Korean J Thorac Cardiovasc Surg 2015;48:193-198 □ Clinical Research □
ISSN: 2233-601X (Print) ISSN: 2093-6516 (Online) http://dx.doi.org/10.5090/kjtcs.2015.48.3.193

Surgical Treatment for Non-Small Cell Lung Cancer in Patients on Hemodialysis due to Chronic Kidney Disease: Clinical Outcome and Intermediate-Term Results

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Background: Patients on dialysis undergoing surgery belong to a high-risk group. Only a few studies have evaluated the outcome of major thoracic surgical procedures in dialysis patients. We evaluated the outcomes of pulmonary resection for non-small cell lung cancer (NSCLC) in patients on hemodialysis (HD). ***Methods:*** Between 2008 and 2013, seven patients on HD underwent pulmonary resection for NSCLC at our institution. We retrospectively reviewed their surgical outcomes and prognoses. ***Results:*** The median duration of HD before surgery was 55.0 months. Five patients underwent lobectomy and two patients underwent wedge resection. Postoperative morbidity occurred in three patients, including pulmonary edema combined with pneumonia, cerebral infarction, and delirium. There were no instances of in-hospital mortality, although one patient died of intracranial bleeding 15 days after discharge. During follow-up, three patients (one patient with pathologic stage IIB NSCLC and two patients with pathologic stage IIIA NSCLC) experienced recurrence and died as a result of the progression of the cancer, while the remaining three patients (with pathologic stage I NSCLC) are alive with no evidence of disease. ***Conclusion:*** Surgery for NSCLC in HD patients can be performed with acceptable perioperative morbidity. Good medium-term survival in patients with pathologic stage I NSCLC can also be expected. Pulmonary resection seems to be the proper treatment option for dialysis patients with stage I NSCLC.

Key words: 1. Dialysis
2. Renal dialysis
3. Pulmonary surgical procedures
4. Thoracic surgery
5. Lung neoplasms

INTRODUCTION

Due to advances in dialysis techniques, the number of patients on long-term dialysis has been increasing [1]. Moreover, a tendency for lung cancer to be detected earlier in dialysis patients has been reported, since these patients undergo more extensive follow-up and are monitored more closely by their doctors [2]. Therefore, it is reasonable to anticipate an increasing number of dialysis patients with lung cancer who require surgery.

Patients on dialysis undergoing surgery are a high-risk group, requiring careful perioperative management [3]. Due to

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Received: September 5, 2014, Revised: November 7, 2014, Accepted: November 8, 2014, Published online: June 5, 2015
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their increased risk of perioperative complications associated with electrolyte imbalance, bleeding, infection, and hemodynamic instability, patients on dialysis are often not considered suitable for major surgical procedures. For this reason, only a few studies have evaluated the outcomes of major thoracic surgical procedures in patients who are on dialysis due to chronic kidney disease (CKD) [1,4,5]. The aim of this study was to evaluate the postoperative outcomes, in terms of complications and survival, of pulmonary resection for non-small cell lung cancer (NSCLC) in patients who are on hemodialysis (HD) due to CKD.

METHODS

We performed a retrospective chart review on all patients who underwent pulmonary resection for NSCLC with curative intent at Samsung Medical Center between January 2008 and December 2013 (n=4,793). Of these patients, we retrospectively reviewed the data of seven patients (five male, two female) who had been receiving HD for CKD at the time of surgery.

The routine preoperative workup included pulmonary function tests, computed tomography (CT) scans of the chest and upper abdomen, F-18-flurodeoxyglucose-positron emission tomography (PET)/CT scans, flexible bronchoscopy, and brain magnetic resonance imaging.

Pulmonary resections were performed via posterolateral thoracotomy in three patients and via video-assisted thoracic surgery in four patients. Lobectomy with systematic lymph node dissection was the preferred procedure. Limited resection without mediastinal lymph node dissection was performed in two patients with peripherally-located clinical T1aN0M0 NSCLC.

All patients were evaluated by nephrologists before the operation, and the dialysis schedule was discussed. Most patients underwent HD on the day before surgery. Intravenous antibiotics were routinely administered intraoperatively and postoperatively, with consideration of the glomerular filtration rate and dialysis schedule. Postoperatively, patients were re-evaluated by nephrologists and usually underwent HD the day after surgery. Conventional or continuous renal replacement therapy (CRRT) was chosen based on the hemodynamic stability and fluid and electrolyte balance of each patient.

