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LUNG CANCER IN SOLID ORGAN TRANSPLANT RECIPIENTS

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Lung cancer remains the leading cause of cancer mortality worldwide. Solid organ transplant recipients are at risk of developing malignant tumors, including lung cancer, due to long-term use of immunosuppressive drugs. Development of cancer, including lung cancer, in this patient cohort, has a number of peculiarities. Moreover, malignant tumors in these patients are difficult to treat and have a poorer prognosis. This review presents a study of the issues concerning the mechanisms of lung cancer development, screening methods and treatment in solid organ transplant recipients.

Keywords: solid organ transplant recipients, immunosuppressive therapy, malignant tumors, lung cancer.

INTRODUCTION

Despite recent advances in immunology, genetics, pharmacology and other sciences, lung cancer remains the leading cause of death among all malignancies. As the number of smokers increases in the world, so does the incidence of lung cancer [1].

The International Agency for Research on Cancer estimates that 2,206,771 new cases of lung cancer were identified in 2020, representing 11.4% of all cancers. The mortality rate was 1,796,144, representing 18% of all cancer deaths in 2020. In men, lung cancer ranks first in mortality rate (21.5% of total mortality), and in women it ranks second place after breast cancer (13.7%) [51]. Solid organ transplantation is the only and so far irreplaceable method of treatment of end-stage diseases when other means of treatment are powerless. The number of solid organ transplants is increasing year by year in the world. The year 2020 is an exception due to the Covid-19 pandemic. According to the International Society for Organ Donation and Transplantation, 113,363 solid organ transplants have been performed worldwide. Solid organs recipients are at risk of developing malignancies, including lung cancer, due to long-term use of immunosuppressive drugs. In addition, malignant tumors in solid organ recipients are difficult to treat and have a worse prognosis [2–8, 52].

INCIDENCE

The overall incidence of malignant tumors in solid organ recipients depends on the country of residence, diet, habits, environmental conditions, and other factors. World statistics give different data on the incidence of malignant tumors in solid organ recipients, depending on the group of patients, age and transplanted organ. The average incidence is 2–6% [9, 10]. The most common tumors are lymphoproliferative diseases and skin cancer. The risk of lung cancer in solid organ recipients ranges from 0.3% to 0.85%, which is similar to the incidence in the general population [9, 10]. There is an increased incidence of lung cancer in lung and heart recipients compared to liver and kidney recipients (the ratio was 5.5, 2.9, 2, and 1, respectively). Heart-lung transplant recipients had a 9.3-fold higher risk of developing lung cancer compared to the general population. The authors concluded that this is associated not only with immunosuppressive therapy, but also with age and long-term smoking history [9, 11]. According to A.-M. Noone et al., among 221,962 solid organ transplant recipients, 15,012 developed cancer (6.76%). Lung cancer was the largest contributor to mortality (3.1%), followed by non-Hodgkin lymphoma (1.9%), colorectal cancer (0.7%), and kidney cancer (0.5%). Non-Hodgkin lymphoma was the largest contributor among children (4.1%) and lung cancer was the largest contributor among solid organ recipients aged ≥50 years (3.7–4.3%). The authors concluded that cancer-attributable mortality increases with age and time since transplantation, and therefore cancer deaths will become an increasing burden as recipients live longer [12]. In a study by E. Yanik et al., among 187,384 solid organ recipients, of which kidney recipients constituted 58%, liver recipients 22%, heart recipients 10%, and lung recipients 4%, 9,323 cancers (4.97%) were detected. The most common was lung cancer (n = 1,993 (1.06%)) [13]. D. Pérez-Callejo et al. analyzed 633 lung transplant patients and found that the most common causes for transplantation were idiopathic pulmonary fibrosis (47.8%) and emphysema (43.4%). During follow-up, lung cancer was detected in 23 of them (3.63%). In 5 patients, lung cancer was an incidental finding in the recipient's explanted lung. In 18 patients, cancer developed de novo in single-lung transplant re-

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cipients (12 cases in the native lung and 6 cases in the donor lung) [14].

