 (70)	6 (60)
IV (%)	3 (30)	0
Completeness of resection (R0, %)	5 (50)	6 (60)
Operating time (min), median [IQR]	292 [201–326]	265 [139–343]
EBL (mL), median [IQR]	575 [412–1025]	600 [125–1550]
Intraoperative		
Transfusion requirement (%)	4 (40)	50 (50)
Clavien–Dindo complications, n (%)		
1–2	5 (50)	4 (40)
3	1 (10)	0
Discharge (POD), median [IQR]	9 [8–13]	7 [5–11]
Adjuvant chemotherapy, yes (%)	6 (60)	6 (60)
Follow-up, median	11	14
Status (%)		
Alive and disease-free	0	6 (60)
Alive with local recurrence	1 (10)	1 (10)
Alive with distant progression	3 (30)	1 (10)
Death for other causes	0	0
Death for cancer	6 (60)	2 (20)

IQR, interquartile range; *IVC*, inferior vena cava; *ENSAT*, European Network for the Study of Adrenal Tumors; *EBL*, estimated blood losses; *POD*, post-operative day

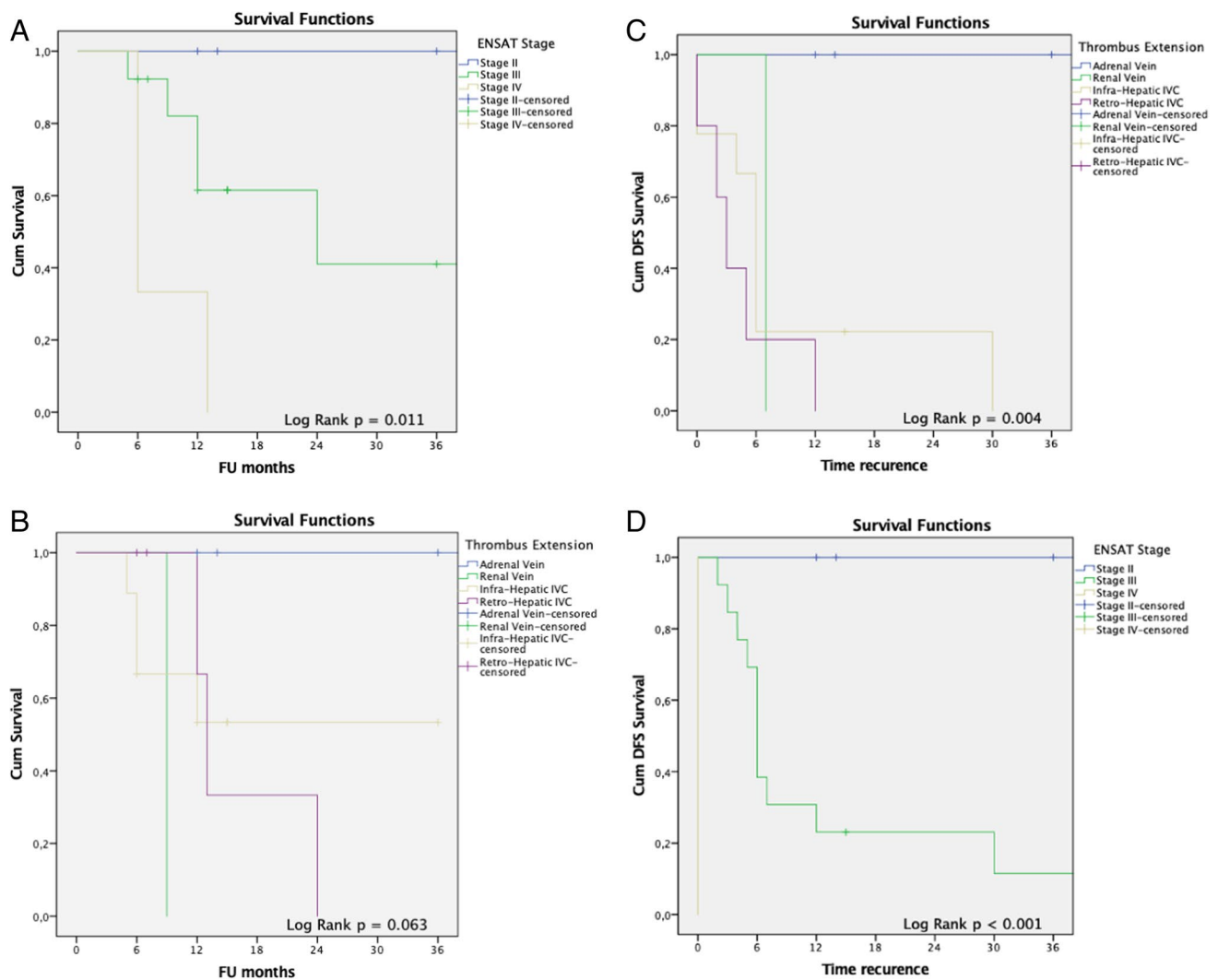


Fig. 2 Kaplan–Meier curve for overall survival (**A** and **B**) and disease-free survival (**C** and **D**) of the patients

a worse prognosis [19, 20]. Positive surgical margin and worse tumor thrombus extension diminish DFS and OS [21].

Our results confirm that the best predictor of recurrence is the pathological TNM stage. The minimally invasive approach is a favorable prognostic factor, although the more favorable oncological characteristics influence the minimally invasive group.

Few series, including patients with ACC and venous tumor invasion, exist in the literature. Laan and colleagues identified 65 patients with advanced ACC, of whom 28 presented with tumor thrombus in the inferior vena cava; this subgroup showed a worse survival after 36 months [3]. Another single-center series from Chiche et al. reported 17 patients with ACC and venous thrombus treated with open surgery: the authors reported

a median survival of 8 months [5]. Similarly, another multicentric study on a group of 38 patients with ACC and neoplastic thrombus reported a median survival of 18 months. Recently, Ciancio et al. collected 33 cases of adrenal tumors with or without tumor thrombus in the inferior vena cava, of whom 11 were ACC, and 8/33 patients had tumor thrombus in the IVC: they managed to get complete resection in all the cases. They reported worse survival for ACC patients with tumor thrombus, as four patients died of their disease [6].

Potentially our study, reporting better outcomes for minimally invasive surgery over open surgery, paves the way for other studies regarding the use of laparoscopic and robotic surgery in advanced adrenal tumors. In the future, this will also be helpful to investigate if there is space for a retroperitoneal

