



Inferior Vena Cava Resection and Reconstruction with Bovine Pericardium for Renal Cell Carcinoma: Complications and Outcomes

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OBJECTIVES	To assess the postoperative complication rate and overall survival when bovine pericardium is used as graft material for inferior vena cava (IVC) reconstructions in patients with renal cell carcinoma (RCC). The ideal graft material is yet to be established, with synthetic grafts widely studied and used in the current literature.
METHODS	We performed a retrospective cohort analysis of consecutive patients who underwent IVC reconstructions as part of resection for RCC, using bovine pericardium as either a patch repair or tubular interposition graft.
RESULTS	A total of 15 patients underwent resection with IVC reconstruction between 2010 and 2018. Nine patients had tubular interposition grafts and 6 had patch repairs. Three patients had Clavien-Dindo grade 3 or higher short-term complications. There was no difference in Comprehensive Complications Index between those who had interposition grafts and patch repairs. Two patients had a long-term graft-associated thrombus requiring temporary anticoagulation. Overall survival was 46.5 months (95% confidence interval [CI] 36.9-56.1). There were no perioperative deaths. All long-term deaths were due to disease progression.
CONCLUSION	Reconstruction of the IVC with a bovine pericardium graft is safe in experienced centers. Bovine pericardium could be considered as the material of choice, given its safety in the immediate postoperative period, ease of use, and patency without routine long-term anticoagulation. Advanced surgical management leads to good overall survival in this cohort with high tumor burden. UROLOGY 134: 143–147, 2019. © 2019 Elsevier Inc.

Renal cell carcinoma (RCC) can involve the inferior vena cava (IVC) due to tumor thrombus or direct invasion. In such circumstances, surgical treatment strategies include resection of the IVC with repair using either an interposition graft or patch. The techniques for resection and reconstruction have evolved over the past 50 years, drawing on experience from both transplantation and cardiothoracic surgery. Reconstruction material can be either synthetic or biological, but the optimal choice is not known.¹ Synthetic material such as polytetrafluoroethylene (PTFE) is widely used in vascular reconstruction and has demonstrated excellent long-term patency.^{2,3} However, thrombosis and graft

infection remain rare but potentially major complications.^{2,4,5} Tissue-engineered vascular grafts may have a role in the future, but have yet to reach widespread clinical adoption.⁶ In recent years, there has been increasing interest in the use of bovine pericardium (BP) as both a patch and tubular replacement, with several case reports in recent years outlining acceptable perioperative morbidity and mortality as well as good long-term function in RCC.^{7,8} Initial results from our center were published in 2013 using both autogenous peritoneo-fascia and BP as materials for a cohort of heterogeneous pathologies.⁹ We present a retrospective cohort analysis on the use of BP in RCC resections only. We hypothesize that the use of BP is safe and negates the need for routine anticoagulation that is often required for synthetic grafts. Additionally, we aim to demonstrate an improved survival in this cohort with advanced malignancy.

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METHODS

We performed a retrospective cohort analysis of consecutive patients who underwent IVC reconstructions as part of oncological resections for RCC from January 2010 to December 2018.

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We included only patients who underwent IVC reconstruction with BP, either as a patch repair or tubular interposition graft. All patients were operated on in either tertiary or quaternary referral centers with intensive care and interventional radiology services available. Hospital medical records were used to collect complication, hospital stay, recurrence, mortality, and histopathology data, and adjuvant therapies. Preoperative status was recorded as per the Charlson Comorbidity Score (CCS).^{10,11} The IVC level involved was measured as per the Mayo staging system.¹² Patients were routinely followed up 4 to 6 weeks after discharge from hospital, with subsequent follow-up determined on a case-by-case basis depending on recovery. All patients had routine postoperative imaging in order to detect recurrence. Specific investigations for graft-related complications were not routine, but rather based on clinical suspicion. The primary outcomes measured were postoperative complications as per the Clavien-Dindo Classification¹³ and Comprehensive Complication Index (CCI),¹⁴ and long-term complications directly related to the graft. The secondary outcome measured was overall survival (OS). Perioperative death was defined as death within the index hospital admission or within 30 days of operation. The manuscript was prepared as per the STROBE statement.¹⁵