PATHOGENESIS AND RISK FACTORS

There are several mechanisms by which solid organ recipients get lung cancer: de novo in the native lung (in the case of a single-lung transplant), in the donor lung, or as a progression of a pre-existing tumor in the explanted lung. Reports about detection of lung cancer in the recipient's explanted lung are not so rare, which suggests that solid organ recipients should be examined more thoroughly before surgery. For example, in Y. Jun Choi et al., out of 247 lung recipients, 6 (2.4%) were diagnosed with lung cancer as an incidental finding in the explanted lung [15]. The probability of donor-transmitted tumor with donor lung is extremely low, but such transmission mechanism exists and it is imperative to perform computed tomography in a potential donor. This is more relevant to lung transplantation. However, reports have cases of lung cancer transmission, for example, with transplanted liver (in this observation, lung cancer metastasis from an undetected nidus was detected in the liver) [16].

Among lung cancer risk factors, besides smoking, which most authors consider to be the main one, Epstein–Barr virus and progression of post-transplantation lymphoproliferative diseases are also distinguished [14]. In addition, development of lung cancer can be influenced by adverse environmental conditions, such as exposure to silica and asbestos. Some terminal stages of diseases for which lung transplantation is performed, such as chronic obstructive pulmonary disease and pulmonary fibrosis, also suggest increased risk of lung cancer in single-lung versus double-lung transplantation. Most authors say that the risk of lung cancer almost doubles after 60 years of age [8, 14, 17–21].

IMMUNOSUPPRESSIVE THERAPY AS A SPECIFIC FACTOR

Loss of immunological surveillance due to decreased antitumor immunity, especially in patients with pulmonary fibrosis whose risk of lung cancer incidence is approximately 7 times higher than in the population, activation of pro-oncogenic viruses, direct carcinogenic effect of immunosuppressive drugs are all specific risk factors for lung cancer in solid organ recipients in comparison with the population [4–6, 12, 22–27].

SCREENING

The possibility of early detection and timely treatment of malignant tumors in solid organ recipients directly depends on periodic screening examinations [25, 28]. Although early diagnosis of lung cancer can improve treatment outcomes in this category of patients, the position of some authors who express doubts about the expediency of screening in solid organ recipients with life-threatening comorbidities or with life expectancy of less than 5–10 years is puzzling [29]. Current English-language guidelines for screening of cancer of various localizations, including lung cancer, for solid organ recipients are based on extrapolation of the results of screening studies in the general population, as well as on understanding of the high risk of lung cancer in this category of patients [29]. In lung recipients with a long history of smoking, despite quitting smoking, close monitoring is a prerequisite for early diagnosis of lung cancer [9].

A screening program to detect lung cancer in the U.S. population revealed that the use of low-dose multislice computed tomography in comparison with radiography reduces lung cancer mortality by 20% [20, 21]. The use of the Lung Imaging Reporting and Data System (Lung-RADS) to interpret the changes detected during screening allows standardization of CT scan description, as well as development of clear guidelines for determining treatment tactics (Table) [30, 31]. Thus, the use of such a data evaluation system for lung cancer diagnosis in solid organ recipients seems promising.

PREVENTION AND TREATMENT

The fundamental method of lung cancer prevention is "cancer vigilance" at all stages of medical care and dynamic monitoring. Besides total smoking cessation, methods of prevention also include "reasonable" minimization of immunosuppression [13, 25].

Lung cancer treatment in solid organ recipients does not differ from that in the population. Treatment strategy depends on the stage, histological structure of the tumor, and presence of concomitant diseases in the recipient [25, 32]. The peculiarities of this category of patients are the fact that chemotherapy within the framework of complex treatment often cannot be carried out in full due to concomitant diseases and the danger of graft rejection caused by reduced dosage of immunosuppressive drugs [3]. In the English-language literature, there are currently no guidelines on changing the immunosuppressive therapy regimen in solid organ recipients after diagnosed lung cancer, although chemotherapy usually decreases the intensity of immunosuppressive therapy [33, 34]. Immunotherapy is now coming to the fore in a number of cases of different tumor types (high PD-L1 expression and tumor mutational burden). However, interference with the immune system can have disastrous consequences in patients on immunosuppressive therapy, as the issue of simultaneous administration of immuno-oncological and immunosuppressive drugs remains unexplored [35]. Surgery is the gold standard in stage I and II non-small cell lung cancer (NSCLC). At the same time, stereotactic ablative radiotherapy (SABR) is the method of choice in patients with stage I NSCLC who are inoperable due to their somatic status [36–38]. However, the safety of SABR has not been evaluated in solid organ recipients,

which is a major drawback for this method. According to G. Drevet et al., surgical method of treatment is more preferable in treatment of lung cancer of stages II and IIIA in cases of resectable tumor and operability of pa-

