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Development of oncological diseases after organ transplantation

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Abstract

With the increase in the population of patients with transplanted organs, the risk of developing oncological diseases has become proportionally high, which may be the cause of poor quality of life, and also of a high mortality among the patients with transplanted organs. The review examines the risk factors, incidence, and the impact of malignant neoplasms on the survival in patients with transplanted organs. The rapid development of clinical transplantology, the use of new drugs and immunosuppression regimens poses new challenges for oncologists and transplantologists. The analysis of oncopathology incidence in patients with transplanted organs allows us to conclude about its impact on the long-term life prognosis and the need to include preventive measures in transplantation practice.

Keywords: oncological diseases, transplantology, incidence, risk factors, post-transplant period

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DNA, deoxyribonucleic acid

HIV, human immunodeficiency virus

HPV, human papillomavirus

IL-1Rα (Interleukin-1β), alpha chain of the interleukin 1 receptor

NHL, non-Hodgkin's lymphoma

PCT, polychemotherapy

SIR, standardized incidence ratio

SMR, standardized morbidity ratio

Introduction

Vital organ transplantation is an up-to-date treatment method that can prolong life and improve its quality for many patients with chronic diseases [1-4]. According to C.N. Graham et al. [5], the mean life expectancy of kidney transplant recipients is 22.79 in the United States years, and 26.58 years in the United Kingdom; these figures make 20.90 years and 20.38 years for recipients with a transplanted liver, respectively; 14.82 years and 15.85 years for recipients with a transplanted heart, respectively, and 9.28 years and 9.21 years for lung transplantation, respectively. In Russia, a 1-year survival rate of recipients reached 93.4% after cadaveric kidney allotransplantation, and 97.2% when transplanted from a live donor, while the overall recipient survival rate for 5 years was 82% [2]. Due to the increase in the life expectancy of

solid organ recipients with immunosuppressive therapy and oncogenic opportunistic infections developing against its background, the risk of developing oncological diseases also began proportionally increasing.

Cancer risk in patients with transplanted organs

Numerous studies indicate a more frequent detection of malignant neoplasms of various locations in recipients with transplanted organs compared to the general population. The cumulative de novo cancer incidence after transplantation is 9-10% in the first 10 years after transplantation and 10-27% within 20 years [3, 6-8]. Based on the analysis of 6 review publications, S.L. Rashti et al. [9] have found that the detection rate of oncological diseases after solid organ transplantation is from 4 to 5% with significant variation in different types of cancer. According to A. Guillemin et al. [10] the risk of developing de novo cancer in recipients with transplanted organs is 2.6 times higher than in the general population. Z. Huo et al. [11] performed a meta-analysis of cancer risk in recipients of transplanted organs based on 72 publications, including a total of 2,105,122 patients. In comparison with the general population, the overall risk of developing cancer pathology in patients after transplantation (standardized incidence ratio [SIR]) was 2.68 times higher, 2.56 times higher in patients with a transplanted kidney, 2.45 times higher in patients with liver transplantation, and 3.72 times higher in patients with heart/lung transplantation.

The increased risk of malignant neoplasms after transplantation does not apply evenly to all types of tumor diseases [12]. For some malignancies, such as lung, liver, and kidney cancers, melanoma and non-melanoma skin cancers, lymphoproliferative diseases, and thyroid cancer, the risk is significantly higher than for the general population. In addition, the risk of malignancies caused by viral infections, including cervical

cancer and anal cancer (human papillomavirus [HPV] 16, 18, 31, 33, 39, 45, 50) is particularly high, as well as non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (Epstein-Barr virus), Kaposi's sarcoma (human herpes virus 8 [HHV8]) and liver cancer (hepatitis C and B viruses) [13-17]. At the same time, for prostate, breast, thyroid, and urinary tract cancers, according to some authors, the detection rate is only slightly higher than the risk for the entire population of the corresponding age group and gender [18-21]. At the same time, it should be noted that the frequency of detection of certain types of cancer varies significantly among different authors who assess the risk of developing cancer in different populations, reaching 10 times for certain types of tumors, as demonstrated in the review publication by S.N. Sherston et al. [18] (Table 1).

