DOI: 10.15825/1995-1191-2019-4-20-25

# EXTRAHEPATIC MALIGNANT NEOPLASMS AFTER LIVER TRANSPLANTATION: THE EXPERIENCE OF A SINGLE TRANSPLANT CENTER

*O.A. Gerasimova[1, 2], V.V. Borovik[1], F.K. Zherebtsov[1], D.A. Granov[1]*

[1] Granov Russian Research Center of Radiology and Surgical Technologies, St. Petersburg, Russian Federation

[2] Saint-Petersburg State University, St-Petersburg, Russian Federation

**Objective:** to evaluate the incidence of *de novo* malignant neoplasms (MN) after liver transplantation (LT) and compare with indicators among the general Russian population. **Materials and methods.** The study included 182 patients who had at least a 6-month follow-up period after LT and had no extrahepatic malignancies before LT. All data were analyzed retrospectively. Statistical processing of the results was carried out using the Statistica program for Windows v.10. **Results.** MN incidence was 5.5% (10 of 182 patients). The average period from transplantation to diagnosis of *de novo* neoplasm was 47.8 months (8 to 144 months). The patients were 3 men and 7 women. Types of *de novo* tumors included digestive system tumor (2 out of 10), hematologic malignant tumor (3 out of 10), skin cancer – melanoma (1 out of 10), urologic cancer (1 out of 10), gynecological (2 out of 10) and base of tongue cancer (1 out of 10). Five patients (50.0%) died, mortality was higher than in other LT patients ($Z = –2.6$; $p = 0.009$). The average follow-up period after detection of neoplasms was 18.8 months. Incidence of malignant neoplasms following LT was 10 times higher than among the general Russian population. No significant differences were found in the incidence of late acute rejection between 10 patients with MN and other 172 patients ($Z = 0.18$, $p = 0.8$). Among surviving patients, 2 patients with lymphomas received tacrolimus immunosuppression monotherapy, while 3 had everolimus-based immunosuppression. **Conclusion.** Incidence of *de novo* extrahepatic malignancies after LT is significantly higher than in the general population. To reduce the incidence of neoplasms in the future, patients should undergo regular screening, proliferative signal blockers should be prescribed, although their effectiveness requires further research.

*Keywords: liver transplantation, de novo malignant neoplasms, incidence, tacrolimus, everolimus.*

## INTRODUCTION

Over the past decade, liver transplantation (LT) has become the treatment of choice for patients with liver failure in end-stage liver disease [1]. Breakthroughs in surgical technology, advances in immunosuppressive therapy, and optimized patient monitoring approaches have all led to improved survival outcomes. In most transplant centers, 1-year post-liver transplant survival is 91% and higher [1, 2]. Longer life expectancy in liver transplant recipients has led to higher incidence of cardiovascular diseases and extrahepatic MN [3, 4]. Obviously, organ recipients are 3–7 times more likely to develop extrahepatic MN than the general population due to the oncogenic effects of prolonged immunosuppression [5–7]. The cumulative frequency is 3–5% by three years and 11–20% by ten years after orthotopic liver transplantation (OLT) [1]. D. Collett et al. report that *de novo* malignancy rate reaches 10% by 10 years after LT [8].

In this retrospective study, the authors analyzed the incidence of post-LT *de novo* extrahepatic malignancies, as well as the types and risk factors.

