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Surgical Treatment Strategy with Combined Cardiopulmonary Bypass for Renal Cell Carcinoma with Tumor Embolism Developed in Inferior Vena Cava

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ABSTRACT

Objective: Renal cell carcinoma (RCC) with tumor thrombus in the inferior vena cava (IVC) presents surgeons with a technical intraoperative challenge because of the need for aggressive surgical management. In this study, we describe our method for surgical management with cardiopulmonary bypass (CPB) and investigate the long-term outcomes of RCC patients with and without CPB.

Methods: Fifteen patients with RCC underwent nephrectomy and IVC thrombectomy from May 2011 to December 2017. We retrospectively reviewed and analyzed the clinical course of all patients. Novick classification was used to assess the level of tumor thrombus extension into the IVC. Patient characteristics, surgical procedures, and postoperative outcome data in both groups were collected.

Results: Twelve patients were male and 3 were female, with an average age of 62.9 ± 10.9 years (range 46 to 82). The average operative times were 824 ± 335 minutes in the patients with CPB and 646 ± 162 minutes in those without CPB (P = .17). The average amount of intraoperative bleeding was 2125 ± 1315 ml in the patients with CPB and 3333 ± 1431 ml in those without CPB (P = .14). The same tendency was observed in patients of Novick levels 3 and 4. The mean observation period was 1061.4 days. No 30-day mortality was noted. There was no significant difference in all-cause survival between the patients with CPB and those without.

Conclusions: We conclude that surgical management with CPB and circulatory arrest may be a viable and safe method of treatment for RCC patients.

INTRODUCTION

Renal cell carcinoma (RCC), the most common tumor within urogenital malignant tumors, accounts for 3% of all solid cancers [Chan 2001]. Overall, RCC incidence rates have continued to increase (on average 2.5% per year), which may be partly attributed to the advancement of image diagnosis devices and methods [Chowdhury 2007]. Moreover, 20% to 30% of RCC patients have developed metastases at the time of diagnosis or after surgical resection [Janzen 2003]. Generally speaking, RCC tends to invade the renal venous system and form a tumor thrombus extension. Approximately 4% to 10% of patients with RCC have tumor thrombus invading the inferior vena cava (IVC), and 1% have tumor thrombus extending into the right atrium, with poor prognosis [Ciancio 2010; Marshall 1988]. However, some studies have demonstrated that 5-year survival rates for patients with tumor thrombi in the absence of metastases after aggressive surgical management were 32% to 68%, and that the level of thrombus was independent of the prognosis [Jemal 2010; Staehler 2000; Bachmann 2005].

In almost all patients with RCC and thrombus extension, radical nephrectomy with tumor thrombectomy is performed. It is known, however, that higher-level tumor thrombectomy requires highly invasive surgery and precise surgical management, which may be associated with high preoperative mortality and complication rates. In particular, increased complications in patients with level 3 and 4 thrombus extension seem to be due to invasive surgical procedures such as cardiopulmonary bypass (CPB) and veno-venous bypass [Ali 2013; Kaplan 2002; Lawindy 2012; Karnes 2008]. Precise excision of an intrahepatic caval tumor (level 3), including the approach to the liver, is performed in cooperation with thoracic surgeons and hepatobiliary pancreatic surgeons [Ciancio 2007; Ciancio 2005]. In cases of suprahepatic thrombus (level 4), CPB and circulatory arrest for complete removal of tumor thrombi are permitted; however, there is controversy regarding appropriate intraoperative management in patients with level 1 to 3 thrombi and whether methods such as CPB are appropriate [Blute 2004; Dominik 2013; Shuch 2011]. IVC cross-clamp and temporary venovenous bypass are among the surgical procedures used to remove tumor thrombi of level 1 to 3 without CPB, but in some cases we have seen unexpected and uncontrolled massive intraoperative hemorrhages. In this report, we investigate surgical management and the necessity of CPB in RCC invading the IVC.

