Long-term outcomes after resection of Stage IV cavoatrial tumour extension using deep hypothermic circulatory arrest


Objectives: Renal neoplasms frequently expand into renal veins and inferior vena cava from the early stages of the disease. In this study, we set out to define the long-term outcomes of patients with Stage IV tumorous cavoatrial extension, undergoing radical nephrectomy with excision of cavoatrial extension in deep hypothermic circulatory arrest (DHCA).

Methods: Thirty-five patients with Stage IV cavoatrial extension of renal cell carcinoma underwent radical nephrectomy combined with en bloc excision of cavoatrial tumour-thrombus extension, performed in DHCA. The preoperative staging of the tumour and assessment of the intravascular position of the tumour were performed using standard imaging techniques, including computed tomography angiography, magnetic resonance imaging and echocardiography. Patient data were collected in the patient data bank and analysed retrospectively.

Results: In this study cohort, we demonstrate acceptable long-term results (the mean overall survival of 4.9 ± 1.0 years and the 5-year survival rate of 40%) and outline several clear predictors for postoperative long-term survival of the patients. Preoperative evidence of remote tumour metastases and tumourous lymph node involvement conversely predicts inferior postoperative survival. However, a high local postoperative tumour recurrence rate does not limit patient survival in this group.

Conclusions: The data provide evidence for perioperative safety and acceptable long-term results of radical nephrectomy with excision of cavoatrial extension in DHCA in patients with Stage IV cavoatrial extension of renal neoplasm. Thus, this radical surgical procedure can provide effective long-term palliation in the absence of evident metastatic disease.

Keywords: Cavoatrial tumour extension • Circulatory arrest • Deep hypothermia • Renal cell carcinoma

Introduction

A tumour-thrombotic extension to the inferior vena cava (IVC) is a frequent and symptomatically severe complication of renal and adrenal tumours, occurring in up to 15% of all cases. The most common renal neoplasm is renal cell carcinoma (RCC), whereby every fifth patient presents IVC involvement [1, 2].

The stages of cavoatrial tumour-thrombus extension were classified previously by Neves [3] and modified by Nesbitt [4] and Staehler [5]: the intravascular tumour is limited to the renal vein (Stage I); the IVC is involved up to the level of the hepatic veins (Stage II); the IVC is occupied up to the level of the diaphragm (Stage III); the cavoatrial extension reaches the right heart cavities including right atrium, right ventricle or even the pulmonary artery (Stage IV). The Stage IV cavoatrial extension is rare, found in 1–5% of the patients, and was the primary focus of this study [6].

Historically, up to 10% of patients with RCC have tumour thrombus involving the renal vein or vena cava, and 1% has tumour thrombus extending into the right atrium. The RCC is the most frequent among neoplasms showing a tendency to expand into renal veins and IVC from the early stages of the disease. Further frequent sources of cavoatrial tumour thrombus are adrenal carcinoma, liver carcinoma, uterine carcinoma and Wilms’ tumour [7].

Inferior venous inflow occlusion by the tumour-thrombotic material is responsible for the severe clinical impairment of Stage IV patients. Symptoms related to recurrent pulmonary emboli, or clinical signs of right heart insufficiency including renal or hepatic dysfunction, varicocele, dilated superficial abdominal veins or lower extremity oedema may be present [8].
Radical surgical tumour removal remains the only therapy for Stage IV cavoatrial extension. Obviously, the extension of tumour thrombus into the vena cava increases the complexity of surgical resection and increases the morbidity and mortality of the patients. Furthermore, previous studies suggested that the extent of tumour extension into the IVC does not alter prognosis, provided the tumour can be completely removed [9].

These tumours remain an interdisciplinary surgical challenge for the team of urologist, cardiac surgeon and cardiac anaesthesiologist [10]. However, the surgical treatment provides the safest and most effective treatment option, as these tumours (excluding Wilms' tumour) are not responsive to conventional chemotherapy or radiotherapy. The first case of nephrectomy and vena cava thrombectomy for RCC that extended into the IVC was described by Berg in 1913. Meanwhile, radical tumourectomy with vena cava thrombectomy has become a safe treatment option in cases of cavoatrial tumour thrombosis, with operative mortality rates ranging from 3 to 13% and an expected 5-year survival ranging from 30 to 72% [5].