## MATERIALS AND METHODS

Analysis included data from 182 patients who underwent liver transplantation at the Granov Russian Research Center of Radiology and Surgical Technologies from 1998 to 2017. All were observed on an outpatient basis for at least 6 months and had no pre-transplant extrahepatic malignancies. Liver transplants were obtained from dead donors. After LT, basiliximab (Simulect®) induction therapy and a standard immunosuppressive therapy (IST) regimen were administered: calcineurin inhibitors (CNIs) (cyclosporin/tacrolimus), corticosteroids and mycophenolic acid. Proliferation signal inhibitors (everolimus) were prescribed to patients with hepatocellular cancer, as well as with CNI nephrotoxicity. After discharge, patients were observed monthly during the first year and then at intervals of 2–3 months. In each

**Corresponding author:** Gerasimova Olga Anatolievna. Address: 70, Leningradskaya str., p. Pesochnyy, St-Petersburg, 197758, Russian Federation.
Tel. (812) 439-66-40. E-mail: ren321@mail.ru

outpatient visit, clinical and laboratory examinations were performed to determine the main indicators of the functional state of the liver. Also carried out were comprehensive abdominal ultrasound, and multispiral computed tomography (MSCT) of the thorax and abdomen, fibrogastroduodenoscopy (FGDS), MRI – once per year during follow-up and according to indications. CNI concentration in the long term for tacrolimus was 3–5 ng/mL, for cyclosporine at point C0 – 100–150 ng/mL.

The results were statistically processed in statistics program Statistica v.10 for Windows. Descriptive and nonparametric statistics methods were used. The Mann–Whitney U test was used for intergroup comparisons. Data with $p < 0.05$ were considered significant.

## RESULTS

Post-LT extrahepatic malignancies were detected in 10 out of the 182 patients. Of the 10 patients, there were 7 women and 3 men, the average age was 46.1 ± 9.4 years and 51 ± 10 years in LT and at the stage of MN diagnosis, respectively. The MN was detected within 8 to 144 months (average 47.8 months, median 36 months) after LT. Average follow-up period from the time MN was diagnosed was 18.8 months. MN incidence was 5.5% of all patients who were discharged for outpatient treatment and survived 6 months after LT. Post-transplant lymphoproliferative disorder (PTLD) was the most common disease – 3 patients (30%). Other MN localizations were: duodenal carcinoid – 1 (10%), gastric adenocarcinoma – 1 (10%), cervical cancer – 1 (10%), uterine adenocarcinoma – 1 (10%), skin melanoma – 1 (10%), base of tongue cancer – 1 (10%), renal cell cancer – 1 (10%).

Of the 10 recipients, 7 (70%) underwent surgery, 3 of which were radical, the rest were cytoreductive or diagnostic in nature. Persistent remission was achieved in 3 patients operated upon for uterine adenocarcinoma, renal cell carcinoma, skin melanoma, and in 2 cases of combined treatment for lymphoma. Treatment of non-Hodgkin's lymphoma after surgery was done according to the R-CHOP polychemotherapy regimen. During polychemotherapy, the IST scheme was modified – only tacrolimus was retained at a minimum concentration of not more than 3 ng/mL. Currently, in 1 patient, the duration of remission is 5 years, 1 patient is in remission for 12 months, having a satisfactory function of liver transplant amidst prolonged-release tacrolimus monotherapy (see table). One patient refused treatment and died from lymphoma progression. Epstein–Barr viral load carriage, which is considered a predictor for development of lymphomas, was detected in 2 out of 3 patients.

In the early postoperative period, 2 patients died of infectious complications: after gastric resection that was performed due to low-grade adenogenic cancer of body of the stomach, and after palliative duodenal resection for peritoneal carcinomatosis. One patient died from progression of cervical cancer one year after verification of diagnosis (T3M1N0) and combined radiation therapy and chemotherapy; one patient died of stroke (hemorrhagic stroke) after successful radiation treatment for base of tongue cancer (table). Thus, out of 10 patients with extrahepatic MN, 5 died (50%). Compared to the group of patients without MN, mortality in the studied small group was significantly higher ($Z = –2.6$, $p = 0.009$).

After cancer detection, the immunosuppression regimen was modified by prescribing a proliferation signal inhibitor (everolimus), without compromising liver transplant function. An exception was 2 patients with lymphomas, since there are no guidelines for the use of everolimus in such patients, there are data from clinical studies [9].