Technique

If required, the liver is mobilised and the short hepatic veins from the caudate lobe to the IVC are ligated. A medial visceral rotation is then performed to expose the IVC. The kidney is dissected, with early ligation of its arterial supply and ureter. The contralateral renal vein is usually encircled and controlled with a vessel loop. The IVC is dissected and, where necessary, the lumbar and ipsilateral adrenal and gonadal veins are ligated. This affords control of the IVC from its origin to the retrohepatic IVC. Where there is extension into the right atrium, the diaphragm and the pericardium are incised to control the intrathoracic portion of the IVC under the guidance of a transesophageal echo. The decision to employ a tubular graft over a patch repair is driven primarily by oncological considerations, with a tubular graft used in cases of full or near-full thickness occlusion of the IVC in order to minimise the occurrence of tumor embolus and assist in achieving clear surgical margins. If an interposition graft is required, the BP (eg, PERI-GUARD Supple, Baxter) is placed around a sized tubular device (eg, a 30 mL syringe) and tubularized with the use of a 60 mm vascular reload on a laparoscopic linear cutting stapler. The graft is sutured to the native vena cava with 4/0 prolene continuous at either end. The contralateral renal vein is then implanted into the graft, end-to-side with 5/0 prolene. The graft is flushed with heparinised saline prior to removing clamps. An intraoperative photo is shown in Figure 1. Selective hepatic vascular isolation was performed in cases that involved grade III or above tumor thrombus. Total or partial IVC isolation is used for patch repairs. Routine postoperative deep vein thrombosis prophylaxis is instigated with subcutaneous heparin 5000 U twice daily.

Statistical Analysis

Data variables are expressed in median, interquartile range (IQR), and percentage as appropriate. Due to non-normal distribution of CCI, Mann-Whitney U tests were used for mean comparisons between groups. Linear regression was used for comparisons with continuous data. Kaplan-Meier analysis was used for OS with the log-rank test statistic used to determine differences in survival distribution. Univariate and multivariate

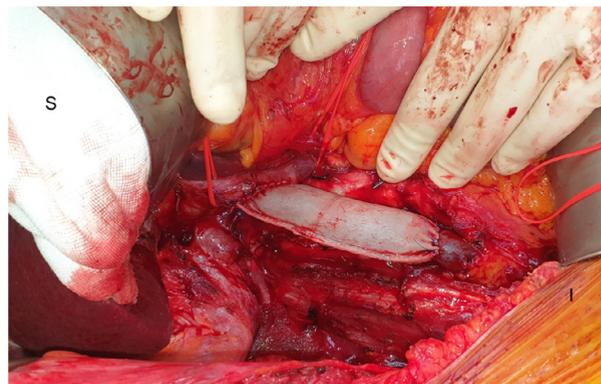


Figure 1. Operative photo of tubular bovine pericardium graft in-situ. I, inferior; S, superior.(Color version available online.)

Cox regression was used to generate hazard ratios. All statistics were generated using IBM SPSS Version 24 with $P < 0.05$ considered statistically significant.

RESULTS

A total of 15 patients were included. Demographics, tumor burden and preoperative status are shown in Table 1. Median (IQR) age was 67 (58-75). Nine patients (60.0%) were male. Median (IQR) CCS was 6.5 (4-8). Two patients (13.3%) were operated on for a local recurrence of previously resected RCC. Five patients (33.3%) were operated on with known metastatic disease. For one of the patients with known metastatic disease the indication was a palliative procedure for recurrent pyelonephritis and hydronephrosis; for the remainder, the goal was complete surgical resection of all known disease with curative intent. One patient had an incidental RCC discovered in addition to an IVC leiomyosarcoma. Ultimately, 7 patients (46.7%) had stage 4 disease and the remainder stage 3. All patients had preoperative imaging with varying combinations of computed tomography, positron emission tomography and/or magnetic resonance imaging. The use of systemic therapy was heterogeneous. One patient had neoadjuvant therapy only with nivolumab, and 1 had both neoadjuvant (temsirolimus) and adjuvant (sunitinib)

Table 1. Patient demographics and pathology.

<i>Demographics</i>	
Age median (IQR)	67 (58–75)
Male sex (n, %)	9 (60.0)
CCS median (IQR)	6.5 (4–8)
Preoperative tumor load (n, %)	
Localised primary	8 (53.3)
Recurrence	2 (13.3)
Known metastatic disease	5 (33.3)
<i>Pathology</i>	
Stage (n, %)	
III	8 (53.3)
IV	7 (46.7)
Clear surgical margins	13 (86.7)
Microvascular invasion	13 (86.7)
IVC invasion	8 (53.3)
Lymphatic invasion	1 (6.7)
Perineural invasion	0 (0.0)

CCS, Charlson Comorbidity Score; IQR, interquartile range; IVC, inferior vena cava.

