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ASSESSMENT OF LIVER GRAFT HYPOXIA VIA ^{18}F-FMISO PET-CT IMAGING

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Objective: drawing on existing literature and the clinical use of radiopharmaceutical (RFP) ^{18}F-FMISO in oncology, this pilot study aims to assess the feasibility of using non-invasive PET-CT imaging to detect hypoxia in liver grafts resulting from ischemia-reperfusion injury. **Materials and methods.** ^{18}F-FMISO uptake in tumors, as visualized by PET-CT, enables the generation of quantitative maps of tissue hypoxia, a technique that is increasingly being explored to guide radiation therapy planning. As part of refining the study methodology, the research team successfully obtained the first PET-CT images demonstrating ^{18}F-FMISO uptake in the liver of a patient at a late postoperative stage following liver transplantation. **Results.** A positive indication of transplant hypoxia was defined as an increase in both the mean and maximum standardized uptake values (SUVs) when measured at 180 minutes post-intravenous injection of the radiopharmaceutical, compared to measurements at 90 minutes. Two imaging series – CT and PET – were acquired. Diffuse uptake of the radiopharmaceutical was observed in the liver, with greater tracer retention relative to background at 180 minutes compared to 90 minutes post-injection. **Conclusion.** The findings suggest the presence of transplant hypoxia despite the absence of biochemical abnormalities. This technique shows promise as a non-invasive diagnostic tool for detecting hypoxic changes in liver grafts. However, further optimization and validation of the technique are necessary.

Keywords: ^{18}F-FMISO, radiopharmaceutical, liver transplant, PET-CT, ischemia-reperfusion injury.

INTRODUCTION

Ischemia-reperfusion injury (IRI) after liver transplantation (LT) is a significant complication, contributing to the development of biliary complications and graft fibrosis. IRI is mediated by multiple mechanisms, including activation of toll-like receptor (TLR) signaling pathways, changes in microRNA expression, production of reactive oxygen species (ROS), modulation of autophagy, and activation of hypoxia-inducible factors. These processes involve a variety of cell types such as sinusoidal endothelial cells, hepatocytes, Kupffer cells, neutrophils, and platelets. Recognized risk factors for IRI in LT include donor liver steatosis, prolonged ischemic time, advanced donor age, and coagulopathies in both the donor and recipient [1].

Liver ischemia-reperfusion injury (IRI) is initiated by hemodynamic alterations and begins during the early stages of organ retrieval and preservation. During warm and cold ischemia, hypoxia-induced metabolic dysfunction develops, leading to damage of hepatocytes, cholangiocytes, and sinusoidal endothelial cells [2]. Restoration of blood flow (reperfusion) exacerbates this injury through transient portal hypertension and hyperdynamic stress. Transient portal hypertension serves as the primary event triggering endothelial damage. Following reperfusion, portal vein pressure can rise sharply from 30–35 cm H_2O to 60–70 cm H_2O [3]. The abrupt surge in blood volume causes direct injury to sinusoidal endothelial cells and exposes the vessel walls to circulating platelets and leukocytes. Platelet aggregation subsequently narrows the venules, and the activated platelets release large amounts of cytokines, chemokines, and vasoactive molecules [4, 5].

The imbalance between vasoconstrictive and vasodilatory factors further aggravates microcirculatory disorders. Levels of the vasoconstrictor peptide endothelin-1 were found to increase 1.6-fold, whereas endothelial nitric oxide synthase, which produces nitric oxide, was found to decrease by 17.4 μmol/L [3]. Disruption of microcirculation exacerbates hyperdynamic stress, which may lead to sinusoidal occlusion and collapse of the space of Disse between endothelial cells and hepatocytes, thereby prolonging tissue hypoxia. Reperfusion injury becomes more devastating due to the massive production of reactive oxygen species, primarily generated by intrahepatic neutrophils and Kupffer cells. In neointimal grafts, mitochondrial dysfunction is more pronounced and multifactorial in nature. Oxidative stress reaches its peak approximately 2–6 hours after reperfusion. As a result of extensive cellular damage, molecular structures are released into the circulation, further activating the innate immune response [6].

