ORIGINAL ARTICLE

Video-assisted thoracoscopic surgery after renal transplantation: A single-institution experience

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Abstract

Introduction: The number of renal transplantations performed for patients with chronic kidney disease has increased in Japan, but little is known about the outcomes in those who subsequently undergo video-assisted thoracoscopic surgery (VATS). We therefore investigated the outcomes of consecutive patients requiring VATS after renal transplantation at our institute.

Methods: We retrospectively collected the clinical data for patients undergoing VATS after renal transplantation between January 2003 and September 2014. Specifically, we compared the serum creatinine level and estimated glomerular filtration rate preoperatively and postoperatively, and investigated the postoperative complications.

Results: In total, 12 patients underwent VATS after renal transplantation during the study period. All patients received two or three immunosuppressive agents. Operative methods used included VATS wedge resection ($n = 4$), segmentectomy ($n = 4$), lobectomy ($n = 2$), mediastinal tumor resection ($n = 1$), and chest wall tumor resection ($n = 1$). No patients required perioperative hemodialysis. There were no intraoperative complications, but one patient developed postoperative hemorrhagic cystitis and another developed pneumonia. One patient developed pneumocystis pneumonia 2 months after left lower lobectomy and required hemodialysis. No further hemodialysis was required by any patient. Of note, no statistically significant differences were observed between the preoperative and postoperative serum creatinine level ($P = 0.666$) and estimated glomerular filtration rate ($P = 0.388$). There were no in-hospital deaths. Univariate analysis revealed no significant risk factors for postoperative complications.

Conclusion: This report showed favorable results for VATS after renal transplantation. However, clinicians must remain vigilant for complications because transplant recipients remain permanently immunocompromised.

Introduction

The number of renal transplantations performed for patients with chronic kidney disease (CKD) in Japan has increased, with approximately 1600 renal transplantations now performed annually (1,2). Thanks to improvements in immunosuppressive agents and perioperative management, the outcomes are increasingly favorable. Although renal transplantation allows patients to be freed from the constraints of hemodialysis, an immunocompromised system and an increased incidence of malignancy are inevitable long-term complications. In addition, when renal transplant recipients undergo further surgery, anesthetic agents and perioperative

management can affect renal function, and immunosuppression can lead to postoperative infections (e.g. wound infection, pneumonia, and pyothorax) and bronchopleural fistulae. Moreover, long-term renal dysfunction after transplantation could influence treatment outcomes. In this study, we report the outcomes associated with video-assisted thoracoscopic surgery (VATS) after renal transplantation at our institute.

Materials and Methods

This was a retrospective study of medical records at a single institution. Informed consent was obtained from all patients and patient anonymity was preserved. This study was approved by the Research Ethics Committee of the Tokyo Women's Medical University (no. 3487).

We reviewed the clinical data for patients who underwent VATS after renal transplantation at our institute between January 2003 and September 2014. Specifically, we investigated the changes in renal function preoperatively and postoperatively, postoperative complications, and risk factors for postoperative complications.

Preoperative management

All patients underwent chest X-ray, CT, preoperative routine blood analysis, and respiratory function tests (excluding those with pneumothoraxes). PET and brain MRI were performed in some patients with tumors. Patients with previous ischemic heart disease underwent echocardiography and myocardial scintigraphy to evaluate their cardiac function before surgery.

Immunosuppressive agents

All patients received two or three immunosuppressive agents, which were continued until the morning of surgery. Immunosuppressants were administered intravenously or orally, and taken via nasogastric tube when patients were unable to take oral agents. Some patients received steroid cover. The transplant surgeons decided the doses of all therapeutic agents, and patients began routine oral therapy on the morning of the first postoperative day.

Intraoperative management

The operations were performed with the patients under general anesthesia. Patients were intubated with a double-lumen endotracheal tube and placed in a right or left lateral decubitus position. Fentanyl, remifentanil, propofol, and vecuronium bromide were used for total intravenous anesthesia. All patients were extubated in the operating room before being returned to their hospital rooms.

Operative method

Patients underwent either three-port VATS or two-port and utility minithoracotomy. An access port or utility minithoracotomy was placed in the fourth or fifth intercostal space, and an assist port was placed in the eighth intercostal space on the posterior axillary line. A 30°, 10-mm thoracoscope was inserted through the camera assist port in the eighth intercostal space. All VATS procedures were performed under thoracoscopic view.

