https://doi.org/10.23873/2074-0506-2020-12-3-199-212


# Extrahepatic malignancies in a liver transplant recipient from a living related donor

I.Yu. Kolyshev*[1], S.E. Voskanyan[1], M.V. Shabalin[1], A.I. Artemyev[1], V.S. Rudakov[1], A.P. Maltseva[1], A.N. Bashkov[1], V.E. Syutkin[2], K.K. Gubarev[1], D.S. Svetlakova[1], M.V. Popov[1], A.I. Sushkov[1], Z.A. Sadykhov[1]

*[1]State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA), 23 Marshal Novikov Str., Moscow 123098 Russia;*

*[2] N.V. Sklifosovsky Research Institute for Emergency Medicine, 3 Bolshaya Sukharevskaya Sq., Moscow 129090 Russia*

*Correspondence to: Ilya Yu. Kolyshev, Cand. Med. Sci., Head of Surgical Department № 1 Center for New Surgical Technologies; Surgery and Transplantology Center Surgeon, Burnasyan Federal Medical Biophysical Center,
e-mail: diffdiagnoz@mail.ru

**Conflict of interests** Authors declare no conflict of interest

**Financing** The study was performed without external funding

**Kolyshev IYu, Voskanyan SE, Shabalin MV, Artemyev AI, Rudakov VS, Maltseva AP, et al. Extrahepatic malignancies in a liver transplant recipient from a living related donor. *Transplantologiya. The Russian Journal of Transplantation*. 2020;12(3):199–212. (In Russ.). https://doi.org/10.23873/2074-0506-2020-12-3-199-212**

***Background.*** *Cancer occurring in recipients of living donor liver transplantation may be characterized by a progressive course requiring an immediate specialized treatment initiation and adjustment of the immunosuppression regimen.*

***Aim.*** *To specify the malignancy development mechanisms and risk factors in the recipients of living donor liver transplantation.*

***Material and methods:*** *275 living donor liver transplantations were made in Burnasyan Federal Medical Biophysical Center of FMBA from 2010 to 2020. Forty two (15.27 %) patients underwent surgery for hepatocellular carcinoma. The median time to the onset of malignancy development was estimated. The incidence of malignancy in general population and in recipients of living donor liver transplantation was compared.*

***Results.*** *The development of neoplastic lesion was registered in 9 cases (3.27%). Malignances were detected in 8 cases (2.90%). Median time to the onset of malignancy development was 48 months. 1, 3, and 5 year overall survival rates were 97%, 96%, 94%;respectively; 1, 3, and 5 year survival rates after transplantation for hepatocellular cancer were 97%, 91%, 91% respectively. Survival rate of patients with De-novo malignancy was 90%.*

***Conclusion.*** *Recipients of living donor liver transplantation have an increased risk of malignancy development that requires a close long-term follow-up.*

**Keywords:** oncology, liver transplantation, living donor, screening, immunosuppression

CMV, cytomegalovirus

CNS, central nervous system

CT, computed tomography

EBV, Epstein-Barr virus

HCC, hepatocellular carcinoma

LT, liver transplantation

PTLPD, post-transplant lymphoproliferative disease
WHO, World Health Organization

## Introduction

In the structure of the population, the patients undergoing a solid organ transplantation represent a specific risk group for the development of oncological diseases. The use of immunosuppressive therapy, especially a multi-component therapy, more than 10 times increases the risk of developing malignant neoplasms and recurrences of oncological diseases, promotes the activation of viruses with potentially oncogenic properties. In patients undergoing liver transplantation (LT), the incidence of malignant neoplasms ranges from 2 to 16%. Meantime, the highest risk of oncology diseases is observed at a year after transplantation, and reaches its maximum after 6–10 years and decreases 16 years after transplantation [1].

At the moment, the following groups of post-transplant malignant neoplasms are usually distinguished in the liver transplant recipients [2]:

1. Donor-related neoplasms:

1a. Cancer transmission: tumours arising after transplantation from a donor with a history of cancer;

1b. Derived inheritance: tumours arising after transplantation from a donor without a previous history of diagnosed cancer

2. Recurrent neoplasms in the recipient: the recurrence of tumours for which LT was performed.

3. De-novo neoplasms in a recipient:

3a. Neoplasms associated with the donor-derived transmission of viral material to a recipient;

3b. Neoplasms that have arisen as a response to the administered immunosuppressive therapy (showing regression with altered immunosuppression).

**Tumours of the first type**

Oncological screening of a potential living related donor or a deceased donor in case of posthumous donation is the most important task at the stages of preparing a patient for transplantation.

Studies by H.M. Kauffman et al. (2002), S.A. Birkeland and H.H. Storm (2002) showed that the incidence of the first type cancer in patients after organ transplantation makes 0.01%, while cancer is detected in liver donors before the donation stage in 3% of cases only [3, 4].

In case of a donor-derived tumour transmission, the cancer might be found in an organ donor both before and after transplantation. At the stage of development of posthumous donor liver transplantation and to our days, one of the most frequent indications to donation has been the brain death resulted from the development of acute cerebrovascular accident. The cerebrovascular accident, even when diagnostic radiology techniques are available, in some cases can mask a hemorrhage in a primary or secondary neoplasm of the brain, that may be hardly differentiated from extensive hemorrhagic stroke and subarachnoid hemorrhages. Recommendations from UNOS, the World Health Organization (WHO), as well as a number of investigators (Buell et al., Kalble et al.) do not prohibit the use of organs from donors with a history of the central nervous system (CNS) malignancies of 1–2 st. dysplasia according to WHO, and a number of others, based on the risk of cancer cell transmissions of up to 0.1%. Using the organs from donors with st. 3-4 multiforme glioblastoma, according to WHO, is possible only in case of

urgent indications to transplantation and a completely impossible obtaining of a more suitable organ [5].

On the part of CNS-non-associated tumours, the most often transmissions observed have been those of renal cell carcinoma (50–65%), choriocarcinoma (10–93%) and melanoma (7–17%). According to UNOS/OPTN, the transmission of tumours of the lung (41%), breast (29%), prostate (29%) and colon (19%) was observed more often than others [6-8].