MATERIALS AND METHODS

Study Design

We retrospectively analyzed all 15 patients who underwent nephrectomy and IVC thrombectomy at Teikyo University Hospital from May 2011 to December 2017. All patients gave informed consent, and the study protocol was approved by the ethics committee of Teikyo University. In accordance with

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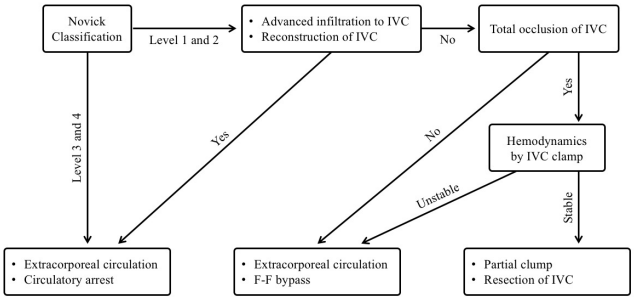

Figure 1. Surgical strategy based on Novick classification. F-F, femoral-femoral; IVC, inferior vena cava.

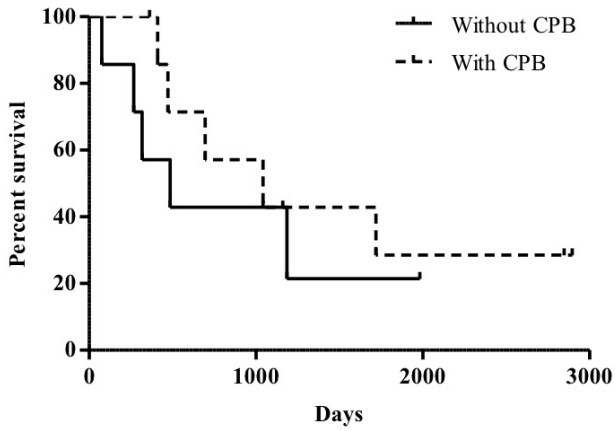

Figure 2. Kaplan–Meier estimates for all-cause survival in patients with and without cardiopulmonary bypass (CPB).

the American Joint Committee on Cancer Staging Manual [Neves 1987], all patients were assessed by hematologic and biochemical investigations, medical history, physical examinations, and diagnostic imaging such as abdominal Doppler ultrasonography, contrast-enhanced computed tomography, or magnetic resonance imaging. When our urologists considered additional evaluations necessary, bone scintigraphy and positron emission tomography were conducted. Novick classification was used to assess the level of tumor thrombus extension into the IVC [Blute 2004; Fuhrman 1982]: level 1, tumor thrombus involving the IVC at the level of the renal vein; level 2, infrahepatic IVC; level 3, intrahepatic IVC; and level 4, suprahepatic IVC or right atrium involvement.

To perform the complete resection of tumor thrombi, in the surgery conference, a medical team consisting of urologists, digestive surgeons, cardiovascular surgeons, and anesthesiologists discussed the classification and the size of tumor thrombus, the thickness of the IVC, and the ability to withstand circulatory dynamics by IVC cross-clamp. No mechanical circulatory support devices were used for the 7 patients without CPB. For those patients, general intraoperative parameters such as arterial pressure and respiratory rate were observed, and cross-clamp (and occasionally partial clamp) was performed for the complete resection of tumor thrombi. For patients with tumor thrombus of level 3, CPB was performed through cannulations of the common femoral artery and venous cava. In particular, where the tumor thrombus reached the junction of the hepatic vein and IVC, standard CPB techniques were used, including cannulation from the right atrium. Patients with tumor thrombus of level 4 underwent nephrectomy and IVC thrombectomy under CPB, except for patients in whom the tumor thrombus did not significantly infiltrate the IVC wall and was removed easily. For patients with severe infiltration to the IVC wall and difficult surgical exfoliation, partial patch repair and partial reconstruction with a vascular prosthesis were performed (Figure 1).

Study Variables and Operative Outcomes

Patient characteristics, surgical procedures, and postoperative outcomes in the patients with and without CPB were collected. Follow-up data were obtained from clinical records in our institution. All data and variables were compared, including intraoperative bleeding, operation time, postoperative coagulation function [prothrombin time (PT) and activated partial thromboplastin time (APTT)], length of stay in intensive care unit (ICU), hospitalization, postoperative metastasis, 30-day mortality, and long-term survival rates.