There were no significant differences in incidence of detected late rejection episodes and effect of bolus administration of corticosteroids in MN patients and other patients ($Z = 0.18$, $p = 0.8$).

The average follow-up period in the group of 10 people from the moment MN was detected was 18.8 months. However, the group was small, and calculations included data from those who died in the early period after non-radical surgical interventions performed in the late stage of the disease.

## DISCUSSION

Records show that extrahepatic cancer in patients undergoing liver transplantation is more common than in the general population [10–13]. According to various centers, incidence of cancerous tumors varies from 2.6 to 26% [14–16]. Incidence of *de novo* cancer is 3 to 5% 1–3 years after liver transplantation and 11 to 20% 10 years after transplantation [1, 2, 16]. The most common malignancies after liver transplantation are skin cancer, lung cancer, PTLD, and Kaposi sarcoma [6, 8].

The Ministry of Health of the Russian Federation estimated the incidence of cancer in Russia in 2018 at 425.4 new cases per 100,000 population [17]. Based on data from our center (Granov Russian Research Center of Radiology and Surgical Technologies), incidence of *de novo* extrahepatic cancer in patients after LT was about 10 times higher than in the general population of the Russian Federation – 5.5%.

Various researchers have identified the main risk factors for development of post-LT cancer. These include old age, alcohol consumption, smoking, oncogenic viruses, excessive insolation and prolonged immunosuppressive therapy [2, 5, 18, 19]. In addition, immunosuppressive therapy contributes to suppression of immune control and lower resistance to certain oncogenic viruses [18, 20, 21]. In the studied group of patients, as well as in a similar Turkish study [22], the average age of recipients at the cancer detection stage was above 50 years – a potential risk factor for cancer development. Unlike other researchers, we did not identify lung cancer among the entire group of recipients. This is likely since there were

Table

**Demographic characteristics of patients with post-transplant *de novo* malignancies**

| S/N | Sex | Age (years) | Diagnosis | IST | MN type | Stage | Treatment | Remission period (months) | Observation period (years) | IST in MN | Status |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 59.8 | Polycystic kidney disease | CyA | Renal squamous cell carcinoma | T1aN0M0 | Surgery | 78 | 21.1 | EVL | Alive |
| 2 | f | 52.2 | Primary biliary cholangitis | TAC + MPA | Duodenal carcinoid | T4NxM1 | Surgery | 0 | 0.9 | TAC | Dead |
| 3 | m | 34.6 | Unspecified cirrhosis | CyA | Splenic lymphoma | – | Refused treatment | 0 | 3.2 | CyA | Dead |
| 4 | m | 57.5 | CHC | TAC + MPA | Gastric adenocarcinoma | T2NxM0 | Surgery | 0 | 3.1 | EVL | Dead |
| 5 | f | 48.5 | Budd–Chiari syndrome | TAC | Endometrial adenocarcinoma | T1aNxM0 | Surgery | 64 | 13.4 | EVL + TAC | Alive |
| 6 | f | 45.5 | Unspecified cirrhosis | TAC + MPA | Cervical cancer | T3bNxM0 | Radiation, chemotherapy | 0 | 9.9 | EVL + TAC | Dead |
| 7 | m | 65.2 | Unspecified cirrhosis | TAC + MPA | Skin melanoma | T1N0M0 | Surgery | 24 | 8.5 | EVL | Alive |
| 8 | m | 53.8 | CHC | EVL + TAC | Base of tongue cancer | T4N1M1 | Radiation therapy | 6 | 1.6 | EVL | Dead |
| 9 | f | 56.5 | CHC | TAC | Non-Hodgkin's lymphoma | II | Surgery, chemotherapy | 56 | 8 | TAC | Alive |
| 10 | f | 34.9 | Retransplantation | TAC | Non-Hodgkin's lymphoma | IVA | Surgery, chemotherapy | 12 | 6.4 | TAC | Alive |

*Note.* IST – immunosuppressive therapy; CHC – chronic hepatitis C.

more women in the observed patient population; smokers were no more than 20% of all outpatients.