Table 1. Relative risk index (standardized incidence ratio) for the development of different types of cancer in different populations*

Tumor Type	USA	Australia	UK
Kaposi's Sarcoma	61.46	200	17.1
Lip cancer	16.78	47.1	65.6
Non-Hodgkin's lymphoma	7.54	9.9	12.5
Non-melanoma skin cancer	13.85	-	16.6
Urinary tract cancer	1.52	4.2	2.4
Liver cancer	11.56	3.0	2.4
Anal cancer	5.84	2.8	10.0
Myeloma	-	2.7	3.3
Melanoma	2.38	2.5	2.6
Cervical cancer	1.03	2.5	2.3
Cancer of lung, trachea, bronchi	-	2.4	1.4
Pancreas, biliary tract cancer	1.46	2.0	1.5
Colorectal cancer	1.24	1.7	1.8
Kidney cancer	4.65	7.3	7.9
Prostate cancer	0.92	1.0	1.1
Breast cancer	0.85	1.0	1.0

Note: *Standardized incidence ratio (SIR); SMR: the ratio of the observed number of new cases to the expected number. It is used as a standard indicator for comparing the frequency of disease development in the studied cohort and the estimated frequency of its development in the population.

The same significant differences are revealed when comparing the publications of other authors (Table 2).

Table 2. Cancer risk in recipients with transplanted organs, according to data from different authors

Author	Type of cancer and risk of its development
H. Schrem et al. [19]	– kidney cancer (SIR 22.46) – thyroid cancer (SIR 10.13) – lymphoproliferative diseases (SIR 8.36) – bladder cancer (SIR 3.24) – melanoma (SIR 3.08) – prostate cancer (SIR 2.22)
G.H. Park et al. [22]	– Kaposi's sarcoma (SIR 565.2) – squamous cell carcinoma (SIR 61.9) – basal cell carcinoma (SIR 11.9)
M. Ekstrom et al.* [23]	– non–Hodgkin's lymphoma (SIR 20.8-66.7) – skin cancer (SIR 20.3-35.2 – lung cancer (SIR 11.7-31.2) – liver cancer (SIR 3.6-51.6) – colorectal cancer (SIR 6.1-19.5)
W.P. Kluijfhout et al.*, [19]	– thyroid cancer (SIR 2.5–3.5)
E. Lengwiler et al. (in descending order of SIR) [20]	– liver cancer – kidney cancer – thyroid cancer – stomach cancer – bladder cancer – oral cancer – pharynx cancer – lung cancer

Note: * − assessments were made for different organ transplants

Patients with transplanted organs have a significantly increased risk of developing cancer. Meantime, the type of organ transplanted does not significantly affect the degree of risk. Data on the predominant type of cancer vary greatly from author to author. Obviously, the key issue is the impact of the cancer pathology development on the survival of patients with transplanted organs.

Impact of the development of malignant diseases on the survival of patients with transplanted organs

The factor of malignant tumor development directly affects the survival of patients with transplanted organs [24, 25]. Cancer-related mortality after organ transplantation ranks second after chronic rejection in these patients in the long-term. In fact, cancer that develops after solid organ transplantation is the only cause of death that is currently increasing in these patients [26, 27].

Higher mortality rates are influenced by two factors: first, when establishing an oncological diagnosis in patients with transplanted organs, immunosuppressive treatment is usually minimized, which increases the risk of graft rejection, and second, the chemotherapeutic stage of treatment is often suboptimal due to concomitant pathology; in addition, possible interactions immunosuppressive and antitumor drugs with negative consequences should be taken into account [10].

There is evidence that a 10-year survival rate of kidney transplant recipients who developed malignant tumors of various location was 79.1%, which was lower than in kidney transplant recipients without malignant neoplasms, and also statistically significantly lower than in patients from the general population who were diagnosed with cancer [28, 29], this includes stratification of patients by age and gender [30]. According to various authors, the relative risk of death from cancer is 2-6 times higher for kidney transplant recipients [15, 31] and 2-4 times higher for liver transplant recipients [15, 32, 33]. Meanwhile, it has been shown that the course of malignant diseases in recipients of solid organs is more aggressive [16, 32]. The rate of cancer recurrence in patients with transplanted organs is 1.6 times higher than in the general population, especially in kidney transplant recipients [34], which leads to a lower median survival of patients after the diagnosis of malignant diseases (2.7