Meantime, polymorphic glioblastoma, melanoma, choriocarcinoma and lung cancer are absolute contraindications for liver donation, while colorectal cancer and breast cancer are relative ones and the transplantation can be performed only if the donor meets the UNOS criteria. In general, with regard to the donor-related cancer transmission risk, the potential donors have been divided into groups of a low risk under 10%, and a high risk of over 10% [8-11].

A donor-derived tumour development from donors without a previous history of malignant disease signs is infrequent. Cases of donor-autopsy detected tumours that later developed in the recipient have been described. No such cases have been found in the patients undergoing living related donor LT. Nevertheless, this issue is very relevant in case of using organs from posthumous donation when the recipient's evaluation and his/her medical record analysis may be insufficiently complete, and therefore comprehensive oncological screening in case of intravital donation is mandatory.

**Tumours of the second type**

Tumour liver diseases are indications for transplantation that is often the only definitive treatment, for example, for hepatocellular

carcinoma (HCC) of the liver in the absence of extrahepatic invasion signs and if the accepted criteria permitting transplantation for HCC are met (Milan, Metroticket, Up-to-7, San Francisco, etc.) [12]. A disease-free 5-year survival, if Milan's criteria are met, makes 50–70%. In some countries of Europe, Asia, and in the United States, liver transplantation is allowed for other types of primary malignancy, such as epithelioid hemendothelioma and cholangiocellular cancer.

LT can also be performed in case of liver metastases from neuroendocrine malignant tumours and colorectal cancer with achieving 5-year disease-free survival rates of 63% and 60%, respectively, if the criteria for a good prognosis have been met. These groups of patients have an increased risk of developing recurrent type 2 tumours. In the Russian Federation, LT operations are not performed for any types of malignant tumours other than HCC. According to the EASL guidelines, transplantation for primary and secondary liver malignancies can be performed to a carefully selected cohort of patients in specialized centres experienced in performing operations on such indications. A history of cured neoplasms is not an absolute contraindication to LT. A 5-year interval between the radical cancer treatment and LT is considered appropriate, depending on the type and stage of the cancer cured.

***Hepatocellular carcinoma***

Among all tumour diseases, LT is most often performed for liver HCC. The recurrence rate of the disease ranges from 10 to 60% and depends on the factors such as: the compliance with the accepted patient selection criteria (MILAN, San Francisco, et al.), the blood level of alpha-fetoprotein and d-carboxyprothrombin (PIVKA-II) before surgery, the tumour differentiation grade, a history of down-stage and/or bridge

therapy, surgical interventions, as well as the selected immunosuppression scheme. If the transplantation has been performed within the Milan criteria, the recurrence rate is 10-15%.

In order to assess the risk of recurrence, a number of assessment tools have been proposed, for example, the RETREAT score, which sensitivity and specificity need further validation [13].

***Hemangioendothelioma***

Hemangioendothelioma is a rare, slow-growing, invasive neoplasm of the liver with a variable prognosis, often with a multicentric growth pattern. The tumour tends to grow along the walls of blood vessels with their invasion and lumen obliteration, which leads to the liver fibrosis development. The most common treatment for this neoplasm is liver resection, however, in case of a large-size tumour, LT may be considered. A disease-free 5-year survival is 38–93%. Factors of an unfavourable prognosis after LT include micro- and macrovascular invasion confirmed by the histological examination, the number of tumour nodes exceeding 10, and their sizes [14-16].

***Cholangiocarcinoma***

In a number of expert centres, LT is performed both for the Klatskin tumour and for the cancer of intrahepatic bile ducts not exceeding 2 cm in diameter. In case of transplantation for Klatskin tumour performed in combination with the Mayo clinic's protocol proposed in 2001 (neoadjuvant chemotherapy with 5-fluorouracil and radiation therapy), a 5-year disease-free survival rate makes 33–63%. According to Rea et al., a 5-year survival rate after LT compares favourably to that after liver resection: 82% versus 21%. Currently, a

prospective controlled trial TRANSPHILL is being conducted to clarify the role of liver transplantation for Klatskin tumour [17–18].

The main method of treatment for cholangiocellular carcinoma of the intrahepatic bile ducts has been and remains liver resection. However, in 2016, G. Sapisochin et al. conducted a retrospective analysis of patient treatment for intrahepatic cholangiocellular carcinoma by means of LT; they found that in case of mononodular lesions up to 2 cm in size, a 5-year survival rate was 65% with a recurrence risk of 18% [19].

***Metastatic liver disease in neuroendocrine cancer***

Liver metastases from neuroendocrine cancer have been an accepted indication to LT due to the tumour biological characteristics that determine its slow growth and less aggressive course of the disease in general. A relapse-free survival in patients after the primary tumour resection, in whom all other treatments have been exhausted, reaches 69 –84%, while non-surgical treatment of such patients provides a survival rate 20 –34%. Predictors of poor prognosis include non-carcinoid tumour forms, primary focus in the pancreas, a high KI67 index, the involvement of over 50% of the liver, low tumour tissue differentiation, recipient's age over 50 years, and the presence of tumour-associated symptoms [20–23].

***Metastatic liver invasion from colorectal cancer***

Surgical management of liver metastases from colorectal cancer is the cornerstone of achieving the best long-term survival. Metastatic liver invasion can occur in 50% of colorectal cancer cases. The parenchyma-preserving method of performing liver surgery, ALPPS operation, is an innovative method of managing patients with colorectal cancer, which allows performing surgical interventions with acceptable results even in a

small residual liver volume or bilobar multifocal lesion. Nevertheless, LT can be performed in a strictly selected group of patients. These patient selection criteria proposed by the SECA-I and -II studies conducted in Norway include tumour size smaller than 5.5 cm, time from the date of diagnosis of at least 2 years, a blood level of cancer embryonic antigen lower 80 μg/L, and a decrease in tumour size in response to chemotherapy, which allows achieving 1-, 3- and 5-year survival rates of 95%, 68%, and 65%, respectively, while the 5-year survival rate of patients with unresectable liver metastases without LT varies from 33 to 50%. Nevertheless, due to the small sample size of patients, the benefits of LT in colorectal metastases require further investigation, being the subject of the TRANSMET, SECA-III, LIVER-T(W)O-HEAL studies [24, 25].