Postoperative management

Cefazolin was used as a perioperative antibiotic. Acetaminophen was used as a postoperative oral analgesia to preserve renal function. We performed blood analysis periodically, evaluating postoperative renal function by serum creatinine (Cr) level (mg/dL) and estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2). The eGFR, used to approximate the glomerular filtration rate, was calculated according to the formula proposed by the Japanese Society of Nephrology, as follows: eGFR (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times age^{-0.287}$, for men, and eGFR (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times age^{-0.287} \times 0.739$, for women (3). This formula was based on the "KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease" produced by Kidney Disease: Improving Global Outcomes and modified for Japanese patients (4). The patients were classified by glomerular filtration rate categories according to the classification of CKD in the 2012 Kidney Disease: Improving Global Outcomes guideline (4): G1 = eGFR ≥ 90 mL/min/1.73 m^2; G2 = eGFR 60–89 mL/min/1.73 m^2; G3a = eGFR 45–59 mL/min/1.73 m^2; G3b = GFR 30–44 mL/min/1.73 m^2; G4 = eGFR 15–29 mL/min/1.73 m^2; and G5 = eGFR < 15 mL/min/1.73 m^2. The last Cr and eGFR data during admission were used for the perioperative serum levels, and the latest Cr and eGFR data during postoperative follow-up were used for the late postoperative data. The postoperative follow-up period was defined as that between the operation and the last follow-up appointment.

Staging of lung cancer

For patients with lung cancer, staging was according to the seventh edition of the TNM classification of lung cancer, as proposed by the UICC and the International Association for the Study of Lung Cancer in 2009. For those patients who underwent pulmonary resection before 2009, staging was matched to the criteria in the seventh edition of the TNM classification.

Statistical analysis

Descriptive statistics of continuous variables were expressed as median and interquartile range, while categorical variables were expressed as a number and percentage. The Wilcoxon signed-rank test with equal variances (two sided) was used to compare the Cr and eGFR preoperatively and postoperatively. Univariate logistic regression analysis was used to investigate the risk factors of postoperative complications. $P < 0.05$ was considered to represent statistical significance. All statistical analyses were performed with SPSS® software, version 21.0 (IBM, Armonk, USA).

Results

The patients' characteristics are shown in Table 1. VATS was performed in 12 patients who underwent renal transplantation at our institute during the study period. Of these patients, eight were men and four were women, with a median age of 62.0 years (interquartile range, 49.8–68.5 years). We investigated changes in renal function preoperatively and postoperatively, as well as the risk factors for postoperative complications.

The median preoperative serum Cr level and eGFR were 1.22 mg/dL (interquartile range, 0.97–1.91 mg/dL) and 47.1 mL/min/1.73 m^2 (interquartile range, 31.6–58.2 mL/min/1.73 m^2), respectively. The number of patients in each eGFR category was as follows: G2 ($n = 3$),

G3a ($n = 4$), G3b ($n = 2$), G4 ($n = 1$), and G5 ($n = 2$). Nine patients (75%) had a high risk of end-stage kidney dysfunction and death due to cardiovascular disease. The ASA score was 2 in seven patients and 3 in five patients. The median period between renal transplantation and VATS was 102 months (interquartile range, 45–183 months).

The primary nephropathy that led to the need for hemodialysis and the main preoperative comorbidities are summarized in Table 1. Cardiovascular disease was the most common preoperative comorbidity ($n = 7$). One patient with cardiovascular disease underwent coronary artery bypass graft for angina pectoris, and two underwent graft replacement or stent grafting for abdominal aortic aneurysms. Three patients had histories of previous malignancy, one had renal cell carcinoma, and another had both renal cell carcinoma and diffuse large B-cell lymphoma.

The immunosuppressant regimens are summarized in Table 2 and involved combinations of cyclosporin, tacrolimus, mycophenolate mofetil, methylprednisolone, and mizoribine. The most common combination ($n = 6$) was tacrolimus, mycophenolate mofetil, and methylprednisolone.