Table 2. Operative and postoperative complication details.

Operative details	
Patch repair (n, %)	6 (40.0)
Tubular graft (n, %)	9 (60.0)
IVC level (n, %)	
I	5 (33.3)
II	4 (26.7)
III	4 (26.7)
IV	2 (13.3)
Simultaneous hepatectomy (n, %)	2 (13.3)
Cardiac bypass (n, %)	1 (6.7)
Pringle manoeuvre (n, %)	4 (26.7)
Operating time median (IQR)	330.5 (225-466.25)
Units PRBC median (IQR)	4 (0-5)
Complications	
Total number median (IQR)	2.5 (0-4)
Grade 3 or higher (n, %)	3 (20.0)
CCI median (IQR)	30.8 (0-40.5)

CCI, comprehensive complication index; PRBC, packed red blood cells.

therapy. Five patients had adjuvant therapy only, using nivolumab, sunitinib, pazopanib, or sorafenib, with 3 of these patients started on systemic therapy after recurrence was discovered postoperatively.

Operative and postoperative details are outlined in Table 2. All operations involved a multidisciplinary team made up primarily of hepatobiliary and urological surgeons. Nine patients (60.0%) had tubular interposition grafts, and the remainder were patch repairs. Two patients (13.3%) underwent en-bloc resections that involved hepatectomy. One of the 2 patients with tumor thrombus in the right atrium was placed on cardiac bypass and the atrial tumor was excised via sternotomy and atriotomy. For the second patient it was possible to resect the tumor via an infradiaphragmatic approach to the intrathoracic IVC. Four patients (13.3%) required the Pringle manoeuvre to achieve hepatic vascular isolation. One patient was placed on aspirin immediately postoperatively. Two patients had preoperative pulmonary embolus diagnosed and were started on therapeutic anticoagulation—one with enoxaparin and the other with a heparin infusion. These treatments were continued postoperatively. One patient was started on warfarin for postoperative atrial flutter. No other patients were placed on routine anticoagulation or antiplatelets. All patients were admitted to the intensive care unit postoperatively.

The total number of postoperative complications ranged from 0 to 6 per patient. Three patients (20%) had at least one Clavien-Dindo grade 3 or higher complication. The median (IQR) CCI was 30.8 (0-40.5). There was no difference in CCI between those who had a patch repair and those who had tubular interposition grafts ($P = 0.78$), between those who had level IV IVC involvement and others ($P = 1.00$), or those who had simultaneous liver resections and those who did not ($P = 0.76$). There was no significant association between CCS and CCI ($P = 0.19$). There was no significant increase in CCI between patients over the age of 75 ($P = 0.07$). No grafts needed to be redone. There were no infective graft complications. Long-term, 2 patients had an IVC thrombus that required therapeutic enoxaparin. One was diagnosed at 18 months postoperatively after a deterioration in renal function was found on routine blood tests, and was associated symptomatically with dyspnoea only. The patient was treated with 6 months of enoxaparin. The second was diagnosed at 3 months postoperatively on venography, performed owing to lower limb peripheral oedema and known iliac

vein thrombosis. This patient was one of those with known pulmonary emboli at the time of operation, and the patient's therapeutic enoxaparin continues at the time of writing, 5 months after diagnosis of the thrombus.

Follow-up period has ranged from 0.39 to 61.2 months. The patient with the minimum period has been lost to follow-up. The OS for this cohort was 46.5 months (95% CI 36.9-56.1) on Kaplan-Meier estimate (Fig. 2). Five-year OS is estimated at 42.9% (95% CI 6.3-79.6). OS for stage 4 patients was 45.5 months (95% CI 32.9-58.0). There were no perioperative deaths. All deaths were due to tumor recurrence or progression of disease. There was no significant difference in OS between those operated on with known metastatic disease and those without ($P = 0.59$), between stage 3 and 4 disease ($P = 0.86$), or between those with tumor invasion of the IVC and not ($P = 0.18$).