**Tumours of the third type**

De-novo tumours are the most common cancer pathology in liver transplant recipients and include those tumours that have developed from recipient's body cells during immunosuppressive therapy. According to various authors, de-novo malignant tumours develop in liver transplant recipients at a risk of 2–11 times higher than that in general population [1]. The most common neoplasms are presented in the Table.

**Table. Risks of developing malignant neoplasms de novo in different localizations in patients who underwent liver transplantation**

| Type | Risk of cancer compared to the general population (times) |
|---|---|
| All kinds of tumors | 2–3 |
| Kaposi's sarcoma | 37–144 |

| | |
|---|---|
| Non-melanoma skin cancer | 6–38 |
| Lip cancer | 20 |
| Lymphoma | 7–13 |
| Cancer of the oropharynx and larynx | 10–15 |
| Anal canal cancer | 3–10 |
| Kidney cancer | 2–4 |
| Colorectal cancer in primary sclerosing cholangitis and primary biliary cirrhosis | 3 |
| Melanoma | 2 |
| Lung cancer | 2 |
| Colorectal cancer | Non-increased |

Significantly more often, these neoplasms have been reported in patients who underwent LT for liver HCC, non-alcoholic fatty disease, and alcoholic cirrhosis. Also, the risk of developing colorectal tumours is higher in patients with primary sclerosing cholangitis and inflammatory bowel disease. Smoking makes an additional negative contribution to the development of tumours of the upper respiratory tract and oropharynx. Tumours of the lung, prostate, liver, and colorectal cancer rank first among the tumours of solid organs. Most often, in addition to non-melanoma skin cancer and other soft tissue neoplasms, post-transplant lymphoproliferative diseases (PTLPDs) can be diagnosed, among which there are the following, according to A.M.Kovrigina [26]:

- non-destructive early lesions: plasmacytic hyperplasia, mononucleosis-like hyperplasia, etc.

- polymorphic cell PTLPD;

- monomorphic cell PTLPD, according to the list of B- and T-cell lymphomas, which resemble: diffuse large B-cell lymphoma, Burkitt's lymphoma, plasmablastic lymphoma, plasmacytoma, multiple myeloma,

peripheral T-cell lymphoma, unspecified lymphoma, classical Hodgkin's lymphoma, hepatosplenic T-cell lymphoma, extranodal NK/T-cell nasal lymphoma; Epstein-Barr virus positive (EBV+) extranodal marginal zone lymphomas (MALT lymphoma).

Lymphoproliferative diseases have a clear relationship with ongoing immunosuppression. The immunosuppression-associated slow-down of T-cell immunity activation leads to the proliferation of herpes viruses, including the EBV that causes PTLPD; their treatment tactics differs somewhat from that in primary lymphomas.

**Immunosuppression and development of post-transplant oncological diseases**

Thomas Starzl, one of the founders of modern transplantation, predicted that using the drugs that suppress immunity would inevitably lead to an increased number of neoplastic diseases. And in fact, each of the immunosuppression regimens to some or another extent increases the incidence of post-transplant oncological diseases. The medicinal drugs most commonly used after related donor LT are calcineurin inhibitors and mTORi, mycophenolic acid agents, and steroid hormones. As for immunosuppressive therapy regimens after living related donor LT, it has been shown that increasing the dose of calcineurin inhibitors - tacrolimus and cyclosporine, and to some extent steroid hormones, is an independent risk factor for HCC recurrence, while mTOR inhibitors reduce this risk. At the same time, cyclosporine has a more pronounced pro-oncogenic property. Calcineurin inhibitors activate tumour growth by affecting the production of interleukin-2, tumour necrosis factor-alpha, transforming growth factor b1, decreasing the cellular apoptosis level and stimulating the synthesis of VEGF in the tumour. Among all immunosuppressants,

rapamycin derivatives have the most pronounced anti-tumour effects, which are expressed by switching off the pro-angiogenic mechanisms activated by mTOR-protein kinase. Mycophenolic acid preparations in experimental studies by Tressler et al. in vitro have shown the presence of anti-tumour properties for models of T-lymphoblastic leukemia, pancreatic cancer, non-small-cell lung carcinoma, colon cancer, etc. Meanwhile, there were also shown the pro-oncogenic properties of these drugs due to a decreased number of homophilic adhesion receptors on neuroblastoma cells, which was associated with increased metastatic activity and tumour invasion [27-28]. Nevertheless, a number of studies have indicated a decreased incidence of de-novo tumours when using the drugs of this group [29]. The most common combination is tacrolimus with steroid hormones, the latter being gradually withdrawn.

**The purpose of the study** was to clarify the developmental patterns, risk factors for oncological pathology of the 1st, 2nd, and 3rd types in patients who underwent living related donor LT.

**The study objectives:**

1. To compare the incidence of oncological diseases in general population and in patients undergoing living related donor LT.

2. To study the timing of the development of cancer or obligate /optional precancers, the relapse-free survival period from the anti-cancer treatment initiation, the relative risks of cancer development compared to those in general population, and the oncology disease-related mortality rates.

## Material and methods

In the period from 2009 to 2020, 275 living related donor LTs were performed at the State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA). We analyzed the incidence of developed malignant neoplasms of the 1st, 2nd and 3rd types, the immunosuppressive therapy regimens, and the screening measures taken. Statistical data were calculated using the Mann–Whitney U test and the Kaplan–Meier methodology.

## Results

### *Cases 1-3*

In 3 cases, the patients were diagnosed with post-transplant lymphoproliferative disease. The living diagnosis was morphologically confirmed in only one case. The patient was diagnosed with grade 4 lymphoma, its B-cell immune subvariant, not classifiable with intermediate signs of diffuse macrocellular carcinoma and Burkitt's lymphoma, with the lesions in the greater omentum, peritoneum at 3 years after LT. The disease onset was characterized by the appearance of an ovary lesion, regarded as a granulosa cell tumour, which required an ovariectomy. Histological examination confirmed the lymphoma presence. The patient received the treatment administered according to the ProMACE CytaBom scheme. In the postcytostatic therapy period, clinical signs of an acute renal failure developed, while the blood level of tacrolimus was 12.9 ng/mL, which required the drug daily dose reduction to the minimum. After blood nitrogenous base levels had been normalized, the cytostatic therapy was continued, and the dose of tacrolimus was

increased until the blood level of tacrolimus of 6 ng/mL was reached. Later, in the postcytostatic period, pulmonary aspergillosis developed, which required the administration of voriconazole. The tacrolimus dose remained the same. The fungal infection of the lungs was cured, which was confirmed both clinically and instrumentally. Later on, 5 more courses of cytostatic therapy were given. Oncological disease-free survival was 9 years.