The operative methods and diagnoses are summarized in Table 3. Segmentectomy involved either right S6, right S8–10, the left upper division or left S6. Lobectomy involved the right lower lobe and the left lower lobe in one case each. In patients with lung cancer who underwent wedge resection or segmentectomy, the tumor

Table 1 Patient characteristics ($n = 12$)

Age (years)	62.0 (49.8–68.5)
Men/women (n)	8/4
VC (L)	3.68 (3.1–3.84)
FEV$_{1.0}$ (L)	2.51 (2.4–2.79)
Preoperative serum Cr level (mg/dL)	1.22 (0.97–1.91)
Preoperative eGFR (mL/min/1.73 m^2)	47.1 (31.6–58.2)
ASA score (2/3)	7/5
Duration after renal transplantation (months)	102 (45–183)
Primary nephropathy (n)	
Cystic kidney	2
Chronic glomerulonephritis	2
IgA nephropathy	1
Acute glomerulonephritis	1
Contrast nephropathy	1
Unknown	5
Preoperative comorbidity (n)	
Cardiovascular	7
Respiratory	1
Metabolic	2
Past history of malignancy	3

Data are presented as median (interquartile range). Cr, creatinine; eGFR, estimated glomerular filtration rate; FEV$_{1.0}$, forced expiratory volume in 1 second; IgA, immunoglobulin A; VC, vital capacity.

Table 2 Combination of immunosuppressive agents ($n = 12$)

Combination	n
FK506 + MMF + MP	6
CyA + MMF + MP	4
CyA + Mz + MP	1
CyA + MZ	1

CyA, cyclosporine; FK506, tacrolimus; MMF, mycophenolate mofetil; MP, methylprednisolone; MZ, mizoribine.

Table 3 Operative methods and diagnoses ($n = 12$)

Operative method	n	Diagnosis	n
Wedge resection	4	Lung cancer	2
		Benign tumor†	1
		Pneumothorax	1
Segmentectomy	4	Lung cancer	3
		Metastatic lung tumor‡	1
Lobectomy	2	Lung cancer	2
Mediastinal tumor resection	1	Pericardial cyst	1
Chest wall tumor resection	1	Hemangiopericytoma	1

†Epithelial granuloma. ‡Metastasis of renal cell carcinoma.

diameter was < 20 mm, chest CT showed no lymph node enlargement, and PET showed no abnormal ^{18}F-fludeoxyglucose uptake in the hilar or mediastinal lymph nodes. Peripheral tumors were resected by wedge resection, and central tumors were resected by segmentectomy. Three patients underwent limited resection because of poor pulmonary function. Hilar and interlobar lymph node sampling was performed during segmentectomy, and systemic mediastinal lymph node dissection was performed during lobectomy. None of the patients required reinforcement of the bronchial stump, bronchoplasty, angioplasty or conversion to open thoracotomy.

The postoperative outcomes are shown in Table 4. There were no intraoperative complications, and none of the patients required a blood transfusion. Postoperative complications occurred in two patients (16.7%), with one developing hemorrhagic cystitis due to adenovirus and the other developing pneumonia. Postoperatively, none of the patients required pleurodesis and there were no hospital deaths.

The median perioperative serum Cr level and eGFR showed no statistically significant differences compared to the preoperative data (Tables 4,5). After a median postoperative observation period of 49.0 months (interquartile range, 27.3–69.5 months), the latest serum Cr level and eGFR also showed no statistically significant differences compared to the preoperative data (Tables 4,5).

In the immediate perioperative period, no patient was reintroduced to dialysis. However, one patient developed pneumocystis pneumonia 2 months after left lower lobectomy by VATS and required hemodialysis during treatment in the intensive care unit. Excluding this case, none required further hemodialysis in the long-term. One patient died of diffuse large B-cell lymphoma, but all other patients survived. Univariate analysis revealed no risk factors for postoperative complications (Table 6).

Table 7 summarizes the characteristics of patients who developed lung cancer. One patient with stage IB disease received adjuvant chemotherapy with tegafur-uracil. No patient suffered lung cancer recurrence during the observation period.

Discussion

In Japan, the 5-year graft survival rate is 92.8% after living donor transplantation and 83.9% after cadaveric donor transplantation (1). Acute tubular necrosis due to hypotension, hypovolemia, and dehydration are the most well-known causes of postoperative renal dysfunction, with reintroduction to hemodialysis an unfavorable postoperative complication. Preoperative CKD, type 1 diabetes mellitus, age ≥65 years, surgery of the great vessels, and cardiopulmonary bypass are recognized risk factors of postoperative renal dysfunction (5). However, some of these risk factors may not necessarily preclude renal transplantation. Indeed, this report showed no significant differences between preoperative and either immediate or late postoperative renal function, with only one patient needing to be reintroduced to hemodialysis, due to pneumocystis pneumonia.