DISCUSSION

Surgical intervention for RCC involving the IVC has been well established.¹⁶⁻¹⁸ In published series, the level of IVC involvement has been demonstrated to have a direct impact on survival.^{19,20} What is less well established is the optimal choice of material for IVC reconstruction, and the short- and long-term complications associated with such operations.

In 1911, Pleasants published the first thorough study on the causes of IVC obstruction.²¹ In this review of a total of 328 patients, 88 presented with obstruction due to new growths — either by extrinsic compression, direct invasion, or tumor thrombus. Renal neoplasms were noted to be the most common. Scherck et al published a comprehensive review of IVC graft techniques in 1974, many from animal models, varying from autologous veins to Dacron and PTFE.²² One technique reported on was the use of bovine collagen tube heterografts, which in 1 small animal model study had a patency rate of 20% at 12 months. The authors concluded that “replacement of venous segments has still not been nearly successful enough to be realistically applied to any but the most desperate of clinical scenarios.” After biological material gained mainstream use in cardiovascular surgery, centers worldwide have incorporated BP into abdominal vascular reconstructions. One of the first case studies describing the use of BP as a patch repair of the IVC was by Del Campo et al in 1994, after the same group experimentally demonstrated acceptable results using it as an interposition graft of the superior vena cava.^{23,24} The same group then used tubularized BP as an interposition graft of the left common iliac vein without long-term complications.²⁵ Its use as an interposition graft of the IVC has remained rare in the literature, although the published case reports and series demonstrate good short-term results.⁷⁻⁹

During manufacture, the treatment of BP with glutaraldehyde confers several benefits, including cross-linking and stabilizing tissue, reducing antigenicity and thrombogenicity, and suppressing bacterial growth during storage. Gamma irradiation has also been demonstrated to achieve sterilization, as have ethanol and propylene oxide.^{26,27} The incidence rate of host reactions to BP has not been well studied in humans, but there is 1 case report of hyperacute