In the second patient, the computed tomography (CT) showed signs of lymphoproliferative disease with foci in the lungs and femur, and a lymphoproliferative disease was suspected. No signs of viral infection (cytomegalovirus [CMV] or EBV) were found. The patient's follow-up for 8 years has shown no signs of tumour progression in this period. The patient does not receive any special treatment for lymphoproliferative disease.

The diagnosis of lymphoproliferative disease in the 3rd patient was made at autopsy 6 years after LT. The patient's condition deteriorated into the graft dysfunction with severe chronic renal failure of grade 3-4 with the associated generalized serologically confirmed CMV and EBV infection that developed 6 years after LT. LT had been performed for cryptogenic liver cirrhosis. At the preoperative and early postoperative stages, there were no signs of the viral infection development; the patient received the "preemptive" antiviral therapy. Autopsy revealed a post-transplant lymphoproliferative lesion, monomorphic type.

Thus, PTLPD was identified in 3 patients, which made 30% of the total number of patients with posttransplant cancer. In all 3 cases, PTLPD was the third type of oncological pathology in post-transplant patients. In 2 cases, PTLPD was undoubtedly related to the activation of viral infection after transplantation.

***Cases 4-5***

Skin neoplasms were found in 2 patients. In one case, a large keratopapilloma was revealed at 4 years after transplantation, and in the other case, squamous cell skin carcinoma TisN0M0 was revealed at 2 years after transplantation, which required a surgical treatment without an adjustment of immunosuppressive therapy. No disease relapses were observed within 8 and 9 years of follow-up, respectively.

***Case 6***

In one patient, 6 months after LT, the control examination revealed cancer of the right half of the colon. Histological examination confirmed the presence of moderately differentiated adenocarcinoma T3N0M0. The patient underwent surgery of right-sided hemicolectomy, D2 lymphadenectomy. A patient who had previously received tacrolimus was switched to everolimus. No chemotherapy was given. Within 4 years after the surgery, no signs of disease progression were noted.

***Case 7***

One patient underwent surgical treatment in the extent of gastrectomy and D2 lymphadenectomy for poorly differentiated gastric adenocarcinoma T2N0M0. The neoplasm was identified at a control follow-up examination 6 years after LT. Monotherapy with tacrolimus was used as the main immunosuppressive agent. No tumour recurrence was seen within 3 years.

***Case 8***

An interesting case was a patient who underwent LT for liver hemangioendothelioma histologically confirmed at the preoperative stage. At 8 months after surgery, the thoraco-abdominal CT scanning revealed suspicious foci in the graft and lungs, which were regarded as fungal infection, for which the patient received the appropriate treatment. Also, there were enlarged lymph nodes in the neck and isolated nodules in the thyroid gland. Fine-needle biopsy revealed signs of papillary thyroid cancer. Scintigraphy showed no other tumour foci in the body. The patient underwent thyroidectomy with central lymphadenectomy. Repeated histological and immunohistochemical examinations of the removed tissue preparation revealed malignant grade 2 liver hemangiosarcoma T3N2M1 with metastases to the thyroid gland and lymph nodes of the neck. The patient received the therapy with sorafenib 800 mg per day. The patient died 2 months after the treatment start. In that case, it was a type 2 neoplasm.

***Case 9***

In 2015, the patient underwent living related donor LT for toxic liver cirrhosis. In 2017, TisN0M0 skin melanoma of the shin (Clark level I) was diagnosed, for which surgery was performed without discontinuation of immunosuppressive therapy. Later on, the patient visited the clinic for a control follow-up examination once every six months. Esophagogastroduodenoscopy performed in 2019 revealed no pathology, while in January 2020, squamous cell carcinoma of the middle third of the esophagus was identified. The patient underwent the surgical treatment in the extent of esophageal resection. The postoperative

histological conclusion was squamous cell carcinoma of the esophagus T1bN0M0. Both neoplasms in the patient were type 3 tumours.

Forty two of 275 patients underwent living related donor LT for HCC, which made 15.27% (Fig. 1).

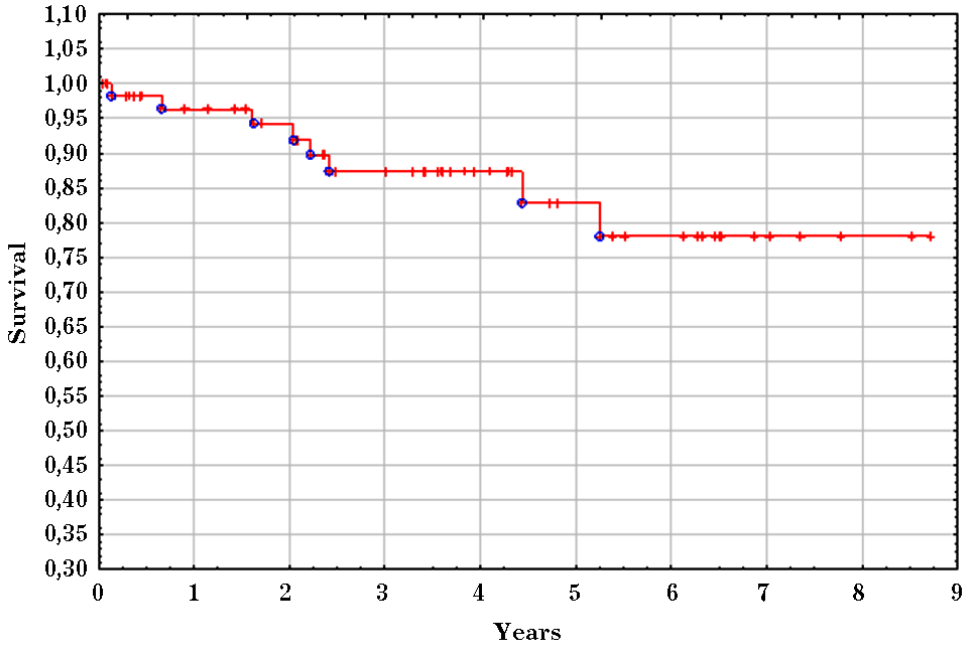


**Fig. 1. Survival (years) of patients after a living related donor liver transplantation for hepatocellular carcinoma**

HCC relapses were identified in 2 patients (4.76%). The graph in Fig. 2 shows 1-, 3-, and 5-year disease-free survival rates that made 97%, 91%, and 91%, respectively.