Table 1. Preoperative profiles

Variable	Value
Patients (male : female)	7 (5 : 2)
Age (yr)	67 (62–70)
Serum values on the day before operation	
Hemoglobin (g/dL)	10.7 (9.4–12.8)
Hematocrit (%)	33 (29.1–39.7)
Urea nitrogen (mg/dL)	63.9 (43.3–81.9)
Creatinine (mg/dL)	8.4 (7.96–13.31)
Hemodialysis duration (mo)	55.0 (10.0–105.3)
Pulmonary function test	
FEV_1 (L)	2.27 (1.66–2.65)
FEV_1 (% of predicted value)	90 (78–119)
Underlying renal disease	
Diabetic nephropathy	5
Hypertensive nephropathy	1
Ischemic nephropathy	1

Values are presented as number or median (range).
FEV_1, forced expiratory volume in one second.

In order to prevent bleeding, we administered a dose of desmopressin every six hours from the day of the operation until the third postoperative day. We sought to maintain preoperative hemoglobin levels >10 g/dL by injecting 2,000 U of erythropoietin subcutaneously twice a week. Additionally, red blood cell transfusion was performed during preoperative dialysis in patients whose hemoglobin level was <10 g/dL. The decision to use adjuvant treatment was made by a multidisciplinary team based on the pathologic stage of the cancer, the general condition of the patient, and the presence of comorbidities.

Patients were evaluated with CT scans every three to four months for the first two years after surgery and every six months thereafter, and were also annually evaluated with PET/CT scans. When recurrence was suspected, we attempted to obtain unequivocal histological or radiological proof. In cases where follow-up was not performed, a telephone interview was conducted to determine outcomes.

RESULTS

There were five men and two women in our study, with a median age of 67 years (range, 62 to 70 years). The preoperative profiles of the patients are presented in Table 1.

The median duration of HD before operation was 55.0 months (range, 10.0 to 105.3 months). The median levels of preoperative blood urea nitrogen and serum creatinine were 63.9 mg/mL (range, 43.3 to 81.9 mg/mL) and 8.4 mg/mL (range, 7.96 to 13.31 mg/mL), respectively. The median hematocrit value was 33.0% (range, 29.1% to 39.7%). The underlying kidney disease was diabetic nephropathy in five patients, hypertensive nephropathy in one patient, and ischemic renal disease in one patient. The median preoperative forced expiratory volume in one second value was 2.27 L (range, 1.66 to 2.65 L) and the preoperative forced expiratory volume in one second value as a percentage of the predicted median was 90% (range, 78% to 119%). The clinical stage of NSCLC was evaluated as IA in three patients and IB in four patients.

The operative outcomes are presented in Table 2 and Table 3. Five patients underwent lobectomy with systematic lymph node dissection. Two patients with peripherally-located clinical stage IA disease underwent wedge resection without lymph node dissection. The pathologic stage of NSCLC was IA in two patients, IB in two patients, IIB in one patient, and IIIA in two patients. The median duration of the operation was 138 minutes and the mean operative blood loss was 120 mL. HD was performed on the day before operation and postoperative dialysis was resumed on the day after surgery in most of the patients. CRRT was administered to a patient with pulmonary edema, and conventional HD was administered to the remaining six patients. The median duration

Table 2. Operative data and postoperative results

Variable	Value
Surgical procedure	
Lobectomy with mediastinal lymph node dissection	5
Wedge resection	2
Surgical approach	
Open thoracotomy	3
Video-assisted thoracic surgery	4
Operation time (min)	120 (62–235)
Blood loss (mL)	150 (10–250)
Chest tube duration (day)	5 (3–11)
Hospital stay (day)	8 (6–20)
Pathologic tumor–node–metastasis stage	
IA	2
IB	2
IIB	1
IIIA	2
Histologic type	
Adenocarcinoma	5
Squamous cell carcinoma	1
Pleomorphic carcinoma	1

Values are presented as number or median (range).

