Original Article

Primary lung cancer in Chinese renal transplant recipients: a single-center analysis

ZHANG Shuxin¹, LIU Yang²

¹Department of Thoracic Surgery, 309 Hospital of PLA, Beijing 100091, China; ²Department of Thoracic Surgery, General Hospital of PLA, Beijing 100853, China

Abstract: **Objective** To evaluate the clinical characteristics and the outcomes of primary lung cancer in renal recipients. **Methods** Between January, 1988 and April, 2015, a total of 2793 consecutive patients underwent renal transplantation at our center. Fourteen (0.5%) patients subsequently developed lung cancer, for which 10 (71.4%) received surgical treatment. **Results** The mean age of the 14 patients with post-transplant lung cancer was 50.2 ± 8.3 years at transplantation, and 10 of them (71.4%) were former smokers. In 9 (64.3%) of 14 patients, the malignancies were detected incidentally and 5 patients were symptomatic. The average interval from transplantation to cancer diagnosis was 65.7 ± 20.1 months. Eleven patients died from cancer in different stages were statistically different (*P*=0.001). The overall 5-year survival rate after diagnosis was 17.9% in these 14 patients. **Conclusion** The risk of primary lung cancer in renal transplant recipients than in the general Chinese population. Routine chest screening for lung cancer in renal transplant recipients may help in early detection and treatment of the malignancy to improve the prognosis.

Keywords: lung cancer; renal transplantation; surgery; immunosuppression; prognosis

INTRODUCTION

Renal transplantation is currently considered the best option for treatment of terminal renal failure. Malignancy is a well-recognized complication of renal transplantation with an estimated 10-year incidence of 20% after renal transplantation^[1], and in some population, post-transplant malignancies have even become the third leading cause of death [2]. Previous studies reported that lung cancer accounted for only 3%-5% of all malignancies after transplantation ^[3-11], and skin malignancies and lymphoma are the most common malignancies in Western countries as compared with urological tumors in Asian countries ^[3, 12, 13]. Due to its rather low incidence, primary lung cancer has been under-emphasized in patients receiving renal transplantation. Nonetheless, as the post-transplant survival of the recipients extends, the incidence of lung cancer increases progressively ^[5, 14]. The goal of this retrospective study was to analyze the clinical characteristics and the outcomes of primary lung cancer in patients after receiving renal transplantation.

PATIENTS AND METHODS

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 Corresponding author:
 LIU Yang,
 E-mail:
 3197583805@qq.com.

Ethical statement

This study was approved by the Ethics Committee of 309 Hospital of PLA and was performed in line with the ethical guidelines of the 2000 Declaration of Helsinki as well as the Declaration of Istanbul (2008). Because of the retrospective nature of the study, the need for informed patient consent was waived.

Study design and patients

Between January, 1988 and April, 2015, a total of 2793 consecutive patients underwent renal transplantation at 309 Hospital of PLA, among whom 14 (0.5%) patients developed lung cancer after the transplantation. All these patients with lung cancer were followed until death or until April, 2015. The data of different variables were collected from the 14 patients, including the demographic data (age at transplantation and gender), smoking history, maintenance immunosuppressive treatment, tumor characteristics (histological results and tumor stage), therapies of tumors (surgery, chemotherapy, and radiotherapy), and outcomes of lung cancer.

Outcome analyses

The survival time of the patients in this context was defined as the period of time between tumor diagnosis and death.

Statistical analyses

The probability of survival of the patients was estimated with Kaplan-Meier method. In addition, survival was analyzed in relation to the age at transplantation, the pathological type of the tumor, tumor stage and the lymph nodes status. The patients' survival according to different modalities of these variables was assessed using the log-rank test. A P value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

Study population

The 14 recipients included 10 men and 4 women with an average age at transplantation of 50.2 years (range, 34-61 years). At the time of tumor diagnosis, 10 (71.4%) of the 14 patients smoked cigarettes ranging from 20 to 90 pack-years (mean 48 pack-years). They were all exposed to dialysis for 2 to 28 months (mean 8.2 months) prior to renal transplantation.