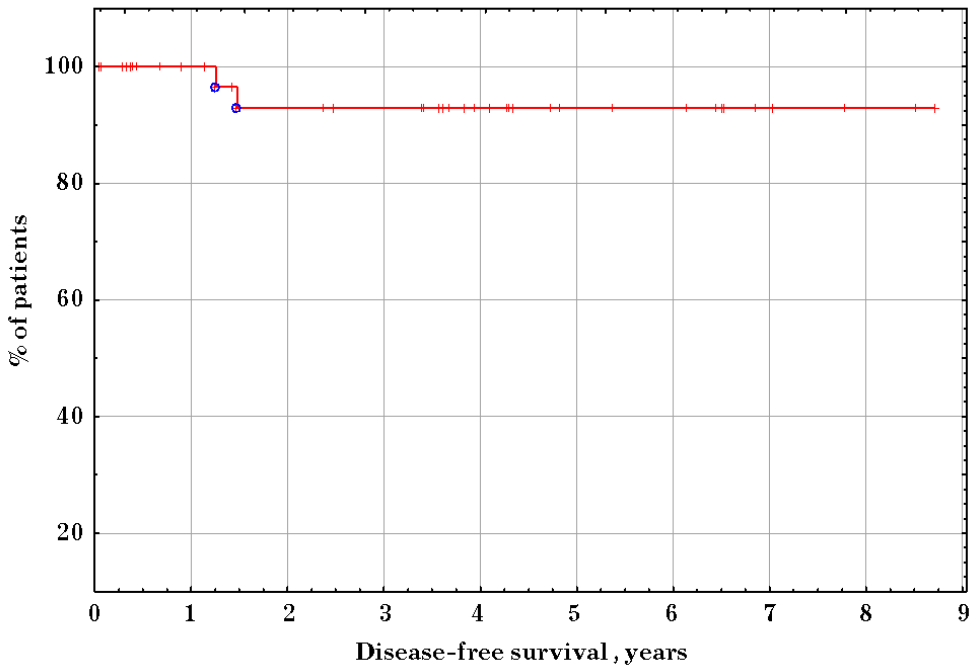


**Fig. 2. Disease-free survival (years) of patients after a living related donor liver transplantation for hepatocellular carcinoma**

When analyzing 275 living related-donor LTs performed from 2010 to 2020, we found that 1-, 3-, and 5-year overall survivals of patients after transplantation were 97%, 96%, and 94%, respectively (Fig. 3).

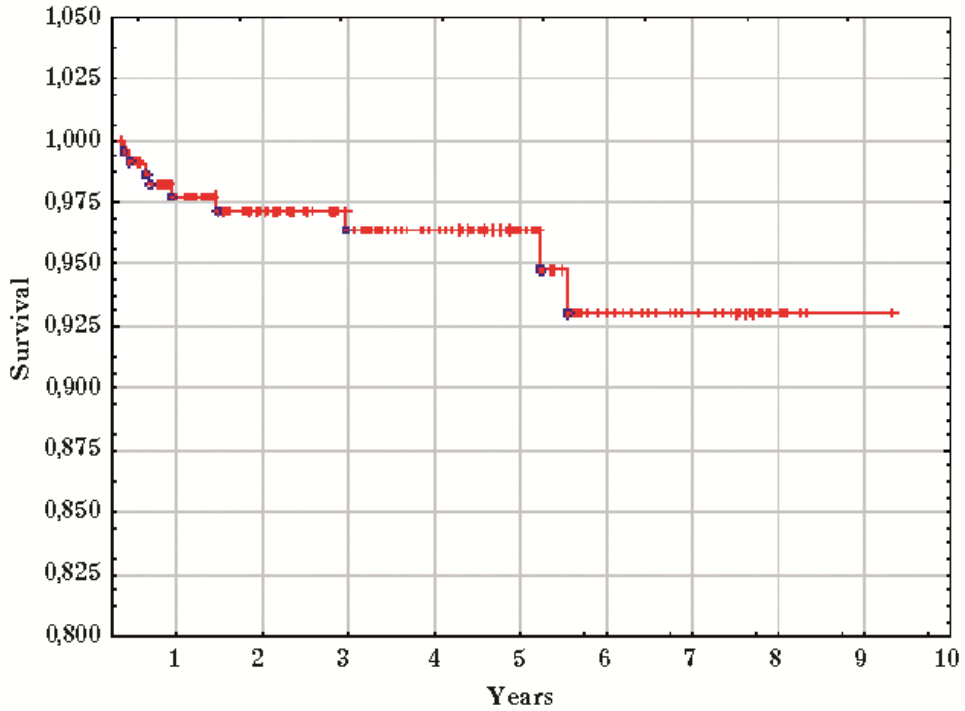


**Fig. 3. Survival (years) of patients after a living related donor liver transplantation**

A 1-, 3-, and 5-year survival in patients with type 3 oncological pathology developed after LT, was 90% (Fig. 4).