Table

Lung-RADS, a system for assessing changes in the lungs detected by MSCT. Treatment tactics and risks of malignancy [31]

Category descriptor	Score	Findings	Tactics	Risk of malignancy	Population prevalence
Incomplete research	0	No data for comparison	Additional MSCT	–	1%
No nodules and definitely benign nodules	1	No lung nodules OR nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules	MSCT in 12 months	<1%	90%
Benign appearance with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	**Perifissural nodule(s)** <10 mm **Solid nodule(s)**: <6 mm new <4 mm **Part solid nodule(s)**: <6 mm **Non-solid nodule(s) (ground-glass nodules, GGN)**: <30 mm OR ≥30 mm and unchanged or slowly growing **Category 3 or 4 nodules unchanged for ≥3 months**			
Probably benign	3	**Solid nodule(s)**: ≥6 to <8 mm OR new 4 mm to <6 mm **Part solid nodule(s)**: ≥6 mm with solid component <6 mm OR new <6 mm **GGN**: ≥30 mm	MSCT in 6 months	1–2%	5%
Suspicious	4A	**Solid nodule(s)**: ≥8 to <15 mm at baseline OR growing <8 mm OR new 6 to <8 mm **Part solid nodule(s)**: ≥6 mm with solid component ≥6 mm to <8 mm OR with a new or growing <4 mm solid component **Endobronchial nodule**	MSCT in 3 months; PET/CT may be used when there is a ≥8 mm solid component	5–15%	2%
Very suspicious	4B	**Solid nodule(s)**: ≥15 mm OR new or growing, and ≥8 mm **Part solid nodule(s)** with: a solid component ≥8 mm OR a new or growing ≥4 mm solid component	MSCT/PET and/or tissue sampling For new large nodules, CT in 1 month to address potentially infectious or inflammatory conditions	>15%	2%
	4X	Category 3 or 4 nodules with additional features or imaging findings that increase the suspicion of malignancy (spiculation, GGN that doubles in size in 1 year, enlarged lymph nodes, etc.)			
Other clinically significant findings (non-lung cancer)	S	May add on to any category	–	–	10%

tients. Traditional radiotherapy and chemotherapy are recommended for treatment of inoperable lung cancer of stage II and locally disseminated lung cancer of stage III. In solid organ recipients, special caution should be exercised when prescribing radiation or chemotherapy due to immunosuppressive therapy, concomitant diseases, frequent presence of renal insufficiency [39].

Video-assisted thoracoscopic surgery (VATS) for anatomical lung resections are increasingly used worldwide to treat various diseases, including primary lung cancer [40]. As surgeons accumulate practical experience and surgical techniques improve, the range of VATS is expanding in various areas of thoracic surgery [40]. The vast majority of thoracic surgeries previously performed traditionally from thoracotomy can be performed using endoscopic equipment from small incisions [41]. In specialized thoracic departments, the number of VATS lobectomies often exceeds the number of open lobectomies performed [41]. The gradual abandonment of thoracotomy in favor of VATS has led to better patients' quality of life while maintaining the same surgical safety [42]. At the time this technology appeared, there were still doubts concerning the radicality of operations performed and long-term survival rate of patients with lung cancer. But now, it is generally accepted that thoracoscopic access for lobectomy for NSCLC does not lead to worse long-term outcomes in patients' survival in comparison with traditional thoracotomy [40]. At the same time, VATS has a number of advantages, namely, a smaller number of complications in early and late postoperative period, and shorter hospital stay [40, 43]. T. Demmy, et al. emphasize that in elderly and debilitated patients, immediate and long-term outcomes of VATS are better than in thoracotomy [41]. According to P. Falcoz et al., early postoperative mortality in VATS lobectomy group in NSCLC patients was twice lower in comparison with open lobectomies [40]. The advantages of VATS are particularly pronounced in elderly patients (over 70 years old), and underweight and predicted low functional scores in the postoperative period (SPH1 <40%) [40]. Reports on the use of VATS in solid organ recipients are rare. M. Al-Ameri et al. comparing immediate and long-term results of uniportal and multiportal VATS accesses in patients with various pathologies of the lungs and mediastinum, came to the conclusion that there are no significant differences in the number of postoperative complications (6% in both groups), and that the 30-day mortality and overall survival at 1 year was 0% and 97% in the uniportal group, and 0.5% and 98% in the multiportal group (P = 0.71). In addition, the author reported faster rehabilitation and shorter hospital stay for uniportal access (76.2% versus 62.1%, P = 0.008) [44]. However, uniportal access is still not widespread according to a survey among members of the European Society of Thoracic Surgeons (ESTS) [45]. J J. Seitlinger et al. note that conversion rate, i.e. conversion from miniaccess to conventional thoracomy, decreases with the improvement of surgical technique and is less than 10% [46]. At the same time, patients undergoing conversion have a higher risk of complications in early and late postoperative period (40.9% versus 16.8%) and mortality (6.8% versus 0.2%) [46]. Meanwhile, open surgery cannot be completely abandoned, because, with all its advantages, VATS is powerless in situations where it is impossible to create adequate working space for safe manipulations inside the thoracic cavity during surgery. (e.g., intolerance to single-lung ventilation) [41]. H. Maeda et al. conducted an interesting study, analyzing 12 cases of VATS in kidney recipients [47]. The authors compared both laboratory parameters, in particular serum creatinine levels, and assessed the glomerular filtration rate before and after surgery and postoperative complications. Operative methods used included VATS wedge resection (n = 4), VATS segmentectomy (n = 4), VATS lobectomy (n = 2), VATS mediastinal tumor resection (n = 1), and VATS chest wall tumor resection (n = 1). All patients received two to three immunosuppressive drugs, and no patients required perioperative hemodialysis. There were no bronchopulmonary complications in the early postoperative period. There were no statistically significant differences between preoperative and postoperative serum creatinine levels and estimated glomerular filtration rate. The authors conclude that such operations are safe in recipients on immunosuppressive therapy [47].