Skin cancer, which is one of the most common types of post-transplant malignant neoplasms, was observed in only 1 patient (10%) in our population. It was detected after melanocytic nevus trauma and was radically operated on.

Chronic alcohol consumption and long-term tobacco smoking were present in only 1 patient (10%) who developed base of tongue cancer and was subjected to conformal irradiation with good clinical effect. However, the patient died of hemorrhagic stroke 6 months after therapy.

PTLD (30%) was dominant in the group of patients participating in our study. Outcomes of treatment for this disorder can be considered satisfactory, since in 2 cases, long-term remission was achieved. Unfortunately, one patient refused treatment – lived in a region far from the transplantation center – and died from progression of the disease.

Tacrolimus (8 patients) and cyclosporine (2 patients) were used as the immunosuppressive agents. Pulse methylprednisolone therapy was performed in 3 patients in the early postoperative period. In our series, we did not use antithymocyte immunoglobulin preparations, which are associated with more frequent PTLD [23]. None of the patients had hyperimmunosuppression during outpatient follow-up period. CNI concentration was monitored regularly and did not exceed 3–5 ng/mL for tacrolimus and 100–150 ng/mL for cyclosporine over a 12-month period after LT. Given the possible trigger effects of the Epstein–Barr virus for PTLD, preoperative screening and subsequent molecular genetic monitoring of this infection may be advisable; there is still insufficient data for mandatory preventive measures [24].

Thanks to improvements in transplantation technologies, liver transplant recipients are living longer, the population of recipients naturally ages, and the risk of developing MN thus increases [25]. Patients should be informed of such risks. Since cancer of the skin, head, neck, lungs and lymphoma is often develop after transplantation [5, 6, 26, 27], patients at risk may need more frequent outpatient visits, possibly preventative administration of proliferation signal inhibitors after discharge from the transplant center.

The use of proliferation signal inhibitors for prevention of MN recurrence or metastasis offered some hope [5] due to their ability to suppress neoangiogenesis. But literature data are contradictory and relate mainly to kidney transplant recipients [28–31]. Nevertheless, all

patients with newly diagnosed MN received everolimus in an average daily dose of 3.5 mg. Blood concentration was maintained at a level of at least 5–8 ng/mL. Increased concentration led to severe side effects. Despite everolimus use, the disease progressed in some cases. This was obviously associated with late diagnosis of MN, possibly with insufficient dose of the drug. The question of reducing incidence of post-LT malignant neoplasm with everolimus in combination with low-dose tacrolimus requires further study [32].

## CONCLUSION

Incidence of *de novo* extrahepatic malignancies after liver transplantation is significantly higher than in the general population. To reduce the incidence of malignant neoplasms in the future, risk factors should be considered, cancer screening should be done, there should be regular outpatient visits and full instrumental examination of such patients. If a tumor is detected, proliferation signal inhibitors should be prescribed.