years compared to the mean survival of recipients without cancer of 8.3 years [35]. Based on extensive clinical data from 221,962 solid organ recipients, according to A.M. Noone et al. [36], 15,012 patients developed a malignant tumor, of whom 13.2% died from its progression. Meantime, the mortality rate of patients depended on the type of developed tumor process. The highest mortality rates were among recipients with advanced lung cancer (3.1%), NHL (1.7%), colorectal cancer (0.9%), and kidney cancer (0.5%). Mortality increased in patients over 65 years of age, as well as at 10 or more years after transplantation (15.7%) [37, 38].

Based on the analysis of data from 11 American Cancer Registries for the period from 1987-2014 (11,416 cases of cancer development after solid organ transplantation), when analyzed separately for 16 types of cancer, higher mortality from cancers among the patients with transplanted organs was revealed for most of them, compared both with the entire population of transplanted patients, and with the general population of cancer patients, especially marked in relation to melanoma (the risk of development is 2.59 times higher), breast cancer (1.88 times), bladder cancer (1.85 times), and colorectal cancer (1.77 times), and to a lesser extent (1.21–1.47 times) in relation to oral, pharyngeal, stomach, and pancreatic cancer, kidney, lung cancer, and B-cell lymphoma. A similar relationship was seen in the subgroup of patients with locally advanced early stages of cancer [39, 40].

Thus, the development of malignant diseases in patients with transplanted organs significantly worsens the prognosis of long-term results after transplantation, and the type of cancer that has developed significantly affects the risk of an unfavorable (fatal) outcome.

Factors influencing the increased risk of developing malignant diseases in patients with transplanted organs

According to most authors, the main factor that increases the risk of cancer in patients with transplanted organs is the need for lifelong immunosuppressive therapy. The effect of prolonged immunosuppression has been confirmed by comparing the incidence of malignant diseases in patients with transplanted organs and patients infected with the human immunodeficiency virus (HIV), which showed similar figures [41]. In a meta-analysis conducted by these authors (7 publications including 444,172 patients infected with HIV and 5 publications including 31,977 solid organ recipients receiving immunosuppressive therapy), it was shown that 20 of the 28 types of cancer studied showed a higher incidence of cancer compared to the general population in both groups.

The mechanism of this impact of immunosuppression can be associated with two types of processes: (1) prolonged immunosuppression increases the risk of developing virus-associated oncological diseases; (2) due to the non-specific effect of most immunosuppressive drugs, the immune system control over tumor cells is disrupted [42].

For a number of oncogenic viruses, such as cytomegalovirus, hepatitis B and C viruses, Epstein-Barr virus, human papillomavirus (HPV 16, 18, 31, 33, 39, 45, 50), it has been established that their presence is a significant risk factor for the development of malignant diseases [43, 44]. Studies have shown that patients with transplanted organs are more likely to develop virus-associated malignancies, such as NHL, Hodgkin's lymphoma, Kaposi's sarcoma, vulvar cancer, cervical cancer, and liver cancer [32, 33, 41, 45, 46].

The negative impact of oncogenic viruses, in particular, HPV type 16, 18, affects the development of malignant tumors of the female

reproductive system (cervical, vaginal, vulvar, anal anal cancer). Patients with transplanted organs have a 3-4-fold higher risk of developing cancer of the reproductive system compared to the general population [47], and this is obviously associated with the presence of HPV type 16, 18, and the vital need for immunosuppressive therapy [47, 48]. The detection rate of HPV in women with transplanted organs is significantly higher than in the general population, accounting for 65% compared to 38% in the general population of women [49]. Almost all cervical cancers, more than 50% of vulvar cancers, 70% of vaginal cancers, and 90% of anal cancers are associated with HPV of high oncogenic risk [50-52]. It has been found that female kidney transplant recipients have a 14-fold increased risk of developing cervical cancer, up to a 50-fold increased risk of developing vulvar cancer, and up to a 100-fold increased risk of anal cancer when HPV is detected in them [53, 54].