Table 3. Comorbidities and operative outcomes

Patient	Age (yr)	Sex	Comorbidities	Procedure	Operative time (min)	Blood loss (mL)	Complication
1	65	F	HTN, colon ca.	Lobectomy with MLND	235	250	Pulmonary edema, delirium, HAP
2	67	M	DM, HTN, prostate ca.	VATS lobectomy with MLND	120	20	NA
3	70	M	DM, HTN, atrial fibrillation, gastric ca.	Lobectomy with MLND	235	200	NA
4	70	M	DM, HTN, angina with percutaneous coronary intervention	VATS wedge resection	85	10	Delirium
5	64	M	DM, HTN, cerebral infarction	VATS lobectomy with MLND	127	200	Tachy-brady syndrome, cerebral infarction
6	70	F	HTN, ischemic cardiomyopathy[a], superior mesentery artery occlusion, essential thrombocythemia	VATS wedge resection	62	50	NA
7	62	M	DM, HTN	Lobectomy with MLND	99	150	NA

HTN, hypertension; ca., cancer; MLND, mediastinal lymph node dissection; HAP, hospital-acquired pneumonia; DM, diabetes mellitus; VATS, video-assisted thoracic surgery; NA, not applicable.
[a]Estimated ejection fraction=20%.

of chest tube placement was five days and the mean hospital stay was eight days. There were no instances of postoperative bleeding that required reoperation, although postoperative complications did occur in three patients. One patient suffered from pulmonary edema and atelectasis combined with hospital-acquired pneumonia. In this patient, a diffuse dense adhesion to the pleural space was found, which resulted in a longer operation time and greater blood loss during the operation. She was treated with CRRT and intravenous antibiotics for 10 days. Another patient, who had a history of cerebral infarction, was diagnosed with tachy-brady syndrome on the day after the operation and underwent temporary pacemaker insertion. The patient became persistently drowsy on the second postoperative day and was diagnosed with acute cerebral infarction. Warfarinization was therefore initiated. The last patient was diagnosed with postoperative delirium. There were no instances of in-hospital mortality, although the patient who suffered from cerebral infarction died of intracranial bleeding 1.1 months after the operation (15 days after discharge).

The patheologic results and medium-term outcomes are presented in Table 4. In the other six patients, the median follow-up duration was 15.3 months (range, 12.9 to 57.5 months). Adjuvant radiotherapy was recommended for one patient diagnosed with parietal pleural invasion and two patients with N2 disease, but all three patients refused adjuvant treatment. During the follow-up period, these three patients experienced recurrence and died due to the progression of the cancer. The remaining three patients are alive with no evidence of disease. The overall survival rate was 43.0%.

DISCUSSION

Despite recent advances in treatments for lung cancer, the overall five-year survival for patients newly diagnosed with NSCLC is only 18% [6], making lung cancer one of the deadliest carcinomas. Surgery remains the standard treatment modality for patients with early-stage NSCLC [7]. Therefore, decisions concerning operability have clear implications for achieving optimal treatment results.

Several studies have assessed the perioperative morbidity and mortality of CKD patients who are on HD and undergo surgery. The morbidity rate of patients who undergo non-cardiac surgery has been shown to vary from 7% to 64% [3,8]. The causes of higher morbidity rates were found to include difficulty in controlling fluid and electrolyte balance, a tendency towards increased bleeding, poor blood pressure control, and a high incidence of coronary artery disease [3,9].

A high morbidity rate after pulmonary resection in patients on HD has also been reported [1,4,5]. In addition to the complications involving fluid and electrolyte imbalance and bleeding that accompany HD, patients may be at increased risk of pulmonary complications after pulmonary resection.

Tsuchida et al. [5] reported a 43% incidence of pulmonary complications in patients on HD who underwent surgery. Obuchi et al. [1] reported that the overall morbidity rate in their study was 27% (3 of 11 patients), and that two of those three patients experienced complications of pneumonia result-

Table 4. Pathologic results and medium-term outcomes

Patient	Histology	Pathologic stage	Disease-free survival (mo)	Overall survival (mo)	Follow-up	Site of recurrence
1	ADC	T3N0M0 IIB	5.2	15.3	Cancer-related death	Lung, pleura
2	ADC	T2aN2M0 IIIA	6.3	12.9	Cancer-related death	Mediastinal LN
3	ADC	T2aN2M0 IIIA	3.8	16.0	Cancer-related death	Mediastinal LN, lung
4	ADC	T1aNxM0 IA	NA	57.5	Alive, no evidence of disease	NA
5	Pleomorphic carcinoma	T2aN0M0 IB	NA	1.1	Death due to brain hemorrhage	NA
6	ADC	T1aNxM0 IA	NA	37.7	Alive, no evidence of disease	NA
7	Squamous cell carcinoma	T2aN0M0 IB	NA	12.9	Alive, no evidence of disease	NA

ADC, adenocarcinoma; LN, lymph node; NA, not applicable.

ing in a prolonged hospital stay.