In patients with extensive cavoatrial extensions reaching out to the right heart chambers as in our patient collective, the use of cardiopulmonary bypass (CPB) with deep hypothermic circulatory arrest (DHCA) is the most common practice. The bloodless surgical field allows optimal visualization of the tumour, reducing the risk of pulmonary embolism and cellular spreading. Further, the risk of warm hepatic and renal ischaemia and incomplete tumour excision are considerably lower [10]. Avoiding CPB with DHCA, on the other hand, lowers the risk of bleeding, but significantly worsens the visualization and exposure of IVC and right atrium, and increases the risk of pulmonary embolism, ischaemic liver and acute tubular renal necrosis [4,11–13].

The outcome of patients undergoing radical resection of RCC extending only into the vena cava, not reaching the right heart chambers has been evaluated in detail. So, the patient prognosis seems to be determined by the staging of the tumour, especially lymph node status, and not by the level of tumour thrombus or the presence of concurrent metastases [11]. However, such prognostic criteria have not been previously described for the patients with Grade IV cavoatrial extension, undergoing en bloc excision of cavoatrial extension, performed in DHCA. Thus, it was the purpose of this study to concentrate on the long-term outcome and prognostic criteria in these patients.

Herein, we report 25 years of experience with patients with RCC and Stage IV cavoatrial extension treated surgically at our institution. We specifically concentrate on prognostic factors and survival predictors in the long-term postoperative follow-up of this disease. To our knowledge, this is the first study to report long-term outcomes specifically of the patients with cavoatrial extension reaching up to the right heart cavities being systematically treated using circulatory arrest under deep hypothermic conditions.

**PATIENTS AND METHODS**

**Patient characteristics**

From December 1988 to February 2013, 35 patients with Stage IV cavoatrial extension of RCC underwent radical nephrectomy combined with en bloc excision of cavoatrial tumour-thrombus extension, performed in DHCA. The preoperative staging of the tumour and assessment of the intravascular position of the tumour were performed using standard imaging techniques, including computed tomography angiography or magnetic resonance imaging and echocardiography. In all patients, the upper limit of the tumour extension reached the right atrium (Grade IV extension). There were 21 female (60%) and 14 male (40%) patients. The median age was 63 years, ranging from 24 to 72 years. Distant metastases were preoperatively detected in 10 (29%) patients, and lymph node metastases were found in 5 (14%) patients. Detailed patient characteristics including histological tumour specification and preoperative TNM staging are listed in Table 1. Advanced age, multimorbidity and severe metastatic spread in the patients represented the main exclusion criteria. However, no standard inclusion criteria could be formulated, as the clinical condition of the patient was pivotal for the decision on operability, which was individually made by the interdisciplinary team of urologist, cardiac surgeon and anaesthesiologist for every single patient.

**Operative technique**

In all cases, the decision on surgical strategy was made within a team, consisting of urological and cardiac surgeons. For all the patients, the tumour exposure was performed through a midline abdominal incision. After exploration of the abdomen to rule out diffuse metastatic disease, a median sternotomy was carried out and the pericardium was opened. The next stage involved the mobilization of the kidney for radical nephrectomy; the ipsilateral adrenal gland, the ureter, the perinephric fat and Gerota’s fascia were included in the resection. Following heparin administration (3 mg/kg), the heart was cannulated for CPB with the arterial return to the ascending aorta and the venous drainage from the right atrium. To avoid disruption of the tumour thrombus, a single short, basket-like, 32-Fr venous cannula was used. Cooling was continued to a core temperature of 18°C. In addition, topical cooling of the head was achieved by plastic bags containing slushed ice. Infrared spectroscopy was used for neuromonitoring. The left ventricle was vented via the right upper pulmonary vein. During cooling, the renal vein and retrohepatic IVC were exposed. Division of the diaphragmatic suspensory ligaments of the liver allowed for increased mobility. Immediately prior to circulatory arrest, the ascending aorta was cross-clamped and 2000 ml of a low-sodium, calcium-free cardioplegia (Bretschneider’s HTK cardioplegia, Köhler Chemie, Bensheim, Germany) were administered for myocardial protection. Extracorporeal circulation was discontinued and the patient’s blood was allowed to drain into the cardiotomy reservoir. After removal of the atrial cannula, the right atrium was opened near the orifice of the IVC. Next, the IVC was entered adjacent to the orifice of the renal vein. The bloodless field allowed for complete visualization of the total extent of the tumour thrombus and facilitated the intravascular tumour extirpation. If necessary, the tumour could easily be removed from the heart, hepatic veins and contralateral renal vein. Figure 1 demonstrates a typical tumour macroscopy with the upper limit of the thrombotic tumour extension reaching the right atrium before and after the extirpation. Vascular reconstruction was accomplished by direct suture (n = 26) or by patch plasty using autologous pericardium (n = 9). After caval reconstruction and closure of the right atrium CPB were re-established, the aortic cross-clamp was removed and the patient was rewarmed.