The protocols for maintenance immunosuppression were cyclosporine, azathioprine and prednisone in 6 patients, tacrolimus, mycophenolate mofetil and prednisone in 3 patients, cyclosporine, mycophenolate mofetil and prednisone in 3 patients, sirolimus, mycophenolate mofetil and prednisone in 1 patient, and cyclosporine, mizoribine and prednisone in 1 patient. The intensity of immunosuppressive therapy was reduced individually at the time of lung cancer diagnosis. Conversion from cyclosporine to sirolimus was prescribed in 2 patients. Any interruption of the immunosuppressive regimen was under nephrologic surveillance.

Characteristics of lung cancer in this population

Before renal transplantation, all the patients underwent chest radiography, but regular postoperative chest screening was not performed as a part of follow-up. The recipients underwent chest computed tomography (CT) only as indicated by clinical symptoms. In 9 of the patients, lung cancer was detected incidentally, and the remaining 5 patients all had clinical symptoms (Tab.1). The mean time from transplantation to diagnosis was 65.7 ± 20.1 months (range, 27-104 months). The methods of pathological diagnosis were CT guided transthoracic biopsy in 3 cases, bronchoscopic biopsy in 6 cases, lymph node biopsy in 1 case and thoracotomy in 4 cases. The most frequent pathological types of lung cancer were squamous cell carcinoma (n=7, 50%) and adenocarcinoma (n=5, 35.7%); adenosquamous carcinoma was detected in 1 case and small cell carcinoma in another. The tumors were in stage IA in 2 cases, stage IB in 1 case, stage IIA in 1 case, stage IIB in 3 cases, stage IIIA in 3 cases, stage IIIB in 2 cases, and stage IV in 2 cases.

Ten (71.4%) of 14 patients were treated with thoracic surgery. The surgical procedure was complete resections in 9 cases (8 lobectomies and 1 bilobectomy with complete mediastinal lymphadenectomy) and palliative resection in another (the patient underwent wedge resection for poor pulmonary function). No patient died during the perioperative period. Two patients developed bacterial pneumonia and recovered uneventfully after improved anti-inflammatory treatment.

Survival analyses

All the 14 patients contributed data to the survival analysis (Tab.2). The patients showed a survival time ranging from 2 to 65 months after the diagnosis of lung cancer. The survival time differed significantly among patients with different tumor stages at diagnosis (P= (0.001) and with different lymph nodes status (P=0.02). We observed a mean survival time of 47.4 months in recipients with lung cancer in stage IIB or lower, 11 months in recipients with stage IIIA disease, and only 2.8 months in patients with stage IIIB or IV disease. The patients with negative lymph nodes had significantly longer mean survival time than those with positive lymph nodes (53.3 months vs 12.6 months). Nevertheless, we found no association of age at transplantation (P=0.68) or pathological types of the tumors (P=0.11) with the survival time of the patients.

During the follow-up, 11 patients died from lung cancer metastasis (n=8) or organ failure (n=3). The remaining 3 patients were alive without tumor recurrence at the time of this current report. The patients showed a median survival time of 15 months, with 2-year and 5-year survival rates of 35.7% and 17.9%, respectively.

DISCUSSION

Epidemiology and risk factors

In renal transplant recipients, the incidence of primary lung cancer was rather low, ranging from 0.1% to 0.8% in different reports ^[3-11, 14-20] (Tab.3). According to findings from National Central Cancer Registry (NCCR) in 2010, the estimated rate of lung cancer was 46.08 per 100 000 in the general population in China ^[21], much lower than the incidence of 0.5% after renal transplantation we report herein. We found a mean time from transplantation to lung cancer diagnosis of 65.7 months, similar to the previously published data ^[15, 17, 22].

The role of immunosuppression in lung cancer development after renal transplantation remains controversial, although it was found to clearly associate with some primary neoplasms in transplant recipients ^[13, 23, 24]. Genebes et al ^[15] presumed that immunosuppression may induce lung cancer independent of a smoking history, but Anyanwu et al ^[25] demonstrated that in heart transplant recipients, immunosuppression was not a causative factor while smoking and advanced age were identified as the causative risks, which was consistent

