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## Surgical treatment of malignant lung tumors in solid organ recipients

### Leczenie operacyjne nowotworów płuc u biorców przeszczepów narządów litych

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#### Abstract

Diagnostic difficulties, serious prognosis and often insufficient response to treatment are all common features of pulmonary complications in solid organ recipients. Some of these complications need invasive diagnostic procedures and surgical treatment or prolonged pharmacological treatment. Tuberculosis, Pneumocystis and fungal infections are examples of infectious complications. Primary lung cancer or metastasis to the lungs developed shortly after solid organ transplantation are oncological complications. Infectious and noninfectious complications are connected with immunosuppression. Treatment of pulmonary complications in solid organ recipients and continuation of immunosuppression therapy can be challenge for therapeutic team. This article presents five cases (2 women and 3 men) of solid organ recipients treated in department of the authors due to lung neoplasms. Four of them were liver recipients and one was recipient of heart. Three patients were treated due to primary lung cancer, additionally in one of them metastasis of lung cancer occurred, two suffered from metastasis of liver cancer (hepatocellular carcinoma) to the lungs. Four patients underwent 6 operation: 2 lobectomies with lymphadenectomy, 1 segmentectomy with lymphadenectomy, 1 bilateral metastasectomy of HCC and 1 metastasectomy of lung cancer. In all cases of primary lung cancer pathological examination revealed squamous cell carcinoma. Immunosuppression schedule, perioperative courses and infectious complications (tuberculosis, disseminated infection, infection of biliary tract, oesophageal candidiasis) in this group were described. All of them were smokers.

**Key words:** malignant lung tumor, organ transplant, immunosuppression

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#### Introduction

Organ transplantation is associated with numerous potential complications. Many of them are related to the respiratory tract and carry a high mortality rate [1–3]. The frequency of pulmonary complications in the course of post-transplant immunosuppression depends on the organ recipients' age, type of transplantation, history of a neoplasm in the past, presence of specific risk factors (HBV, hepatitis B virus, HCV, hepatitis C virus, tuberculosis), and cigarette smoking [4, 5]. Neoplasms are

one of such complications. Neoplasms of the skin, kidneys, lymphatic system (PTLD, *post-transplantation lymphoproliferative disorders*), sarcomas, as well as cancers of the large intestine, lungs, prostate, stomach, pancreas, and other organs are the most common [4, 6]. Neoplasms in organ transplant recipients may develop *de novo*, may be transmitted from the donor together with the transplanted organ, or may be the recurrence of an earlier disease in a recipient [4, 7]. The time between organ transplantation and diagnosis of neoplasm is often shorter than 7 years [8]. Interestingly, risk factors

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for neoplasm development in heart transplant recipients include female sex and young age [9]. The treatment of lung neoplasms in organ transplant recipients is similar to that in other groups of patients and depends on the disease's stage and type. In early stages of non-small cell lung carcinoma the surgical treatment is applied with the immunosuppressive treatment continued throughout the perioperative period. Cases with advanced disease (quite frequent in organ transplant recipients) are, like in other groups of patients, treated systemically or symptomatically [10].

Another group of complications related to immunosuppression are infections. The lungs are the most common site of infections in lung and heart transplant recipients, and the second most common site of infections in liver transplant recipients. Respiratory tract infections are less frequent in kidney transplant recipients [1, 11]. Lung tuberculosis is one of the most difficult therapeutic issues in this group of patients. It affects 0.5–5% of transplant recipients [1, 12]. The immunosuppression promotes activation of a latent infection (dormant tuberculosis) and development of miliary or disseminated forms of the disease [11, 12]. Considering the increasing number of transplantations and newly diagnosed neoplastic diseases, we decided to share our experience.

### Case reports

The presented group consisted of 5 cases (2 women and 3 men), aged 48–64 years (median age 61 years). Four patients were liver transplant recipients, and one was a heart transplant recipient (table 1). In three cases coexisting primary lung cancer was detected, and in two cases lung metastases of hepatocellular carcinoma (being a reason for the earlier liver transplantation) were diagnosed.

Altogether six surgeries were performed in four patients (two patients were operated on twice). One patient was treated for pulmonary tuberculosis.