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Unfortunately, IRI remains an inevitable consequence of LT and continues to pose a significant challenge due to the associated risks of early graft dysfunction and graft loss. Although the molecular mechanisms underlying IRI are gradually being elucidated, effective preventive and therapeutic strategies are still lacking. Early injury to the graft is driven by disruptions in microcirculatory regulation, impaired redox homeostasis, and mitochondrial dysfunction, which collectively initiate the immune cascade. Both innate and adaptive immune responses contribute to the progression of graft injury through adhesion and recruitment of macrophages, neutrophils, and dendritic cells, as well as activation of lymphoid cells, natural killer cells, and cytotoxic T lymphocytes.

Recent studies have identified several new biomarkers that may better predict early graft injury following LT. One such biomarker is lactate. Elevated lactate levels in the liver and systemic circulation are observed during IRI as a result of increased glycolysis following impaired microcirculation and prolonged hypoxia. Given that hepatocytes are responsible for metabolizing more than 70% of circulating lactate, an increase in blood or graft lactate levels, or a decrease in lactate clearance, likely reflects graft dysfunction. An arterial blood lactate level greater than 5 mmol/L has been proposed as an IRI biomarker, with a positive predictive value of 35.5% [7]. The reported sensitivity and specificity were 0.39 and 0.83, respectively. However, because lactate levels are highly dynamic and lactate can be produced by any tissue experiencing hypoperfusion, relying solely on arterial lactate as a biomarker may be insufficient for accurately predicting early IRI.

In the later postoperative period, persistent graft ischemia may be maintained by inadequate perfusion and redistribution of hepatic blood flow. Prolonged ischemia can contribute to the formation of non-anastomotic biliary strictures and the development of secondary biliary cirrhosis.

An angiographic study combined with fluorometry is currently required to diagnose hypoperfusion of the liver transplant, as noninvasive diagnostic methods such as ultrasound and multislice computed tomography may not reliably detect perfusion disorders [8]. However, angiographic studies are invasive, performed in hospital settings, and carry a risk of complications. The search for noninvasive diagnostic alternatives has led researchers to explore the use of positron emission tomography-computed tomography (PET-CT) in outpatient settings with the injection of the isotope ^{18}F-fluoromisonidazole (^{18}F-FMISO). Given the isotope's mechanism of marking hypoxic areas, it is hypothesized that ^{18}F-FMISO PET-CT may be applicable for assessing both early ischemia-reperfusion complications and ineffective arterial blood supply in the later stages after LT. To date, such studies have not been conducted in the Russian Federation. A prospective study is planned to evaluate patients with liver transplant perfusion disorders at different postoperative periods.

^{18}F-FMISO marks hypoxia in solid tumor tissues, and considerable experience has been accumulated regarding its application in oncology. The radiopharmaceutical contains a nitroimidazole molecule labeled with fluorine-18 [9, 10]. After administration, the nitroimidazole enters cells via the bloodstream and can undergo oxidation-reduction reactions mediated by xanthine oxidase. In normoxic (oxygenated) cells, the reduced nitro group can be reoxidized to its original form by molecular oxygen (O_2), enabling the radiopharmaceutical to exit the cells. In contrast, in hypoxic cells, the reduced nitro group cannot be reoxidized due to the lack of oxygen, resulting in stable binding of the radiopharmaceutical to the cells.

The accumulation of ^{18}F-FMISO in tissues is inversely proportional to the local oxygen levels. The distribution of hypoxic tissue can then be quantitatively visualized using PET [11, 12]. In oncology, ^{18}F-FMISO uptake provides a quantitative hypoxia map that can guide strategies such as radiation dose escalation. Several methods have been developed for quantifying and delineating hypoxic tumor volumes, including the tumor-to-blood ratio (TBR), tumor-to-normal ratio (TNR), and compartmental modeling approaches [13].