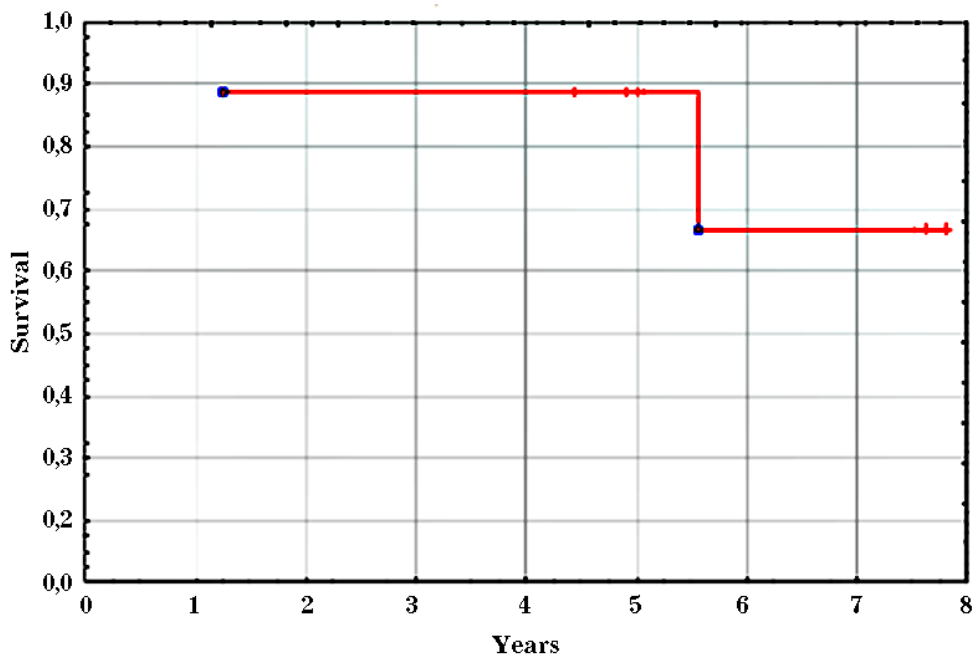


**Fig. 4. Survival (years) of patients after a living related donor liver transplantation who developed type 3 cancer**

The overall incidence of type 2–3 neoplasms was 3.27% (9 cases). Proliferative diseases (type 3 tumours) were registered in 1.09% of patients (3 cases), while actually malignant neoplasms developed in 2.9% of cases (8 cases). This value is comparable with world statistics on this issue (12% [Haagsma et al.]; 5.7% [Jain et al]; 21% [Watt et al.]). Mortality from malignant neoplasms was 0.72%. The median period of neoplasm development after transplantation was 48 months. The patient survival rates within 5 years after transplantation between the cases with neoplasms of the 2nd and 3rd types revealed after surgery and the absence of oncological pathology did not differ.

The patient survival rates within 5 years after transplantation did not differ between the cases of the 2nd and 3rd type neoplasms revealed after surgery and the cases of no oncological disease.

**Discussion**

In most studies on the post-LT cancer development presented in the Medline, Science Direct databases, tacrolimus in combination with steroid hormones were used as the main immunosuppression therapy scheme.

In our sample, all patients with cancer received baseline therapy with tacrolimus and steroid hormones; one patient was switched to everolimus later. In the total group of patients who underwent LT, 90.9% also received either tacrolimus and steroid hormone therapy or tacrolimus monotherapy; 9.01% of patients were treated with everolimus. Thus, there is no clear relationship between immunosuppression and the development of oncological processes. The facts of concurrently diagnosed EBV + PTLPD, as well as the early development of the

ascending colon cancer, suggest a negative impact of immunosuppression in terms of the development of tumour diseases in liver recipients. In this regard, screening examinations aimed both at identifying graft pathology, and at early detection of oncological diseases, optional and obligate precancers become fundamental issues for patients undergoing living related-donor LT.

The prognosis for the treatment of oncological diseases in patients on immunosuppression is significantly worse than in the general patient population both in terms of graft survival, and the oncological part per se. For example, a 5-year survival in patients with colorectal cancer can reach 75%, while after transplantation the survival of such patients does not exceed 42% [30]. Both the recipient and the donor should undergo a comprehensive preoperative evaluation. In addition to the recommended and standard designated examinations, including diagnostic radiology techniques, flexible endoscopy, examinations by a urologist and a gynecologist, it is important to assess the presence of anti-EBV and anti-CMV antibodies, which transmission can become fatal for the recipient. In the postoperative period, the strategy of preemptive therapy for herpesvirus infections seems to be the most reasonable in terms of preventing the lymphoma development. A regular annual examination should mandatory include gastroduodenoscopy, colonoscopy or capsule endoscopy, abdominal ultrasonography and abdominal CT scanning aimed at detecting tumours of solid organs and lymphadenopathy signs, as well as the assays for antibody titters to herpes viruses, for the blood concentration of tumour markers, and the examinations by different medical specialists at least once a year.

## Conclusions

The analysis performed has shown that benign and malignant neoplasms in patients after living related donor transplantation develop more often than in the general population. Oncological diseases in liver transplant recipients significantly affect the mortality rate after transplantation. Lymphoproliferative diseases predominate by detection rate. Oncological screening of patients before and after transplantation is the cornerstone of cancer prevention and should include the full range of available tests.

1. A living related-donor liver transplantation either for hepatocellular cancer or for other reasons is a risk factor for the development of oncological pathology of the 2nd and 3rd types.

2. Liver recipients should undergo comprehensive screening both for the assessment of the graft function, and for the early diagnosis of a post-transplant tumour disease.

## References

1. Zhou J, Hu Z, Zhang Q, Li Z, Xiang J, Yan S, et al. Spectrum of de novo cancers and predictors in liver transplantation: analysis of the scientific registry of transplant recipients database. *PLoS One.* 2018;11(5):e0155179. PMID: 27171501 https://doi.org/10.1371/journal.pone.0155179

2. Ganghi MJ, Strong DM. Donor derived malignancy following transplantation: a review. *Cell Tissue Bank.* 2007;8(4):267–286. PMID: 17440834 https://doi.org/0.1007/s10561-007-9036-1

3. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target of rapamycin inhibitors is

associated with a reduced incidence of de novo malignancies. *Transplantation.* 2005;80(7):883–889. PMID: 16249734 https://doi.org/10.1097/01.tp.0000184006.43152.8d

4. Birkeland SA, Storm HH, Lamm LU, Barlow L, Blohme I, Forsberg B. Cancer risk after renal transplantation in the Nordic countries. *Int J Cancer.* 1995;60(2):183–189. PMID: 7829213 https://doi.org/10.1002/ijc.2910600209