Case No.	Symptom	TNM	Stage	Histology	Treatment	Survival (month)	Current Status
1	Cough	T3 N2 M0	IIIA	Squamous cell carcinoma	Biolobectomy	6	Deceased
2	Blood stained sputum	T3 N2 M0	IIIA	Squamous cell carcinoma	Wedge resection	10	Deceased
3	Asymptomatic	T1a N0 M0	IA	Squamous cell carcinoma	Lobectomy	36	Alive
4	Asymptomatic	T3 N0 M0	IIB	Squamous cell carcinoma	Lobectomy	38	Alive
5	Asymptomatic	T2b N1 M0	IIB	Squamous cell carcinoma	Lobectomy+radiotherapy	15	Deceased
6	Asymptomatic	T4 N2 M0	IIIB	Small cell carcinoma	Chemotherapy	3	Deceased
7	Asymptomatic	T1b N0 M0	IA	Adenocarcinoma	Lobectomy	53	Deceased
8	Asymptomatic	T2b N1 M0	IIB	Adenocarcinoma	Lobectomy+chemotherapy	22	Deceased
9	Asymptomatic	T2a N0M0	IB	Adenocarcinoma	Lobectomy	65	Deceased
10	Fever	T2b N1 M1a	IV	Squamous cell carcinoma	Palliative radiotherapy	3	Deceased
11	Asymptomatic	T2a N1 M0	IIA	Adenocarcinoma	Lobectomy+chemotherapy	41	Alive
12	Asymptomatic	T1a N2 M0	IIIA	Adenocarcinoma	Lobectomy+chemo- radiotherapy	17	Deceased
13	Cough	T3 N3M0	IIIB	Adenosquamous carcinoma	Palliative radiotherapy	7	Deceased
14	Back pain	T3 N1 M1b	IV	Squamous cell carcinoma	None	2	Deceased

Tab.1 Tumor characteristics and survival data in each case

with the findings in others studies ^[24, 26].

Prolonged duration of dialysis has been considered as a potential risk for malignancy. Several studies ^[10, 27, 28] demonstrated that the increased time on dialysis was significantly and independently associated with lung cancer in renal transplant recipients. In this present study, all the 14 recipients underwent dialysis before transplantation. The cumulative exposure to toxins on dialysis needs to be evaluated for its potential risk for malignancies in renal transplant recipients.

Therapeutic procedures

For recipients with early-stage lung cancer (stage I-II), complete resection is considered as the standard surgical treatment, but in patients in stage IIIA, the role of surgery is questionable. In our patients, 3 patients with stage IIIA disease underwent operation, and their mean survival time (11 months) was longer than that of patients with stage IIIB-IV disease (mean 2.8 months). For patients with stage IIIB-IV disease, the benefits of chemotherapy and radiotherapy should be carefully weighed against their severe adverse effects, which can be potentially fatal in these patients.

Intense immunosuppression results in accelerated disease progression and a lowered survival of the patients ^[11, 29, 30]. Reduction of immunosuppression reduction appeared to have a positive effect on tumor progression

and on the prognosis. In our cases, we reduced the immunosuppression to about half of the original dose in patients with early-stage tumors. Mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus, are known to have both immunosuppressive and anti-neoplastic activities ^[1, 13, 31]. Several studies demonstrated that mTOR inhibitor was associated with a significantly lowered incidence of primary malignancies including lung cancer ^[32, 33-36]. In our patients, only 1 patient received sirolimus-based regimen in the maintenance treatment with a duration of 6 years from the transplantation to the diagnosis. Two patients had conversion from cyclosporine to sirolimus for tumor metastases, but their survival time was only 6 and 3 months. Due to the small sample size in this study, we could not draw a definite conclusion regarding the protective effect of sirolimus.

Prognosis

The cumulative intense immunosuppression disrupts the antitumor surveillance and accelerates tumor progression ^[11, 17, 18, 22]. Ahmed et al ^[17] reported that 75% of the renal transplant recipients with stage IIIB-IV lung cancer had a mean survival of only 2 months, but the early-stage patients had significantly better prognoses: half of the patients with stage I-II disease survived for a mean of 47.4 months after radical resection. Early

Tab.2 Survival analysis in the study population (estimated by the Kaplan-Meier method)

Characteristics	n	Mean survival (<i>Mean±SD</i> , month)	Log-rank test (P value)
Histology			
Squamous cell carcinoma	7	21.4±2.8	0.11
Adenocarcinoma	5	43.2±15.3	
Other	2	5.0±5.4	
Age group (yr)			
34-49	6	43.7±12.5	0.68
50-61	8	27.8±10.0	
Tumor stage			
1-11	7	47.4±12.2	0.001
IIIA	3	11.0±6.4	
IIIB-IV	4	2.8±1.0	
N (lymph node) status			
N-	4	53.3±0	0.02
N+	10	12.6±2.5	

diagnosis and surgical treatment may obtain favorable prognosis in the recipients with early-stage lung cancer.