**Follow-up and statistics**

Patient data were analysed retrospectively and collected in the patient data bank. The institutional review board has approved the collection and publication of the patient data. For complete
follow-up, survivors or nearest of kin have been contacted, if the patient had not been seen recently in the outpatient department. All ordinal variables are given as median and range due to non-parametric distribution and analysed by SPSS 15.0 (SPSS, Inc., Chicago, IL, USA). Survival was analysed by Kaplan–Meier with log-rank test (Mantel–Cox). \( P < 0.05 \) was considered statistically significant.

### RESULTS

#### General results

All the 35 patients with Stage IV cavoatrial extension of RCC underwent radical nephrectomy combined with en bloc excision of cavoatrial tumour-thrombus extension, performed in DHCA. The median

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**Table 1: Patient characteristics**

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Figure 1: Representative intraoperative macroscopy of Grade IV cavoatrial extension of renal cell carcinoma before and after extirpation. (A) Infradiaphragmatic portion of inferior vena cava with visible intraluminal involvement of left renal vein. (B) Intraoperative view into the right atrium with mobilized cavoatrial extension reaching up to the tricuspid valve. (C) Extirpated tumour including the tumourous left kidney and the cavoatrial extension in preserved length. 1: Inferior vena cava; 2: left renal vein; 3: lever; 4: superior vena cava; 5: right atrial cavity; 6: head of cavoatrial extension; 7: extirpate of tumourous left kidney; and 8: cavoatrial tumour extension.
duration of extracorporeal circulation was 159.3 ± 56.6 min; the circulatory arrest time was 18.3 ± 8.8 min. No era-dependent changes in CPB or DHCA time were found (Supplementary Fig. 1). A mean volume of 4645 ± 2297 ml erythrocyte concentrate and 2199 ± 1331 ml fresh frozen plasma had to be given during the operation and perioperatively. The median duration of ICU stay was 9.9 ± 10.6 days and the overall in-hospital time was 27.9 ± 24.8 days. There were no intraoperative deaths; 2 patients died on the ICU (due to respiratory failure in one patient and multiple organ failure in the second patient). The postoperative complications were as follows: severe bleedings, defined as a bleeding volume of more than 1000 ml during the first 12 h (17%), caval thrombosis (11%), respiratory failure (14%), renal failure (11%), cardiac failure (3%), need for reoperations (9%), neurological disorders (6%) and neuropsychological disorders (23%).

**Patient survival**

The mean overall survival of the patients was 4.9 ± 1.0 years (95% confidence interval: 2.8–6.8 years) and the 5-year survival rate was 40% (Fig. 2). To elucidate the impact of the tumour histological type (clear-cell carcinoma, n = 19; chromophil carcinoma, n = 4; atypical, n = 3 or combination of multiple histologies, n = 8) on the patient survival, we looked into the survival statistics depending on the histological tumour type. No significant differences in long-term survival were found between the groups of patients with different histological tumour types (data not shown). Further, we analysed the relevance of the preoperative presence of initial remote metastases for the long-term survival. Patients without preoperative metastases (n = 25) have a significantly better long-term survival compared with patients with initial remote metastases of renal carcinoma (n = 10). The mean survival of metastasis-free patients was 4.9 ± 1.1 years (95% confidence interval: 2.7–7.0 years) and that of patients with preoperative proof of metastases was 1.3 ± 0.5 years (95% confidence interval: 0.4–2.1 years), P ≤ 0.05 (Fig. 3A).