#### Case 1:

A 64-year-old female, who underwent liver transplantation in 1996 due to drug-induced cirrhosis. Immunosuppressive treatment schedule consisted of: cyclosporine (100 mg/day), azathioprine (25 mg/day), and prednisolone (5 mg/every other day). In Jan 1999 she was diagnosed with pneumonia, the symptoms of which partially subsided after non-specific treatment. Six months later another acute respiratory tract infection was diagnosed. At that time tuberculosis was recognised and a 4-drug treatment in typical doses (INH — isoniazid, RMP — rifampicin, EMB — ethambutol, SM — streptomycin) was applied. The immunosuppressive treatment was continued. In the course of the treatment, symptoms of injury of vestibulocochlear nerve and liver occurred. The antituberculous treatment was withdrawn for 4 weeks, and after that continued with use of INH, RMP, and EMB. Clinical and radiological improvement as well as sputum smear AFB conversion was achieved. The treatment was stopped after 12 months. The post-transplantation course was also complicated with oesophageal candidiasis requiring repeated endoscopic procedures of dilatation of the strictures. She had been a cigarette smoker since 2003. In 2008 two tumours of the right lung were detected on a radiological examination. Transthoracic fine-needle biopsy of one of them showed non-small cell lung carcinoma (NSCLC). She was treated surgically. Resection of segments I and VI of the right lung with lymphadenectomy was performed. The postoperative period was complicated with gastrointestinal bleeding. Histopathologi-

**Table 1. Summary of presented solid organ transplant recipients**

Patient no.	Sex	Age	Transplanted organ	Lung -organ	Histology tumor	TNM	Side	Treatment	Infectious complications
1	Female	64	Liver	Primary	Squamous carcinoma	T2aNoMo / I B	Right	Segmentectomy	TBC, candidiasis
				Metastatic	Squamous carcinoma	T2aNoM1a / IV	Left	Wedge resection	
2	Female	62	Liver	Metastatic	HCC	M1	Left and Right	Wedge resection + chemotherapy	None
3	Male	61	Heart	Primary	Squamous carcinoma	T2aNoMo /IB	Right	Upper right lobectomy	None
4	Male	48	Liver	Metastatic	HCC	M1	Right	Symptomatic	None
5	Male	61	Liver	Primary	Squamous carcinoma	T1bNoMo /IA	Right	Upper right lobectomy	Sepsis

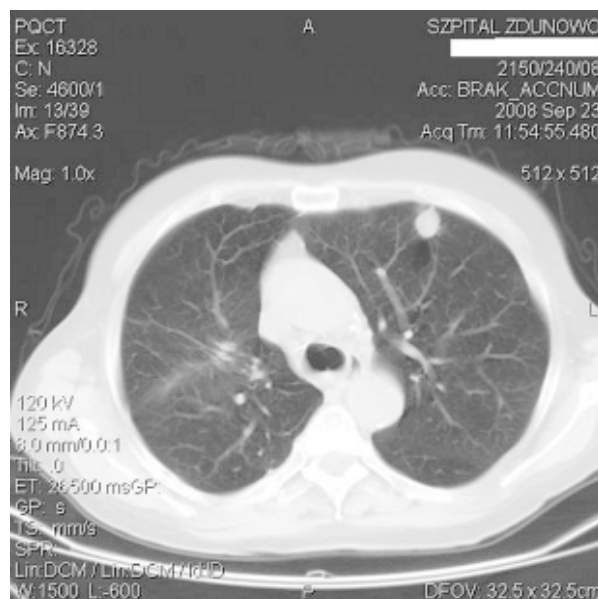
cal examination revealed squamous cell carcinoma in segment I and post-tuberculous foci in segment VI. There were no metastases to lymphatic nodes, so the carcinoma stage was established as T2aN0M0/IB. A year later a metastatic lesion in the left lung was diagnosed as well as multiple papillomatous skin changes within the upper extremities and chin. The patient was operated on again, this time without any complications (Fig. 1). The patient was lost for further follow-up.