Medications are also an important factor in achieving favorable outcomes. The anesthetic agents used in our patients rarely affect renal function when given in normal doses because they are mainly metabolized by the liver (6–9). In Japan, non-steroidal anti-inflammatory drugs, which can adversely affect renal function, are widely used for postoperative analgesia, but we use acetaminophen in patients with CKD. We usually use cefazolin as a perioperative antibiotic. As this agent is metabolized by the kidney, it is important to adjust the dose according to eGFR. In general, prophylactic

Table 4 Postoperative characteristics

Perioperative serum Cr level (mg/dL)	1.19 (0.89–1.79)
Perioperative eGFR (mL/min/1.73 m^2)	47.7 (32.5–63.6)
Operative time (min)	123.0 (59.8–189.3)
Blood loss (mL)	18.5 (5–37)
Duration of drainage (days)	3.0 (3.0–4.3)
Hospital stay (days)	7.5 (7.0–9.5)
Postoperative complication, *n* (%)	2 (16.7)
Pneumonia	1
Hemorrhagic cystitis†	1
Latest serum Cr level (mg/dL)	1.18 (1.05–1.74)
Latest eGFR (mL/min/1.73 m^2)	45.9 (30.3–51.7)

Data are presented as median (interquartile range). †Due to adenovirus.Cr, creatinine; eGFR, estimated glomerular filtration rate.

Table 5 Comparison of serum Cr level and eGFR with preoperative values

					P-value*
Serum Cr level (mg/dL)	Preoperative	1.22 (0.97–1.91)	Perioperative	1.19 (0.89–1.79)	0.666
			Latest	1.18 (1.05–1.74)	0.625
eGFR (mL/min/1.73 m^2)	Preoperative	47.1 (31.6–58.2)	Perioperative	47.7 (32.5–63.6)	0.388
			Latest	45.9 (30.3–51.7)	0.477

P-value in Wilcoxon signed-rank test.Data are presented as median (interquartile range).Cr, creatinine; eGFR, estimated glomerular filtration rate.

Table 6 Univariate analysis for risk factors of postoperative complication

Variables	OR	95%CI	*P*-value*
Age (years)	1.187	0.859–1.640	0.298
Male	Reference		
Female	2.333	0.107–50.982	0.590
Preoperative Cr (mg/dL)	0.287	0.13–0.654	0.433
Preoperative eGFR (mL/min/1.73 m^2)	1.035	0.958–1.118	0.338
Age at transplantation (years)	1.136	0.911–1.417	0.256
Duration after transplantation (months)	0.995	0.977–1.014	0.632
Operative time (min)	0.991	0.964–1.019	0.532
Intraoperative bleeding (mL)	0.948	0.829–1.084	0.437

P-value in univariate logistic regression analysis. CI, confidence interval; Cr, Creatinine; eGFR, estimated glomerular filtration rate; OR, odds ratio.

Table 7 Characteristics of patients with lung cancer (*n* = 7)

Histology (*n*)	
Adenocarcinoma	4
Squamous cell carcinoma	3
Pathological stage (*n*)	
IA	5
IB	2
Duration after kidney transplantation (months)	96 (66–222)
Age at kidney transplantation (years)	52.0 (48.5–58.5)
Postoperative observation periods (months)	48.0 (31.5–64.0)

Data are presented as median (interquartile range).

antibiotics are continued until the first postoperative day in our institute. A surgeon can prolong the duration of administration because renal transplant patients receive some immunosuppressive agents that may lead to postoperative complications. It is also important to consult with the transplant surgeon or nephrologist when deterioration of renal function is observed in the perioperative period. Steroid cover is essential for transplant patients when managing immunosuppressive agents and replacing oral agents with intravenous agents.

Various operations were employed in our patients (Table 3). After surgery, postoperative complications included hemorrhagic cystitis due to adenovirus and pneumonia. Hemorrhagic cystitis is an uncommon complication after thoracic surgery and may be related to immunosuppression. In addition, although pneumocystis pneumonia occurred in one patient, no causality can be inferred with the operation because it developed 2 months after discharge. Villamizar *et al.* reported lower morbidity with lower rates of pneumonia, sepsis, and renal failure after thoracoscopic lobectomy than after thoracotomy (10). They also reported that renal transplant recipients may benefit from VATS. However, if critical accidents such as massive bleeding occur, the operative approach should be converted to open thoracotomy to perform surgery safely. Univariate

analysis of our data showed no risk factors for postoperative complications, probably due to the small sample size and low complication rate. We excluded combinations of immunosuppressive agents as an explanatory variable because dosages were individualized for patients. It is also difficult to compare different immunosuppressive agents directly, particularly because they do not have equivalent efficacies.