Similarly, patients with lymph node metastases (n = 5 or 14% of all patients) have a significantly inferior long-term survival compared with patients without lymph node involvement (n = 30). The mean survival of patients with metastasis-free lymph nodes was 3.0 ± 2.0 years (95% confidence interval: 3.2–7.8 years) and that of patients with preoperative evidence of metastatic lymph node involvement was 0.2 ± 0.1 years (95% confidence interval: 0–1.9 years), P = 0.01 (Fig. 3B). Even worse is the survival rate for the patients with preoperative evidence of both, lymph node and remote metastatic spread, which was found in 3 patients (9% of all

**Figure 2:** Postoperative survival of patients undergoing radical nephrectomy combined with en bloc excision of cavoatrial extension in deep hypothermic circulatory arrest. Overall patient survival after radical nephrectomy combined with en bloc excision of cavoatrial tumour-thrombus extension, performed in deep hypothermic circulatory arrest. Data are given by Kaplan–Meier survival plot.

**Figure 3:** Preoperatively evident remote and lymph node metastases are predictive for inferior postoperative survival of patients undergoing radical nephrectomy with excision of cavoatrial extension in deep hypothermic circulatory arrest. (A) Postoperative survival of patients with preoperative evidence of remote metastases (M1+, n = 10) compared with that of patients without remote metastases (M0, n = 25) after radical nephrectomy with excision of cavoatrial extension in deep hypothermia. (B) Postoperative survival of patients with preoperative evidence of lymph node metastases (N1+, n = 5) compared with that of patients without lymph node involvement (N0, n = 30) after radical nephrectomy with excision of cavoatrial extension in deep hypothermia. (C) Postoperative survival of patients with preoperative evidence of lymph node and remote metastases (N1+ and M1+, n = 3) compared with that of patients without metastasis combination (n = 32) after radical nephrectomy with excision of cavoatrial extension in deep hypothermia. Data are given by Kaplan–Meier survival plot. *P ≤ 0.05, **P ≤ 0.01 by the Mann–Whitney U-test.
The mean survival of R-0 patients was 6.3 ± 0.7 years (95% confidence interval: 4.9 ± 1.0 years) and that of R-1 patients was 0.7 ± 0.3 years (95% confidence interval: 0.1–1.4 years), P ≤ 0.05 (Fig. 4).

### Local tumour recurrence

We further analysed the tendencies of local tumour recurrence in the operated patients. The overall tumour recurrence rate was 31% (11 patients developed a recurrent tumour) and time to the first recurrence was 1.6 ± 1.5 years for these patients. Although the survival of patients with tumour recurrence episodes seems to indicate a tendency towards inferior outcome, no significance could be reached here: the mean survival of patients with recurrent tumours was 2.5 ± 0.6 years (95% confidence interval: 1.3–3.7 years) and that of recurrence-free patients (n = 24) was 6.1 ± 1.5 years (95% confidence interval: 3.2–8.9 years), P = 0.34 (Fig. 5).

### DISCUSSION

In this study, we set out to analyse the long-term outcomes of the patients with Stage IV cavoatrial extension of RCC, undergoing radical nephrectomy combined with en bloc excision of cavoatrial extension, performed in DHCA. In our study cohort, we could demonstrate acceptable long-term results and outline predictors for postoperative long-term survival of the patients.

To clarify the impact of radical procedure on primary morbidity, perioperative mortality and long-term survival rates, we analysed our patients with Grade IV cavoatrial extension retrospectively. The results demonstrated an acceptable mean overall survival rate (4.9 ± 1.0 years) and a 5-year survival rate of 40%. However, comparing these results with the previously published outcomes, [1] fails as most patient cohorts are heterogenic in terms of cavoatrial extension grade. In our study, we assessed only the results referring to the patients with extension grade IV (cavoatrial extension reaching right heart chambers).

Interestingly, the histological type of the tumour had no impact on the patient survival in this study population. Previously, the tumours that remain inside the renal capsule have not metastasized to any lymph nodes, have been described to have a similar 5-year survival regardless of an extension of IVC thrombus [14, 15]. According to our data, the overall patient survival is also similar regardless of the primary histology, once the tumour extension has reached the right heart cavities.