PROGNOSIS

The course of malignant tumors, including lung cancer, is more aggressive in solid organ recipients. Prognosis and life expectancy are determined by the stage of the disease, the presence of N2 status, driver mutations, the degree of pathomorphosis, treatment regimen, etc. [20, 25, 48]. According to G Drevet et al., the 5-year survival rate of resectable lung cancer after surgical treatment was 40.6%, which is comparable with the survival rate in the population (40.7 to 50%) [9]. L. Nora Chen et al. report that the median survival of lung recipients after lung cancer diagnosis was 32 months (IQR, 10–52 months), which is significantly lower compared to the general population [48]. S. Zhang et al. reported a 17.9% overall 5-year survival rate in kidney recipients after lung cancer diagnosis [49]. K. Sigel et al., having investigated 597 cases of lung cancer detection in solid organ recipients, concluded that the survival rate of solid organ recipients, not including lung recipients, is worse in comparison with patients with lung cancer in the population [50]. It is necessary to treat the literature data with caution, since all the above prognostic factors should be considered, first of all, the lesion of regional lymph nodes. Survival rate is also directly affected by the adequacy of lymphodissection performed during surgery. It should also be noted that in some cases, it is difficult to compare the results of different authors, because in

different years, different TNM classification was used to assess tumor spread.

CONCLUSION

Despite conflicting data from various authors, reports suggest an increased risk of lung cancer in solid organ recipients, especially lung and heart-lung recipients. Given the increasing role of malignant tumors, including lung cancer, in the overall mortality of solid organ recipients, as well as increased life expectancy of solid organ recipients, the development of screening and prevention of lung cancer in solid organ recipients is a timely and urgent task. In our opinion, we must be critical of the recommendations of some authors that screening in solid organ recipients with life-threatening comorbidities and a life expectancy of less than 10 years is inappropriate. Creation of an evidence-based screening program aimed at early detection of lung cancer in solid organ recipients (e.g., the Lung-RADS data evaluation system, which has proven to be excellent in the United States), would allow early treatment to be initiated. The choice of optimal treatment tactics for lung cancer in solid organ recipients requires further study. As data accumulates, it will be possible to make a conclusion about the safety of chemotherapy and immunotherapy in this category of patients. Surgical treatment of lung cancer in solid organ recipients does not fundamentally differ from that in the population, and VATS is not inferior to open surgeries, having at the same time a number of advantages. Introduction of minimally invasive methods of surgical treatment of lung cancer in this category of patients will shorten the patient's stay in the hospital, and significantly speed up rehabilitation since there is less pain and less surgical trauma.

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