5. Braun-Parvez L, Charlin E, Caillard S, Ducloux D, Wolf P, Rolle F, et al. Gestational choriocarcinoma transmission following multiorgandonation. *Am J Transplant.* 2010;10(11):2541-2546. PMID: 20977645 https://doi.org/10.1111/j.1600-6143.2010.03275.x

6. Knoop C, Jacobovitz D, Antoine M, de Francquen P, Yernault JC, Estenne M. Donor-transmitted tumors in lung allograft recipients: report on two cases. *Transplantation.* 1994;57(11):1679–1680. PMID: 8009606

7. Zelinkova Z, Geurts-Giele I, Verheij J, Metselaar H, Dinjens W, Dubbink HJ, et al. Donor-transmitted metastasis of colorectal carcinoma in a transplanted liver. *Transpl Int.* 2012;25(1):e10–e15. PMID: 22050293 https://doi.org/10.1111/ j.1432-2277.2011.01380.x

8. Kim B, Woreta T, Chen PH, Limketkai B, Singer A, Dagher N, et al. Donor-transmitted malignancy in a liver transplant recipient: a case report and review of literature. *Dig Dis Sci.* 2013;58(5):1185–1190. PMID: 23242807 https://doi.org/10.1007/s10620-012-2501-0

9. Kashyap R, Ryan C, Sharma R, Maloo MK, Desai R, Collett D, et al. Cancer transmission from organ donors-unavoidable but low risk. *Transplantation.* 2012;94(12):1200–1207. PMID: 23269448 https://doi.org/10.1097/TP.0b013e318272df41

10. *Guide to the safety and quality assurance for the transplantation of organs, tissues and cells.* Council of Europe; 2004.

Available at: https://www.coe.int/t/dg3/health/Source/GuideSecurity2_en.pdf [Accessed July 6, 2020]

11. Desai R, Neuberger J. Donor transmitted and de novo cancer after liver transplantation. *World J Gastroenterol.* 2014;20(20):6170–6179. PMID: 24876738 https://doi.org/10.3748/wjg.v20.i20.6170

12. Maltseva AP, Syutkin VE, Kolyshev IYu, Rudakov VS, Svetlakova DS, Sadykhov ZA, et al. Transplantation in oncology: the future of a multidisciplinary approach. *Transplantologiya. The Russian Journal of Transplantation.* 2019;11(3):218–233. (In Russ.). https://doi.org/10.23873/2074-0506-2019-11-3-218-233

13. Mehta N, Heimbach J, Denise M, Harnois DO, Sapisochin G, Jennifer L, et al. Validation of a risk estimation of tumor recurrence after transplant (RETREAT) score for hepatocellular carcinoma recurrence after liver transplant. *JAMA Oncol.* 2017;3(4):493–500. PMID: 27838698 https://doi.org/10.1001/jamaoncol.2016.5116

14. Lerut JP, Orlando G, Adam R, Schiavo M, Klempnauer J, Mirza D, et al. The place of liver transplantation in the treatment of hepatic epitheloid hemangioendothelioma: report of the European liver transplant re-gistry. *Ann Surg.* 2007;246(6):949–957. PMID: 18043096 https://doi.org/10.1097/SLA.0b013e31815c2a70

15. Grotz TE, Nagorney D, Donohue J, Que F, Kendrick M, Farnell M, et al. Hepatic epithelioid haemangioendothelioma: is transplantation the only treatment option? *HPB (Oxford).* 2010;12(8):546–553. PMID: 20887322 https://doi.org/10.1111/j.1477-2574.2010.00213.x

16. Lai Q, Feys E, Karam V, Adam R, Klempnauer J, Oliverius M, et al. European liver intestine transplant association (ELITA). Hepatic epithelioid hemangioendothelioma and adult liver transplantation:

proposal for a prognostic score based on the analysis of the ELTR-ELITA registry. *Transplantation.* 2017;101(3):555–564. PMID: 28212256 https://doi.org/10.1097/TP.0000000000001603.

17. Goldaracena N, Gorgen A, Sapisochin G. Current status of liver transplantation for cholangiocarcinoma. *Liver Transpl.* 2018;24(2):294–303. PMID: 290024405 https://doi.org/10.1002/lt.24955

18. Lee DD, Croome KP, Musto KR, Melendez J, Tranesh G, Nakhleh R, et al. Liver transplantation for intrahepa-tic cholangiocarcinoma. *Liver Transpl.* 2018;24(5):634–644. PMID: 29024405 https://doi.org/10.1002/lt.25052

19. Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, et al. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: international retrospective study supporting a prospective assessment. *Hepatology.* 2016;64(4):1178–1188. PMID:27481548 https://doi.org/10.1002/hep.28744

20. Moris D, Tsilimigras D, Ntanasis-Stathopoulos I, Beal EW, Felekouras E, Vernadakis S, et al. Liver transplantation in patients with liver metastases from neuroendocrine tumors: A systema-tic review. *Surgery.* 2017;162(3):525–536. PMID: 28624178 https://doi.org/10.1016/j.surg.2017.05.006

21. Nguyen NT, Harring TR, Goss JA, O'Mahony CA. Neuroendocrine liver metastases and orthotopic liver transplantation: the US experience. *Int J Hepa-tol.* 2011;2011:742890. PMID: 22254141 https://doi.org/10.4061/2011/742890

22. Frilling A, Li J, Malamutmann E, Schmid KW, Bockisch A, Broelsch CE. Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. *Br J Surg.* 2009;96(2):175–184. PMID:19160361 https://doi.org/10.1002/bjs.6468

23. Le Treut Y, Gregoire E, Belghiti J, Boillot O, Soubrane O, Mantion G, et al. Predictors of long-term survival after liver transplantation for metastatic endocrine tumours: an 85-case French multicentric report. *Am J Transplant.* 2008;8(6):1205–1213. PMID: 18444921 https://doi.org/10.1111/j.1600-6143.2008.02233.x

24. Adam R, Kitano Y. Multidisciplinary approach of liver metastases from colorectal cancer. *Ann Gastroenterol Surg.* 2019;3(1):50–56. PMID: 30697610 https://doi.org/10.1002/ags3.12227