Yamamura *et al.* reported that following open heart surgery after renal transplantation, prosthetic valve endocarditis occurred in one patient who underwent a double valve replacement (11). In thoracic surgery, prosthetic devices are sometimes used to reconstruct the chest wall and vessels. It is possible that transplant recipients have higher risks of postoperative infection in such scenarios, and using autograft reinforcement of the bronchial stump should be considered in those cases (12–14). In addition, a previous report showed that acute allograft failure occurred in 8 of 57 patients who underwent cardiac surgery and that preoperative renal dysfunction was associated with early adverse events (e.g. deaths, major infectious complications, and allograft failure requiring temporary or permanent hemodialysis) (15). It is possible that there is a high risk of morbidity and mortality in renal transplant recipients requiring concomitant cardiac and pulmonary surgery or combined resection with cardiopulmonary bypass.

In this study, four patients developed adenocarcinoma and three patients developed squamous cell carcinoma. It is known that malignancies occur more frequently in transplant recipients (16–20), with renal cell carcinoma being approximately 15-fold more common than in the general population (18). However, Kasiske *et al.* reported the incidence of primary lung cancer after renal transplantation to be only two-fold higher, and Agraharkar *et al.* reported its incidence less frequently (18,19). Some authors have found that age at renal transplantation was associated with incidence of malignancy; for example, age ≥40 years was considered relevant by Hsiao and Hsu, and age ≥60 years by Agraharkar *et al.* (19,20). In comparison with the general population, age <40 years at renal transplantation and >10 years post-transplantation have been associated with higher rates of cancer (20). Of note, our results were comparable to these reports.

All patients with lung cancer in this study had pathological stage I disease. This may have been because transplant patients periodically undergo chest X-ray or CT after transplantation as part of their routine follow-up care. Although five patients in this study underwent limited resection, we consider lobectomy and mediastinal lymph node dissection to be the standard operative method for lung cancer in renal transplant patients and general patients. We did not choose limited resection

only for patients with a previous history of renal transplantation. Interestingly, no recurrence was observed in any patient.

To date, we are unaware of any reports of the prognosis of lung cancer after renal transplantation. In contrast, there have been several reports concerning hemodialysis patients with lung cancer (21–23). In this case, the prognosis of lung cancer is considered poor in patients undergoing dialysis because of immunosuppression and death from other diseases. Indeed, Takahama *et al.* reported that the 5-year survival of patients was just 70% (22), and Matsuoka *et al.* reported that of 25 deaths, 12 did not die of cancer (23). It is therefore inferred that lung cancer in renal transplant recipients would have a poor prognosis for the following three proposed reasons. First, the long duration of hemodialysis before renal transplantation causes systemic arteriosclerosis, which increases the risk of cardiovascular disease. Second, calcineurin inhibitors such as cyclosporin and tacrolimus can worsen the prognosis of cancer because they are associated with tumor growth, invasion, and metastasis (24). Third, renal dysfunction itself can affect the prognosis of cancer, with chronic renal dysfunction often present in transplant recipients. Even when renal transplantation is successful, renal function rarely improves beyond category G2–G3b (25). In fact, most of our patients were classified as no better than category G3a. It is conceivable that limited chemotherapy and dose reduction to protect renal function influences the prognosis of patients requiring adjuvant therapy.

Study limitations

This study was retrospective in design and included a small number of patients who were heterogeneous. Further case collection with long-term follow-up is needed to clarify the outcomes of VATS after renal transplantation. Unfortunately, the prognosis of lung cancer following renal transplantation also remains unclear based on this report, because all lung cancer cases were stage I and there were no recurrences. Finally, because fewer renal transplantations are performed in Japan than in Western countries, any future study should aim to be multicenter in design.

Conclusions

This study showed no postoperative mortality, deterioration of renal function, or need to reintroduce hemodialysis following VATS after renal transplantation. Although the outcome of the surgery was favorable, our data were limited by the small sample size and single-center retrospective design. In the absence of more definitive research, it is necessary for clinicians to remain aware that transplant patients are permanently immunocompromised.

Acknowledgments

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