### Case 2:

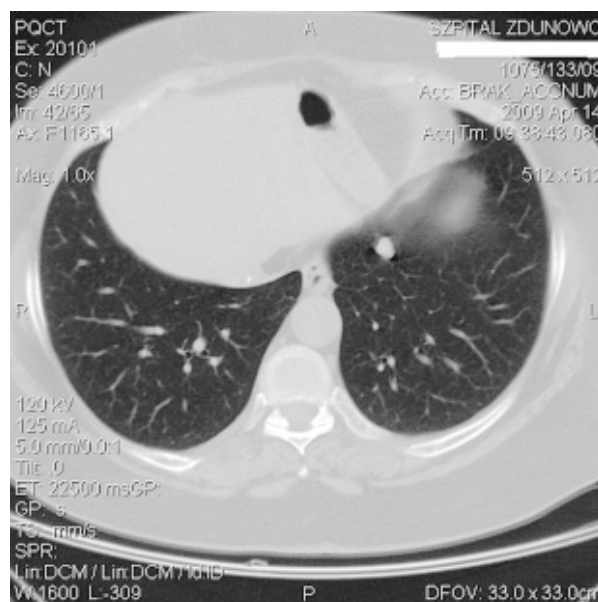
A 62-year-old female, who underwent liver transplantation in 2007 due to hepatitis C - induced cirrhosis and hepatocellular carcinoma (HCC). Immunosuppressive treatment schedule consisted of: mycophenolate mofetil (1,0 g/day), tacrolimus (2,0 g/day). She was a cigarette smoker (10 pack years). In 2008 a chest CT scan showed small nodules (< 5 mm), which remained under surveillance. CT scan in 2009 showed progression of one of the nodules in the lower left lobe (12 x 9 mm) (Fig. 2). Wedge resection was performed, and the perioperative course was uncomplicated. Histopathological examination confirmed a metastasis of hepatocellular carcinoma (from the explanted liver). The patient was given chemotherapy. Routine check-up in 2011 revealed a metastatic lesion (16 mm) in the right lung. The patient was operated on again; marginal resection was performed and the histopathological characteristic of the removed nodule was identical as before. The chemotherapy was continued. The patient remains in follow-up.

### Case 3:

A 61-year-old male, who underwent heart transplantation due to ischaemic and postinfarction cardiomyopathy. The immunosuppression scheme included cyclosporine A (150 mg/day) and mycophenolate mofetil (2,0 g/day). He was a cigarette smoker (32 pack years). In 2009 a tumour in segment III of the right lung, 4.6 cm in diameter, was detected on a radiological examination (Fig. 3). Clinical symptoms were typical (cough, pain in the area of right scapula, weakness, low-grade temperature). The preliminary diagnosis of NSCLC was obtained from fine-needle transthoracic biopsy. Preoperative echocardiographic evaluation revealed ejection fraction (EF) of 55–60%. Right upper lobectomy with complete lymphadenectomy was performed and the perioperative course was uncomplicated. Histopathological examination confirmed diagnosis of squamous cell carcinoma in stage pT2aN0M0/IB. The last follow-up contact was made in 2011.



**Figure 1.** Chest CT scan shows tumor 15 mm in the third segment of the left lung. Postoperative changes are visible in the right lung



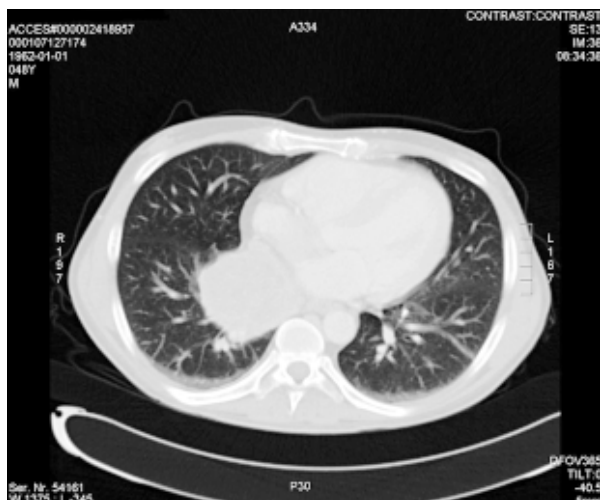
**Figure 2.** Chest CT scan shows tumor size 12 x 9 mm in the basal segments of the left lung

### Case 4:

A 48-year-old male, who underwent liver transplantation in 2009 due to hepatitis C and hepatocellular carcinoma (HCC). Three months later retransplantation was done due to hepatic artery thrombosis. Immunosuppressive treatment schedule consisted of rapamycin (2 mg/day) and prednisolone (5 mg/day). He was a cigarette smoker (5 pack years). Family history included lung cancer in his brother. In 2010 a CT scan showed tumour masses in the retroperitoneal space and in the ri-