Statistical Analysis

Differences between the 2 groups were examined with Mann–Whitney U test for continuous variables and Fisher's exact test for categorical data. A P value <.05 was considered statistically significant. The Kaplan–Meier method for survival analysis and the log-rank test were used. Surgical complications were classified by the Clavien–Dindo grading system [Dindo 2004].

Ethical Approval

All subjects enrolled in this research gave their informed consent, which, alongside the described protocol, has been approved by the institutional committee on human research.

RESULTS

Twelve patients were male and 3 patients were female, with an average age of 62.9 ± 10.9 years (range 46 to 82). Eleven patients had tumors on their right kidneys, and 4 patients had tumors on the left (Table 1). Novick classification of all 15 patients showed 1 patient of level 1, 1 patient of level 2, 9 patients of level 3, and 4 patients of level 4 (Table 1). The average operative times were 824 ± 335 minutes in the patients with CPB and 646 ± 162 minutes in the patients without CPB. The average amount of intraoperative bleeding was 2125 ± 1315 ml in the patients with CPB and 3333 ± 1431 ml in the patients without CPB (Table 2). For the level 3 and 4 patients, the average operative time and the average amount of intraoperative bleeding in the patients without CPB were 637 ± 142 minutes and 3078 ± 732 ml, respectively. There were no significant differences in operation time and intraoperative bleeding between the groups. Indeed, the

Table 1. Patient characteristics and surgical procedure (n = 15)*

Characteristic	Value
Age (y)	62.9 ± 10.9
Female sex	3 (20.0)
Affected side = right	11 (73.3)
Novick classification (all patients)	
1	1
2	1
3	9
4	4
Novick classification (patients with CPB)	
1	0 (0)
2	0 (0)
3	4 (44.4)
4	4 (100.0)
IVC technique	
Partial resection	6
Partial resection + RA incision	5
Partial incision + RA incision + pancreas/spleen resection	1
Incision	2
Incision + RA incision	1

*Data are mean ± SD or n (%) unless noted otherwise. CPB, cardiopulmonary bypass; IVC, inferior vena cava; RA, right atrium.

Table 2. Operative characteristics according to Novick classification*

Characteristic	CPB	No CPB	*P*
All patients	n = 8	n = 7	
Operation time (min)	824 ± 335	646 ± 162	.17
Bleeding (ml)	2125 ± 1315	3333 ± 1431	.14
ICU length of stay (d)	6.6 ± 4.3	3.3 ± 2.9	.07
Hospitalization (d)	31.6 ± 14.8	26.5 ± 23.7	.31
Novick levels 3 and 4	n = 8	n = 5	
Operation time (min)	824 ± 335	637 ± 142	.18
Bleeding (ml)	2125 ± 1315	3078 ± 732	.08
ICU length of stay (d)	6.6 ± 4.3	2.0 ± 0.8	.03
Hospitalization (d)	31.6 ± 14.8	15.3 ± 3.1	.03

*Data are mean ± SD unless noted otherwise. CPB, cardiopulmonary bypass; ICU, intensive care unit.

postoperative coagulation function of both groups had no significant difference (PT, 16.1 ± 1.4 seconds in the patients with CPB and 16.8 ± 1.4 seconds in the patients without CPB, *P* = .19; APTT, 34.2 ± 4.8 seconds in the patients with CPB and 37.2 ± 3.4 seconds in the patients without CPB, *P* = .11).

There was no significant difference in the average ICU length of stay or average hospitalization between the groups; however, for the level 3 and 4 patients, these variables in the patients with CPB were significantly different from those without CPB (Table 2). No 30-day mortality was noted. Of 15 patients, only 1 (with CPB) had lung metastasis 2 years after RCC resection (P = .47). Follow-up was completed in all cases, with a mean follow-up time of 1061.4 days. Kaplan–Meier survival analysis showed no significant difference in all-cause survival between the patients with CPB and those without (*P* = .49; Figure 2).