approach for this malignancy, especially if the thrombus is below the IVC, where a retroperitoneal approach could speed further the surgery recovery and shorten the length of stay in the hospital.

Our work is not exempt from limitations. First, the retrospective design and the number of patients are critical limits. However, a prospective design and a more significant number of cases for sporadic clinical presentations are almost impossible to realize. Second, patients treated with a mini-invasive approach were selected with lower dimensions and lower stage and were treated mainly in China; this does not allow us to obtain any definitive conclusion regarding the mini-invasive surgery; however, we wanted to report the experience. Last, the median follow-up time was relatively short, although it allows preliminary conclusions in very aggressive diseases.

Conclusion

Our study reports acceptable surgical outcomes for patients affected by ACC with venous invasion treated with open and mini-invasive approaches. Furthermore, the disease-free survival of patients with venous invasion from ACC is influenced by the staging and the extension of the venous invasion; the clinical stage affects the overall survival. Therefore, the mini-invasive approach seems feasible in selected patients, but further studies investigating the oncological outcomes are needed.

Authors' contributions AO, protocol/project development, data collection, data analysis, and manuscript writing/editing. KL, protocol/project development, data collection, and data analysis. EC, protocol/project development, data collection, and data analysis. LL, protocol/project development and data collection. GW, protocol/project development and data collection. GM, manuscript writing/editing. PD, manuscript writing/editing and data analysis. ST, protocol/project development. DA, manuscript writing/editing. MS, protocol/project development. CF, protocol/project development. QH, protocol/project development. SN, protocol/project development. BW, protocol/project development, data analysis, and manuscript writing/editing. XM, protocol/project development, data analysis, and manuscript writing/editing. XH, protocol/project development. FP, protocol/project development, data analysis, and manuscript writing/editing. CT, protocol/project development, data analysis, and manuscript writing/editing. XZ, protocol/project development, data analysis, and manuscript writing/editing. All authors read and approved the final version of the manuscript.

Declarations

Ethical approval Not applicable.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

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