**Figure 3.** Tumor diameter 4 cm visible in the upper part of the right lung



**Figure 4.** Lesion size 8,4 × 5,9 cm in the right lung with infiltration of the mediastinum in the region of left atrium

ght lung, located close to the mediastinum. The size of the tumour in the chest was 8 cm (Fig. 4). On admission the patient complained of intense coughing. The diagnosis of metastasis of primary hepatocellular carcinoma from the explanted liver was obtained from transthoracic fine-needle biopsy. Due to the advanced stage of the disease only symptomatic treatment was applied. The patient was lost to follow-up.

#### Case 5:

A 61-year-old male, who underwent liver transplantation in 2009 due to HCC. Immunosuppressive treatment schedule consisted of tacrolimus (6 mg/day). He was a cigarette smoker (17.5 pack years). In 2010 he developed post inflammatory stricture of external biliary ducts in the cour-

se of sepsis, and drainage had to be performed. In 2011 routine CT and MRI (*magnetic resonance imaging*) of the chest showed a lesion (22 mm) in segment IX of the right lung. The diagnosis from fine-needle transthoracic biopsy was squamous cell carcinoma. On admission he complained of coughing. Right lower lobectomy with radical lymphadenectomy was performed. The ultimate diagnosis of squamous cell cancer in T1bNoMo/IA stage was established. The patient remains in follow-up. The last contact was made in 2011.

### Discussion

Neoplasms occur more frequently in organ transplant recipients (4–18%) than in the general healthy population, and the frequency increases in proportion to the duration of immunosuppressive therapy — by 1–2% for each year [4, 13].

In organ transplant recipients the frequency of lung cancer is 0.2–0.6%, regardless of which organ was transplanted [10, 14]. According to some authors, the frequency of lung cancer in organ transplant recipients is not significantly higher than in the rest of population if age, sex, and risk factors are taken into the consideration [14, 15]. The number of newly diagnosed cancers increases in the general population affecting all other related issues. It has been noticed that frequency of lung cancer in heart transplant recipients has reached 4.1%. The phenomenon was explained as a result of tobacco smoking, causing both ischaemic heart disease and lung cancer development [14, 16]. In the group of organ transplant recipients in whom lung cancer was diagnosed, smokers counted for 93% [14]. All patients described by us were tobacco smokers. In the majority of them (3/5) primary lung cancer was present, which supports the theory of lung cancer development as a result of nicotine in organ transplant recipients [10, 17]. In organ transplant recipients, similarly as in the general population, non-small cell lung cancer dominates [10, 14, 18]. All primary lung cancers diagnosed in patients from our group were squamous carcinomas. The primary lung cancers were diagnosed 12 and 2 years after liver transplantations (cases 1 and 5) and 7 years after heart transplantation (case 3).

The lungs are also the most common site of metastases after liver explantation due to HCC. They usually appear within 2 years after the transplantation [1]. In two of our patients (2 and 4) metastases of hepatocellular cancer appeared in the lungs in a similar interval of time after the transplant surgery. Most probably, the micrometastases

were already present in the lungs at the time of liver transplant surgery, but the techniques allowing for their detection were not available. Neoplastic cells originating from a primary tumour may migrate to various organs in the form of microscopic foci and may stay dormant for many years (*tumour dormancy*) [19]. The regulating mechanisms induce transformation of undetectable and inactive metastases into actively growing tumours. In the opinion of many authors, neoplasms in organ transplant recipients are characterised by quick progression and worse response to treatment and prognosis.

Oncological and infective complications related to immunosuppressive treatment after organ transplantations are very dangerous and potentially lethal [1, 11, 12, 16, 20–22]. One of the consequences of this is the program of systematic screening check-ups in the organ transplant recipient population. Probably, as in the general population, the best results of treatment can be achieved in early stage lung cancers. The surgical treatment of isolated metastatic lesions in lungs is the most effective mode of therapy. The problems related to overlapping competences such as treatment of lung cancer, treatment of tuberculosis, and aspects of clinical transplantology should be solved by the creation of multidisciplinary teams. Some centres in the country and abroad fulfil these criteria.

### Conflict of interest

The authors have no conflict of interest to report.

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