*The authors declare no conflict of interest.*

## REFERENCES


1. Nacional'nye klinicheskie rekomendacii. 2016 g. http://transpl.ru/files/rto/transpl_pecheni.pdf. Transplantaciya pecheni.
2. *Liu ZN, Wang WT, Yan LN.* Liver Surgery Group. *De novo* malignancies after liver transplantation with 14 cases at a single center. *Transplant Proc*. 2015; 47 (8): 2483–2487. doi: 10.1016/j.transproceed.2015.08.008.
3. *Pruthi J, Medkiff KA, Esrason KT, Donovan JA, Yoshida EM, Erb SR et al.* Analysis of causes of death in liver transplant recipients who survived more than 3 years. *Liver Transpl*. 2001; 7 (9): 811–815. doi: 10.1053/jlts.2001.27084.
4. *Fung JJ, Jain A, Kwak EJ, Kusne S, Dvorchik I, Eghtesad B. De novo* malignancies after liver transplantation: a major cause of late death. *Liver Transpl*. 2001; 7 (11 Suppl 1): 109–118. doi: 10.1053/jlts.2001.28645.
5. *Pillai AA.* Management of *de novo* malignancies after liver transplantation. *Transplant Rev (Orlando)*. 2015; 29 (1): 38–41. doi: 10.1016/j.trre.2014.11.002.
6. *Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ et al.* Spectrum of cancer risk among US solid organ transplant recipients. *JAMA*. 2011; 306 (17): 1891–1901. doi: 10.1001/jama.2011.1592.
7. *Herrero JI. De novo* malignancies following liver transplantation: impact and recommendations. *Liver Transpl*. 2009; 15, Suppl 2: 90–94. doi: 10.1002/lt.21898.
8. *Collett D, Mumford L, Banner NR, Neuberger J, Watson C.* Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. *Am J Transplant*. 2010; 10 (8): 1889–1896. doi: 10.1111/j.1600-6143.2010.03181.x.
9. *Witzig TE, Tobinai K, Rigacci L, Ikeda T, Vanazzi A, Hino M et al.* Adjuvant everolimus in high-risk diffuse large B-cell lymphoma: final results from the PILLAR-2 randomized phase III trial. *Ann Oncol*. 2011; 29 (3): 707–714. doi: 10.1093/annonc/mdx764.
10. *Herrero JI, Lorenzo M, Quiroga J, Sangro B, Pardo F, Rotellar F et al. De novo* neoplasia after liver transplantation: an analysis of risk factors and influence on survival. *Liver Transpl*. 2005; 11 (1): 89–97. doi: 10.1002/lt.20319.
11. *Aberg F, Pukkala E, Hockerstedt K, Sankila R, Isoniemi H.* Risk of malignant neoplasms after liver transplantation: a population-based study. *Liver Transpl*. 2008; 14 (10): 1428–1436. doi: 10.1002/lt.21475.
12. *Buell JF, Gross TG, Woodle ES.* Malignancy after transplantation. *Transplantation*. 2005; 80 (2 Suppl): 254–264. doi: 10.1097/01.tp.0000186382.81130.ba.
13. *Penn I.* Occurrence of cancers in immunosuppressed organ transplant recipients. *Clin Transpl*. 1998: 147–158. PMID: 10503093.
14. *Adami J, Gäbel H, Lindelöf B, Ekström K, Rydh B, Glimelius B et al.* Cancer risk following organ transplantation: a nationwide cohort study in Sweden. *Br J Cance*r. 2003; 89 (7): 1221–1227. doi: 10.1038/sj.bjc.6601219.
15. *Saigal S, Norris S, Muiesan P, Rela M, Heaton N, O'Grady J.* Evidence of differential risk for posttransplantation malignancy based on pretransplantation cause in patients undergoing liver transplantation. *Liver Transpl*. 2002; 8 (5): 482–487. doi: 10.3748/wjg.v20.i20.617010.
16. *Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Sanchez W, Gores GJ.* Long-term probability of and mortality from *de novo* malignancy after liver transplantation. *Gastroenterology*. 2009; 137 (6): 2010–2017. doi: 10.1053/j.gastro.2009.08.070.
17. Sostoyanie onkologicheskoj pomoshchi naseleniyu Rossii v 2018 godu (red. A.D. Kaprina, V.V. Starinskogo, G.V. Petrovoj). M.: MNIOI im. P.A. Gercena – filial FGBU "NMIC radiologii" Minzdrava Rossii, 2019. 236 s.
18. *Xiol X, Guardiola J, Menendez S, Lama C, Figueras J, Marcoval J et al.* Risk factors for development of *de novo* neoplasia after liver transplantation. *Liver Transpl*. 2001; 7 (11): 971–975. doi: 10.4254/wjh.v7.i7.942.
19. *Burra P, Shalaby S, Zanetto A.* Long-term care of transplant recipients: *de novo* neoplasms after liver transplantation. *Curr Opin Organ Transplant*. 2018; 23 (2): 187–195. doi: 10.1097/MOT.0000000000000499.
20. *Finkenstedt A, Graziadei IW, Oberaigner W, Hilbe W, Nachbaur K, Mark W et al.* Extensive surveillance promotes early diagnosis and improved survival of *de novo* malignancies in liver transplant recipients. *Am J Transplant*. 2009; 9 (10): 2355–2361. doi: 10.4254/wjh.v8.i12.533.
21. *Dunn GP, Old LJ, Schreiber RD.* The immunobiology of cancer immunosurveillance and immunoediting. *Immunity*. 2004; 21 (2): 137–148. doi: 10.1016/j.immuni.2004.07.017.
22. *Egeli T, Unek T, Ozbilgin M, Agalar C, Derici S, Akarsu M et al. De novo* malignancies after liver transplantation: a single institution experience. *Exp Clin Transplant*. 2019; 17 (1): 74–78. doi: 10.6002/ect.2017.0111.