Generally, major pulmonary resection is accompanied by some pulmonary damage and edema. Patients on hemodialysis experience considerable difficulty in maintaining fluid balance, and are therefore more vulnerable to pulmonary edema. Pulmonary edema can also trigger hypoxemia and pneumonia [5]. In the current study, we experienced one case of pulmonary edema combined with hospital-acquired pneumonia. While the patient required intensive care and a prolonged hospital stay, he was successfully managed with CRRT and intravenous antibiotics.

In our center, we applied intrapulmonary doses to prevent bleeding and sought to maintain preoperative hemoglobin levels ＞10 mg/dL by injecting erythropoietin. Several studies have reported that desmopressin and erythropoietin help prevent postoperative bleeding in uremic patients, due to triggering an improvement in platelet function [10-13]. Additionally, red blood cell transfusion was performed during preoperative dialysis in patients whose hemoglobin level was below the target. These strategies may be useful not only in minimizing bleeding, but also in reducing reduce blood transfusion requirements that can cause volume overload. In order to prevent pulmonary edema, fluid intake was restricted to 2 L/day. Only one case of pulmonary edema was reported, and we succeeded in minimizing dialysis-related complications.

Although the overall complication rate was 43%, which is higher than that found in the general population [14], it was possible to manage most complications through careful postoperative care, and all patients were discharged within 20 days of hospitalization. There was one case of short-term mortality, in which a patient who had a history of brain infarction before the operation died of traumatic brain hemorrhage after discharge. The traumatic brain hemorrhage was warfarin-related, not dialysis-related. Based on these results, we propose that preoperative dialysis itself is not a contraindication for pulmonary resection. However, since most patients on dialysis have other comorbidities, much consideration and effort should go into planning the operation and preventing postoperative complications.

Obuchi et al. [1] reported an overall five-year survival rate of 28.0% in the 11 patients in their study who underwent hemodialysis after surgery. Interestingly, four of the six deaths in their study were due to non-cancer causes, and the survival rate was 37.5% in patients with stage I disease. In the current study, the overall five-year survival rate was 34.3%. Of the four patients with stage I NSCLC in our study, only one patient died. This patient had a history of cerebral infarction and suffered from a brain hemorrhage. Meanwhile, all patients with pathologic stage II or III NSCLC experienced recurrence, with a mean disease-free survival time of only 5.1 months. There is no clear consensus on the preferable adjuvant treatment of NSCLC in patients who are on dialysis due to CKD. Chemotherapy has never been routinely administered to such patients and has never been shown to be sufficiently effective [15], and we believe that chemotherapy would have been harmful to our patients considering their comorbidities. Therefore, instead of chemotherapy, we recommended adjuvant radiotherapy to all three patients with pathologic stage II or III NSCLC, but they refused further treatment. Insufficient adjuvant treatment may explain their low survival rate. Nevertheless, pulmonary resection, including the procedures that involved limited resection, was an effective treatment for early lung cancer with an acceptable morbidity rate. The primary limitation of this study is that our data should be interpreted with caution due to the limited number of patients.

In conclusion, pulmonary resection for NSCLC in patients on HD due to CKD can be performed with acceptable postoperative morbidity, and most morbidities can be controlled with careful postoperative care. Good medium-term survival in patients on HD due to CKD who are found to have pathologic stage I NSCLC can also be expected after surgical treatment. Pulmonary resection appears to be the proper treatment option for dialysis patients with stage I disease, and careful patient selection and postoperative care should be emphasized.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

This study was supported by a Grant of the Samsung Vein Clinic Network (Daejeon, Anyang, Cheongju, Cheonan; Fund No. KTCS04-026).

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