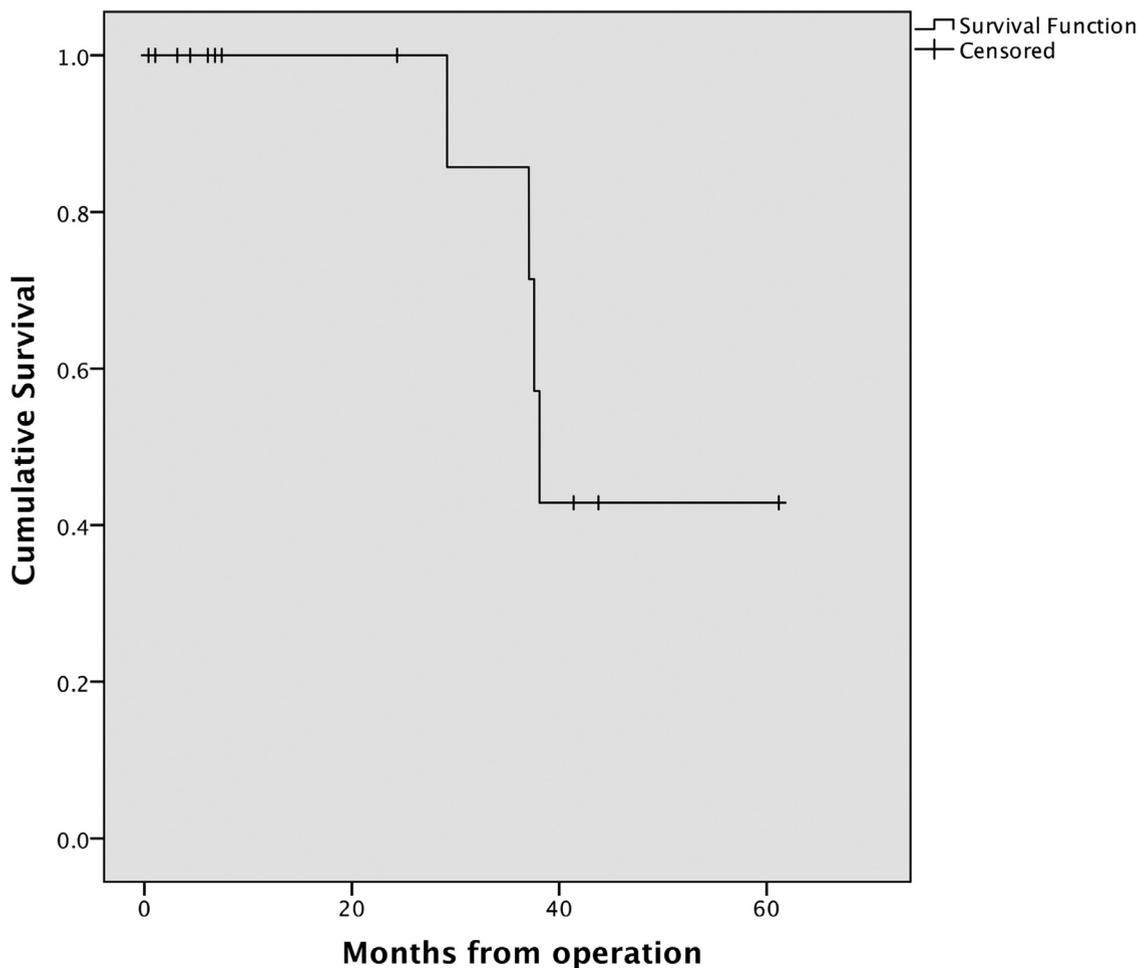


Figure 2. Overall survival.

rejection of an aortic valve replacement in the literature.²⁸ Calcification due to immune response and subsequent failure has been studied in heart valve replacement, but this has not been established in vascular reconstructions.⁶ BP has been demonstrated to be a safe material for use in infected fields and has shown good long-term resistance to thrombotic complications, negating the need for routine long-term anticoagulation.^{7,9,29} In the authors' country, BP is an easily accessible material available from multiple manufacturers. Whilst this study does not include a formal cost analysis, the raw material cost is not vastly different in terms of total amount (approximately AUD\$750 for a sheet of BP and AUD\$480 for a PTFE tubular graft).

Our current series presents several important results. To our knowledge this is the largest cohort of patients with BP IVC reconstructions for RCC. When performed in hospitals with appropriate surgical subspecialties, anaesthetics, and intensive care units available, the short-term complications are acceptable given the large tumor burden and otherwise poor survival outlook for these patients. There was no significant difference in CCI between patients with tubular grafts and patch repairs, and no significant association between CCI and CCS or age over 75. We did not perform routine imaging to detect graft-associated complications postoperatively, although patients underwent

routine follow-up imaging for the purpose of detecting recurrence, as well as routine clinical examination for post-operative complications including those related to the graft. There were 2 long-term graft-associated thrombotic complications, which required temporary anticoagulation only. There were no short- or long-term infective complications. Interpretation of our survival data is difficult owing to low numbers; however, we demonstrated excellent OS for stage 4 patients in particular, with an estimated OS of 49.3 months. Stage 4 patients treated with targeted therapies alone have been shown to have a median survival of approximately 28 months.³⁰

PTFE is more ubiquitous for either patch repairs or interposition grafts compared to BP.^{3,5,31} The 2 major complications associated with PTFE are thrombosis and graft infection. Both are rare in published series but potentially lead to the need for re-do surgery.^{2,4} Thrombotic risk often leads to routine use of long-term anticoagulation.^{3,32} Our study agrees with previous works suggesting that long-term anticoagulation for BP grafts is not necessary, although patients should be monitored for signs and symptoms of IVC obstruction.^{7,31} BP also confers an ease-of-use benefit to the surgeon, having similar consistency to a large vein and being able to be shaped to a specific IVC caliber at the time of implant.

This paper has several limitations. As a retrospective cohort analysis, it is subject to confounding factors that were not collected and is reliant on accurate documentation of complications so that they can be categorized as per Clavien-Dindo. Follow-up is not standardized across all patients, and long-term graft-associated complications are not specifically screened for, although all patients undergo postoperative imaging for recurrence detection. Our cohort size means that survival data and statistical comparisons are difficult to interpret.

CONCLUSION

Reconstruction of the IVC with a BP graft is safe in experienced centers where appropriate subspecialty teams are available, including anaesthetics and intensive care. Major complications of Clavien-Dindo grade 3 or higher were uncommon. There was no significant difference in CCI between patients who had tubular interposition grafts and patch repairs. Compared to the more ubiquitous PTFE graft, BP negates the need for routine long-term anticoagulation, although patients should be reviewed regularly long-term for signs or symptoms of thrombosis. BP also demonstrates resistance against infective complications. In this cohort with high tumor burden, OS with advanced surgery appears to be improved over systemic therapy only.

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