The adverse effects of immunosuppression are not limited to only an increased risk of infection with oncogenic viruses. Immunosuppression can contribute to carcinogenesis by suppressing the mechanisms involved in the immunological control over oncogenesis or by direct DNA damage [26].

There are a number of studies devoted to the relationship of cancer development and various immunosuppressive agents, dosage regimens and duration of immunosuppressive therapy [6, 55, 56]. The impact of each drug on cancer risk remains controversial, and the increased risk of cancer may be mediated by the overall burden of immunosuppression to a greater extent than by the agent itself [6]. According to X. Wang et al. [57], the oncogenic risk increases in proportion to the cumulative dose of immunosuppressive drugs. However, there is evidence that some immunosuppressive drugs may have a pro-oncogenic effect. In particular, cyclosporine A can inhibit the repair mechanisms of damaged DNA, as

well as azathioprine and prednisolone (although to a lesser extent). In addition, some immunosuppressants can activate neoangiogenesis and the ability of cells to invade, which also increases the risk of cancer [42].

Many immunosuppression regimens involve the induction therapy using antibodies against T lymphocytes. Some studies have shown that such induction of immunosuppression is associated with an increased risk of developing malignant diseases [17, 58]. The use of thymoglobulin in the induction immunosuppression increases the risk of developing lymphoproliferative diseases after kidney transplantation compared to agents acting on the alpha chains of the interleukin-2 receptor (IL-2Rα) or in the absence of induction therapy [12, 17]. There is also evidence that the overall increase in the incidence of epithelial malignancies, in particular, melanoma, bladder cancer, colorectal cancer, oral and pharyngeal cancer, kidney and lung cancer, that are currently treated with specific antibodies, is associated with ongoing immunosuppression, leading to immune survival of tumor cells [59]. At the same time, according to R.C. Graham et al. [60], current induction immunosuppression does not increase the risk of developing malignant diseases in patients after liver transplantation.

If a number of immunosuppressants have a pro-oncogenic effect, then other up-to-date immunosuppressive agents can have an anti-oncogenic effect. Such drugs include inhibitors of the mTOR signaling pathway receptor (sirolimus, everolimus), for which a number of studies have shown a decrease in the incidence of de novo malignancies, as well as the mortality of recipients from all causes, after organ transplantation compared to other immunosuppressants, in particular cyclosporine and mycophenolates [61-63]. The anti-oncogenic effect of mTOR inhibitors is related to the fact that the signaling pathway is not only involved in suppressing the alloimmune response by blocking T-lymphocyte signals

via IL-2, but is also a critical part of the chain that is activated in tumor cells [64].

In addition to the fact that mTOR inhibitors reduce the risk of cancer after organ transplantation, they have a positive effect in recipients with already developed malignant diseases. Therefore, a number of authors recommend that when cancer is detected in recipients with transplanted organs, the immunosuppression regimen should be changed with switching to mTOR inhibitors, but recommendations for modifying immunosuppressive therapy regimens have not yet been developed [59, 65, 66]. It should be taken into account that mTOR inhibitors (sirolimus, everolimus) have an effect mainly in virus-associated forms of cancer. Meantime, since they have a cytostatic rather than cytotoxic effect, their effect consists more in stabilizing the tumor process rather than in tumor regression [67].

All these data suggest that, although there are some results on the effect of the immunosuppression type on cancer development after organ transplantation, there is no clear evidence that the strategy of immunosuppressive treatment affects the risk of cancer pathology. This entails a difficult decision for transplantologists when choosing the optimal immunosuppressive therapy regimen, especially in patients with a high risk of developing malignant diseases.

Other factors that affect the increased risk of cancer in patients with transplanted organs include so-called unmodifiable factors, in particular, age, gender, type of underlying disease, and sun exposure.

According to E.A. Engels et al. [15, 22], the age and male gender are recognized risk factors associated with the development of malignant neoplasms after organ transplantation, although according to other authors, gender differences do not affect the degree of cancer risk [7, 68], and a number of authors have identified a greater susceptibility to cancer

in women-recipients compared to men [28, 33, 69]. At the same time, many authors note that the statistical data on the detection of malignant diseases in female recipients of solid organs is significantly influenced by the development of tumor pathology of the female reproductive system (cancer of the vagina, vulva, uterus, and cervix), including due to HPV infection [50, 55, 70, 71]. At the same time, according to other authors, women are at a higher risk of developing cancer pathology of various location after organ transplantation [25, 72].