25. Andres A, Oldani G, Berney T, Compagnon P, Line PD, Toso C. Transplantation for colorectal metastases: on the edge of a revolution. *Transl Gastroenterol Hepatol.* 2018;3:74. PMID: 30363763 https://doi.org/10.21037/tgh.2018.08.04

26. Kovrigina AM. EBV-positive lymphoproliferative diseases: a new concept and differential diagnosis (literature review and case reports). *Clinical oncohematology.* 2018;11(4):326–37. https://doi.org/10.21320/2500-2139-2018-11-4-326-337

27. Rodríguez-Perálvarez M, Tsochatzis E, Naveas MC, Pieri G, García-Caparrós C, O'Beirne J, et al. Reduced exposure to calcineurin inhibitors early after liver transplantation prevents recurrence of hepatocellular carcinoma. *J Hepatol.* 2013;59(6):1193–1199. PMID: 23867318 https://doi.org/10.1016/j.jhep.2013.07.012

28. Kanazawa H, Fukuda A, Mali VP, Rahayatri TH, Hirata Y, Sasaki K, et al. Chemotherapy-induced B-cell depletion in hepatoblastoma patients undergoing AB0-incompatible living donor liver transplantation. *Pediatr Transplant.* 2016;20(3):401–407. PMID: 27012966 https://doi.org/10.1111/petr.12675

29. Aguiar D, Martínez-Urbistondo D, D'Avola D, Iñarrairaegui M, Pardo F, Rotellar F. Conversion from calcineurin inhibitor-based

immunosuppression to mycophenolate mofetil in monotherapy reduces risk of de novo malignancies after liver transplantation. *Ann Transplant.* 2017;22:141–147. PMID: 28302995 https://doi.org/10.12659/aot.901556

30. Rompianesi G, Ravikumar R, Jose S, Allison M, Athale A. Incidence and outcome of colorectal cancer in liver transplant recipients: a national, multicentre analysis on 8115 patients. *Liver Int.* 2019;39(2):353–360. PMID: 30129181 https://doi.org/10.1111/liv.13947

**Information about authors**

Ilya Yu. Kolyshev, Cand. Med. Sci., Head of Surgical Department No. 1 of the Center for Novel Surgical Technologies, State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA), http://orcid.org/0000-0002-6254-130X

40% − review of publications on the topic, collection of statistical information and its analysis, writing the text of the manuscript;

Sergey E. Voskanyan, Corr. Member of RAS, Prof., Head of the Surgery Department with the Courses of Oncology, Anesthesiology and Resuscitation, Endoscopy, Surgical Pathology, Clinical Transplantation and Organ Donation, the Institute of Postgraduate Professional Education at the State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA), Deputy Chief Doctor for Surgical Care, Head of the Center for Surgery and Transplantation at the State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA), http://orcid.org/0000-0001-5691-5398

7% − editing the text of the article, collection of statistical information and its analysis, writing the text of the manuscript;

Maksim V. Shabalin, Cand. Med. Sci., Surgeon, the Center for Surgery and Transplantation, State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA), http://orcid.org/0000-0002-4527-0448

4% − development of the study design, review of publications on the topic, collection of statistical information and its analysis, writing the text of the manuscript;

Aleksey I. Artemyev, Cand. Med. Sci., Head of the Surgical Department, the Center for Surgery and Transplantation, State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA), http://orcid.org/0000-0002-1784-5945

7% − editing the text of the article, collection of statistical information and its analysis, writing the text of the manuscript;

Vladimir S. Rudakov, Cand. Med. Sci., Surgeon, the Center for Surgery and Transplantation, State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA), http://orcid.org/0000-0002-3171-6621

3% − development of the study design, collection of statistical information;

Anna P. Maltseva, Surgeon, State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA), http://orcid.org/0000-0003-1192-9598

7% − development of the study design, collection of statistical information;

Andrey N. Bashkov, Cand. Med. Sci., Head of the Department for Diagnostic Radiology and Radionuclide Imaging, State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological

Agency of the Russian Federation (FMBA), http://orcid.org/0000-0002-4560-6415

5% − editing the text of the article, collection of statistical information and its analysis, writing the text of the manuscript;

Vladimir E. Syutkin, Dr. Med. Sci., Leading Research Associate, Department for Liver Transplantation, N.V. Sklifosovsky Research Institute for Emergency Medicine, http://orcid.org/0000-0001-8391-5211

9% − editing the text of the article, collection of statistical information and its analysis, writing the text of the manuscript;

Konstantin K. Gubarev, Cand. Med. Sci., Head of the Surgical Department for the Coordination of Human Organ and(or) Tissue Donation, State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA), http://orcid.org/0000-0001-9006-163X

4% − editing the text of the article, collection of statistical information and its analysis, writing the text of the manuscript;

Darya S. Svetlakova, Surgeon of the Surgical Department for the Coordination of Human Organ and(or) Tissue Donation, State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA), http://orcid.org/0000-0002-2274-6204

3% − editing the text of the article, collection of statistical information and its analysis, writing the text of the manuscript;

Maksim V. Popov, Endovascular Radiology Physician for Diagnosis and Treatment, the Department of Diagnostic and Treatment Techniques in Interventional Radiology, State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological

Agency of the Russian Federation (FMBA), http://orcid.org/0000-0002-6558-7143

3% − review of publications on the topic, collection of statistical information and its analysis, writing the text of the manuscript;

Aleksandr I. Sushkov, Cand. Med. Sci., Head of the Laboratory for Novel Surgical Technologies, State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA), http://orcid.org/0000-0002-1561-6268

5% − editing the text of the article, collection of statistical information and its analysis, writing the text of the manuscript;

Zamin A.O. Sadykhov, Postgraduate Fellow of the Department of Surgery with the courses in Oncosurgery, Endoscopy, Surgical Pathology, Clinical Transplantation, and Organ Donation, the Institute of Postgraduate Professional Education State Research Center – Burnasyan Federal Medical Biophysical Center of Medico-Biological Agency of the Russian Federation (FMBA), http://orcid.org/0000-0001-9594-7966

3% − collection of statistical information and its analysis.

*Received: May 12, 2020*
*Accepted for publication: May 28, 2020*