Further, we analysed the impact of preoperatively diagnosed remote metastases and metastatic lymph node involvement on the overall outcome. In our cohort, the patients without preoperative metastases had a significantly better long-term survival compared with those patients with initial metastases of renal carcinoma. This is controversial to the previously described findings that the prognosis is primarily dependent on the lymph node involvement, but not on the presence of distant metastases, which seemed to have no significant influence on the long-term survival [8, 11]. However, also in our patient collective, the preoperative evidence of lymph node involvement is a clear negative predictor for the long-term patient outcome. The inferiority of long-term survival is even more dramatic in patients having both remote metastases and tumour lymph node involvement already before the operation.

Furthermore, according to our data, patients with R-0 (no microscopic evidence of cancerous cells in resection margin) tumour resection have a significantly better long-term survival compared with...
patients with R-1 (microscopic evidence of cancerous cells in resection margin) tumour resection. Our data go in hand in hand with the recently published evidence of increased local recurrence rate in patients with the invasion of RCC into vein wall at the resection margin [16]. Our finding further underlines the importance of good surgical visibility of a bloodless operation field, as it can only be reached using CPB with DHCA. Although even this technical advantage of CPB with DHCA cannot completely prevent R-1 resections, it obviously helped to avoid R-2 resection (macroscopic evidence of cancer in resection margin), as none of those were described in our patient collective.

However, the necessity of DHCA remains a controversial issue over the last decades. Various groups consider the use of circulatory arrest unnecessary in many cases or even dangerous due to coagulopathic states [8, 17, 18]. In this context, the perioperative interdisciplinary approach including an aggressive coagulation regime after weaning of CPB is of utmost importance. Other groups prefer the technique including CPB and DHCA and report acceptable complications rates [10]. Our data demonstrate DHCA to be safe and helpful, especially in terms of surgical visibility. As assessed for our dataset, no time-dependent evolution of the operative technique was observed. So, no continuous decrease in bypass or circulatory arrest time was found, as it could have been expected for classical learning curve-related effects. Instead, the duration of the DHCA or CPB needed rather seems to depend on the severity and extension of the local tumour spread, than on the experience of the surgeon or the technical progress. During the years of our clinical experience with this operation, we have constantly been following the standard institutional protocol for CPB in patients undergoing circulatory arrest. This included standard cannulation strategy, cardiac arrest with the standard crystalloid myocardial protection, left ventricular venting and standard use of deep hypothermia. The maintained protocol of the procedure allowed performing valid analysis of patients treated within the different decades. We hope that the report on our experience can further contribute to the discussion about the best available technique in these patients. For instance, the use of moderate hypothermia and alternative myocardial protection protocols might be thus evaluated in further studies.

The patients, undergoing the procedure are advanced stage tumour patients with the considerable rate of remote metastases (preoperatively diagnosed in 28% of the patients). Thus, the question of tumour recurrence and its relevance for the long-term outcomes is highly relevant. According to our data, the overall tumour recurrence rate was high with 31% (11 patients developed a recurrent tumour) and time to the first recurrence was 1.6 ± 1.5 years after the operation. The patients with postoperative tumour recurrence were treated according to the standard oncological protocols including chemotherapy, irradiation or surgery based on the interdisciplinary tumour board decision. Surprisingly, however, the tumour recurrence did not significantly influence the long-term survival compared with the non-recurrence of tumour. Thus, while the potential tumour recurrence seems to have no significant negative impact on the patient survival, this finding justifies the frequently vast palliative indication for these patients, which definitely improve the clinical symptoms.

In conclusion, our data provide strong evidence for perioperative safety and acceptable long-term results of radical nephrectomy combined with an epi ocision of cava caval extension, performed in DHCA in patients with Stage IV cava caval extension of RCC. We show that preoperative evidence of remote tumour metastases and tumourous lymph node involvement can predict inferior postoperative survival. Further, we describe high postoperative tumour recurrence rate in these patients, which is, however, not limiting the patient survival. Thus, radical nephrectomy with excision of cava caval extension in DHCA can be safely applied as a curative approach, taking into the consideration the negative impact of evident tumour metastases.

SUPPLEMENTARY MATERIAL
Supplementary material is available at EJCTS online.

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Conflict of interest: none declared.

REFERENCES