Discussion

Generally speaking, when discussing the use of CPB in patients with RCC and IVC thrombus, both intraoperative bleeding and dissemination of tumor cells should be considered [Carrascal 2008]. The most common concern among surgeons in the application of CPB seems to be increased bleeding owing to full heparinization and hypothermia during CPB. Conversely, however, the use of CPB can actually provide a bloodless field while facilitating tumor incision and reducing the risk of tumor embolization [Belis 2000]. Although cross-clamp, and not auxiliary devices such as CPB, seems to be sufficient for many cases of level 1 and 2 thrombi, it is necessary to consider the risk of unexpected bleeding, because actual intraoperative findings have shown infiltrations of IVC that could not be detected by CT imaging. Moreover, in patients with level 3 and 4 thrombi, the use of CPB is thought to be indispensable, because resection of the tumor and safe detachment of the severe adhesion depend on controlling intraoperative bleeding.

Regardless of Novick classification, our patients underwent CPB and tumor resection without severe complications. The current findings also demonstrate that ICU length of stay and hospitalization were significantly prolonged in the patients with CPB, but there were no significant differences in coagulation function, operation time, or intraoperative bleeding with and without CPB. It is nonetheless crucial to consider the risks associated with CPB for each patient, because risks of up to 40% for serious complications, including renal and hepatic failure and postoperative sepsis, have been reported by some investigations [Chowdhury 2007; Magouliotis 2018].

The use of CPB is involved in the surgical procedures for RCC removal. Surgical options for IVC reconstruction include (1) direct repairment for small defects of IVC, (2) patch repair for large defects of IVC, and (3) graft replacement for severe invasion to the IVC wall [Dellaportas 2017]. Although direct repair is appropriate for patients with a small defect and mild invasion of IVC after RCC removal, patch repair and graft replacement with CPB are suitable in cases of severe and extensive IVC invasion to help stabilize the fluctuation of circulatory dynamics by IVC cross-clamp. Additionally, although the procedure of IVC cross-clamp should require a temporary IVC filter because several possible complications, including pulmonary embolism, are induced by

intraoperative procedures, circulatory arrest with CPB may allow for the detection of remaining tumor and also prevent the occurrence of pulmonary embolism induced by floating tumor mass [Novick 1990]. Particularly, because most patients who have intraoperative acute pulmonary embolism also have high mortality, CPB may be an essential method for the prevention of unnecessary complications. Thus, of the available surgical options for the removal of RCC, the use of CPB should be considered.

Few studies have examined the correlation between CPB and tumor cell dissemination. The dissemination of tumor cells by CPB is a controversial subject. Some reports demonstrated that there was a low possibility of the dissemination and progression of tumor cells under CPB [Novick 1990; Langer 2016]. It is worth noting that no patients under CPB in our study so far have experienced metastasis of renal cell carcinoma. One report demonstrated that CPB could be involved in the dissemination of cancer cells by temporary immune suppression through changing the balance of cytokines, including interferon-γ, interleukin (IL)-10, IL-6, and IL-8 [Sablotzki 1997]. A recent retrospective cohort of 43,347 patients who underwent coronary artery bypass graft (CABG) surgery with and without CPB examined cancer risk and mortality [Pinto 2013]. A statistically significant increase in the risk of skin melanoma and lung cancer was observed in CABG patients with CPB versus those without CPB. The current study showed that 1 patient under CPB had subsequent lung metastasis; however, there was no significant statistical difference between the patients with and without CPB. Although there is no clear consensus currently whether surgical procedures with CPB correlate with tumor cell dissemination, further research may enable us to provide the optimal surgical strategy for patients with cancer and cardiovascular diseases.

Study Limitations

This study was subject to limitations. The decision to use CPB was carefully considered depending on the specificities of each patient. Moreover, the size of the study was quite small (15 patients), and the follow-up time was fairly moderate. Although surgical outcomes at our single center might not be representative of a general patient cohort, we intend to continue to investigate the benefits of this management in future cases.

Conclusion

In this study, we conclude that a surgical strategy with CPB and circulatory arrest for RCC patients can be safely performed.

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