23. *Hertig A, Zuckermann A.* Rabbit antithymocyte globulin induction and risk of posttransplant lymphoproliferative disease in adult and pediatric solid organ transplantation: An update. *Transpl Immunol*. 2015; 32 (3): 179–187. doi: 10.1016/j.trim.2015.04.003.
24. *Allen UD, Preiksaitis JK.* Post-transplant lymphoproliferative disorders, Epstein–Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019; 23: e13652. doi: 10.1111/ctr.13652. [Epub ahead of print].
25. *Doycheva I, Amer S, Watt KD. De novo* malignancies after transplantation: risk and surveillance strategies. *Med Clin North Am*. 2016; 100 (3): 551–567. doi: 10.1016/j.mcna.2016.01.006.
26. *Euvrard S, Kanitakis J.* Skin cancers after liver transplantation: what to do? *J Hepatol*. 2006; 44 (1): 27–32. doi: https://doi.org/10.1016/j.jhep.2005.10.010.
27. *Belloni-Fortina A, Piaserico S, Bordignon M, Gambato M, Senzolo M, Russo FP et al.* Skin cancer and other cutaneous disorders in liver transplant recipients. *Acta Derm Venereol.* 2012; 92: 411–415. doi: 10.3748/wjg.v21.i29.8753.
28. *Mathew T, Kreis H, Friend P.* Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. *Clin Transplant*. 2004; 18 (4): 446–449. doi: 10.1001/jamadermatol.2015.5548.
29. *Flechner SM, Glyda M, Cockfield S, Grinyó J, Legendre Ch, Russ G et al.* The ORION study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients. *Am J Transplant*. 2011; 11 (8): 1633–1644. doi: 10.1111/j.1600-6143.2011.03573.x.
30. *Schena FP, Pascoe MD, Alberu J, del Carmen Rial M, Oberbauer R, Brennan DC et al.* Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation*. 2009; 87 (2): 233–242. doi: 10.1186/2047-1440-2-S1-S3.
31. *Alberú J, Pascoe MD, Campistol JM, Schena FP, Rial Mdel C, Polinsky M et al.* Sirolimus CONVERT Trial Study Group. Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. *Transplantation*. 2011; 92 (3): 303–310. doi: 10.1097/TP.0b013e3182247ae2.
32. *De Simone P, Carrai P, Coletti L, Ghinolfi D, Petruccelli S, Precisi A et al.* Everolimus vs mycophenolate mofetil in combination with tacrolimus: a propensity score-matched analysis in liver transplantation. *Transplant Proc*. 2018; 50 (10): 3615–3620. doi: 10.1016/j.transproceed.2018.07.011.

*The article was submitted to the journal on 29.08.2019*