Screening

Malignancies are reported to account for 18% of all deaths in renal transplant recipients ^[37]. Such malignancies are found often incidentally in chest examinations, as was the case in 9 (64.3%) of our patients. Most of the asymptomatic cancers might have been detected by systematic surveillance of the chest after renal transplantation.

So far no clear recommendations are available for lung cancer surveillance in renal transplant recipients. Screening with chest roentgenograms, as stated by several investigators, is inadequate ^[17, 22, 25, 26]. Chest CT markedly enhances the detection rate (especially for lung nodules) ^[38]. In the current study, 71.4% of the patients reported tobacco use, and the nonsmokers showed a longer interval before the diagnosis of lung cancer (mean 86.5 months) than the smokers (mean 57.4 months). We thus recommend annual chest CT examination for the recipients or biannual examination for heavy former smokers.

Limitations

This study has several limitations. Firstly, the

Tab.3 Incidence of primary lung cancer reported in the literature

First author (Ref.)	Year of publication	Total renal transplant recipients	No. of patients	Incidence (%)
Zhang et al ^[3]	2014	30 632	28	0.09
Tessari et al ^[4]	2013	3537	18	0.51
Sampaio et al ^[5]	2012	123 380	608	0.49
Engels et al ^[14]	2011	102 654	517	0.5
Ju et al ^[6]	2011	2630	6	0.23
Genebes et al ^[15]	2010	1993	10	0.5
Padilla et al ^[16]	2009	1539	10	0.65
Vegso et al $[7]$	2007	2852	15	0.53
Webster et al ^[8]	2007	15 183	104	0.68
Ahmed et al ^[17]	2004	3750	8	0.21
De Perrot et al ^[18]	2003	1735	3	0.17
Pedotti et al ^[9]	2003	3521	7	0.2
Birkeland et al ^[10]	2000	1821	15	0.82
Delcambre et al ^[19]	1996	564	2	0.35
Kehinde et al ^[20]	1994	492	4	0.81
Barrett et al	1993	876	3	0.34
Current study	-	2793	14	0.5

retrospective nature of the study may result in underestimation of the actual incidence of primary lung cancer in the renal recipients. Secondly, we did not examine the possibility that lung cancer was derived from the organ donors as previous studies suggested ^[39]. Thirdly, due to the small sample size in this single-center study, we could not perform a multivariate analysis of the patients' survival to fully interpret the survival differences.

Conclusion

The incidence of primary lung cancer might be much higher in renal transplant recipients compared with the general population in China. Lung cancer can develop late in the post-transplant period and is often associated with a poor prognosis. Nevertheless, early diagnosis and surgeries may obtain more favorable outcomes in these patients. We recommend annual chest CT monitoring of the renal transplant recipients especially the heavy smokers and those with dialysis prior to the transplantation.

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肾移植术后并发原发性肺癌的单中心研究

张书新1,刘阳2

¹解放军第309医院胸外科,北京 100091;²解放军总医院胸外科,北京 100853

摘要:目的回顾性分析肾移植术后原发性肺癌的临床特点及预后。方法自1988年1月~2015年4月期间,2793例患者在我院接受肾移植手术。14例(0.5%)患者随后发展为肺癌,其中10例(71.4%)接受了手术治疗。结果 肾移植时患者的平均年龄为50.2±8.3岁。14例肺癌患者中,10例(71.4%)有吸烟史。9例(64.3%)为偶然发现,而有症状者仅为5例。从移植手术到肺癌诊断的平均时间间隔为65.7±20.1个月。统计结果显示,不同肿瘤分期病人的生存率具有统计学差异(P=0.001)。随访期间有11例死于肿瘤转移或器官衰竭,3例存活。肺癌诊断后的总体5年生存率为17.9%。结论 肾移植术后原发性肺癌的危险性可能高于一般人群。肾移植术后常规胸部检查可早期发现原发性肺癌,对于及早施行手术、改善预后很有必要。 关键词:肺癌;肾移植;外科手术;免疫抑制;预后

收稿日期:2016-04-11 作者简介:张书新,主治医师,E-mail: 1250739535@qq.com 通信作者:刘 阳,主任医师,教授,博士生导师,电话:010-66938013,E-mail: 3197583805@qq.com