The risk of developing cancer after a lung transplant increases with the age of recipients over 55 years (overall risk factor 2.89, being 2.8 in men, and 2.94 in heavy smokers (for over 20 years)) [17]. In lung transplantation, in addition to the impact of the elderly age of the donor and recipient, the risk of developing malignant neoplasms increases with bilateral lung transplantation [15], mainly due to the more frequent development of NHL. In patients undergoing lung transplantation for chronic obstructive pulmonary disease, tobacco use is a risk factor for developing lung, liver, and colon cancer [73, 74]. Meanwhile, according to M. Ekstrom et al. [23], in these patients, univariant statistical analysis showed that only the recipient's age was a significant factor, but in multivariate analysis, none of such factors as the donor and recipient age, gender, body mass index, duration of tobacco smoking, type of transplantation, degree of the donor and recipient histocompatibility, immunosuppression scheme, or waiting time for the transplantation was a significant prognostic factor.

With kidney transplantation, population-based studies have shown that younger recipients of both genders are at a higher risk of developing cancer [69], which is partly due to the rarity of malignancies in the general population at a younger age [25, 75]. There are data on other risk factors for this category of recipients, in particular, the type of underlying

disease (polycystic kidney disease [76], the type of donor (post-mortem donor and expanded criteria donor, including unintentional transfer of tumor cells from the donor are factors of a higher risk of cancer) [77], the duration of dialysis therapy, acute rejection, race [78].

The risk of developing de novo liver cancer in liver transplant recipients is higher in patients with alcoholic liver cirrhosis, sclerosing cholangitis, and viral hepatitis C. Liver transplant recipients have an increased risk of developing lymphoproliferative diseases, skin, lung, and colon cancers, but not the breast cancer.

Thus, data on the significance of unmodifiable factors that increase the risk of developing malignant neoplasms after organ transplantation, such as demographic data, lifestyle factors, and causes of the development of the chronic disease, are very contradictory and do not yet allow us to draw definite conclusions.

Opportunities for screening recipients with transplanted organs for cancer development

Due to the increased risk of cancer development in patients with transplanted organs, the task of active screening of these patients for early detection of cancer pathology is urgent. Further development of approaches to the prevention and screening for early diagnosis of malignancies can play an important role in reducing the burden of malignancies in recipients with transplanted organs. The prevention of morbidity and mortality associated with malignant neoplasms after transplantation should be considered as the main end point in solid organ transplantation programs [38, 72]. The clinical guidelines reflect the regular screening of malignant diseases for all patients with transplanted organs, and are based on the principles of early detection in the general population [31]. There is little data available on the implementation of

routine screening, the management of risk factors and interventional therapy for organ transplant recipients.

There are certain guidelines for early detection of female reproductive organ malignancies, which have been developed for post-transplant patients receiving immunosuppressive therapy, but the screening protocol is based on the protocol developed for patients infected with HIV. There are also screening guidelines for skin cancer in patients with a transplanted kidney [79]. In general, we can conclude that the issue of screening patients with transplanted organs for early detection of malignant diseases is still inadequately developed. There are certain recommendations for early diagnosis of virus-associated cervical cancer, as well as for skin cancer, but no recommendations have been developed for other locations of tumor pathology.

Conclusion

The analysis of the literature convincingly demonstrates an urgent problem of the development of malignant diseases in patients after transplantation and its impact on the long-term life prognosis. With an increase in the life expectancy of these patients, the risk of developing cancer increases. The main factor that increases the risk of developing a malignant pathology is the need for lifelong immunosuppressive therapy; a number of other factors (age, gender, type of underlying disease, oncogenic viruses) also have a significant impact. Early detection of the risk of malignant diseases is of key importance, as the efficacy of polychemotherapy in patients with transplanted organs is lower than in the general population. In order to improve the treatment efficacy for these patients, it is important to take into account the pro-oncogenic and anti-oncogenic effects of various immunosuppressive drugs, and to make appropriate adjustments to the immunosuppressive therapy scheme;

however, but generally accepted recommendations on this issue have not yet been adopted.

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