Large-scale clinical trials using ^{18}F-FMISO have not yet been conducted; however, evidence from small, early imaging studies suggests that FMISO-based hypoxia assessment may predict survival outcomes and certain locoregional parameters in patients with head and neck cancer and other malignancies. The use of hypoxia imaging to guide radiotherapy remains an area of active investigation [14].

Despite its ability to detect hypoxic regions in tumor tissues, the specificity and sensitivity of ^{18}F-FMISO imaging remain subjects of ongoing debate [15]. In addition to oncological applications, there is growing scientific interest in using FMISO for cardiac hypoxia imaging. However, experience in this field is limited, partly due to the minimal contrast between target and background, as well as delayed imaging times required because of the radiotracer's slow blood clearance [16].

We present a clinical case demonstrating the diagnostic potential of PET-CT with ^{18}F-FMISO for detecting ischemic injury in a liver transplant. This experience was obtained for the first time during the refinement of liver imaging techniques using this method.

CLINICAL CASE

Patient O., born in 1962, underwent LT on May 6, 2022, at the Russian Research Center of Radiology and

Surgical Technologies in St. Petersburg. The indication for LT was a combination of primary biliary cholangitis and primary sclerosing cholangitis, resulting in decompensated biliary cirrhosis (MELD-Na score of 20).

In the early postoperative period, on postoperative day 13, hemodynamically significant stenosis of the inferior vena cava (IVC) was identified, requiring endovascular stenting. Despite this intervention, angiography revealed persistent signs of hepatic artery stenosis. On postoperative day 20, splenic artery embolization was performed to optimize hepatic arterial blood flow. Post-embolization, the patient developed fever and systemic inflammatory response due to splenic infarcts, necessitating intensive infusion and antibacterial therapy.

The patient was discharged on postoperative day 38 with a functioning liver graft for outpatient follow-up. During the long-term postoperative period, complications arose, including the development of common bile duct (CBD) stricture, requiring multiple hospitalizations for interventional procedures such as drainage, balloon plasty, and CBD stenting.

A control angiogram detected no IVC stenosis. However, the patient continued to experience recurrent episodes of cholangitis, requiring periodic courses of antibacterial therapy. Immunosuppressive therapy consisted of a two-drug regimen: prolonged-release tacrolimus and mycophenolic acid.

At the time of PET-CT with ^{18}F-FMISO (27 months after LT), laboratory parameters reflecting liver function remained within normal ranges. No special preparation was required prior to the study. The radiopharmaceutical ^{18}F-FMISO was administered intravenously at a dose of 3.7 MBq per kilogram of body weight.

Imaging was performed using a Siemens mCT40 PET/CT scanner (Siemens, Germany). Two sequential scans were conducted: 90 and 180 min after administration of the radiopharmaceutical. The first scan covered the region from the top of the head to the thighs (whole-body protocol), while the second scan focused solely on the abdominal region. Each scan included a topogram, a non-contrast-enhanced CT performed during free breathing, and PET acquisition. The first scan required approximately 20 minutes, while the second scan took about 10 minutes.

Image processing was performed using an AW Volume Share 7 workstation (GE Healthcare, USA).

Each series of images was reconstructed in three anatomical planes: axial, coronal, and sagittal, as well as in a three-dimensional (3D) format. In addition, PET and CT image series were fused (Figs. 1–3).

^{18}F-FMISO uptake in the liver was assessed in both studies using visual analysis and a semi-quantitative method based on the standardized uptake value (SUV). For each PET series, the maximum and mean SUV values across the entire liver volume were measured.

An increase in mean and maximum SUV at 180 minutes compared to 90 minutes was interpreted as a positive result, indicating the presence of graft hypoxia. Each imaging session generated two series: CT and PET.

Since such a study had not been previously performed, interpretation of the results posed a significant challenge. Nevertheless, given the patient's clinical history, there was sufficient reason to suspect ongoing hypoxia in the graft despite satisfactory liver function tests.

As shown in the presented images (Figs. 1–3), there was a noticeable increase in the uptake of the radiophar-

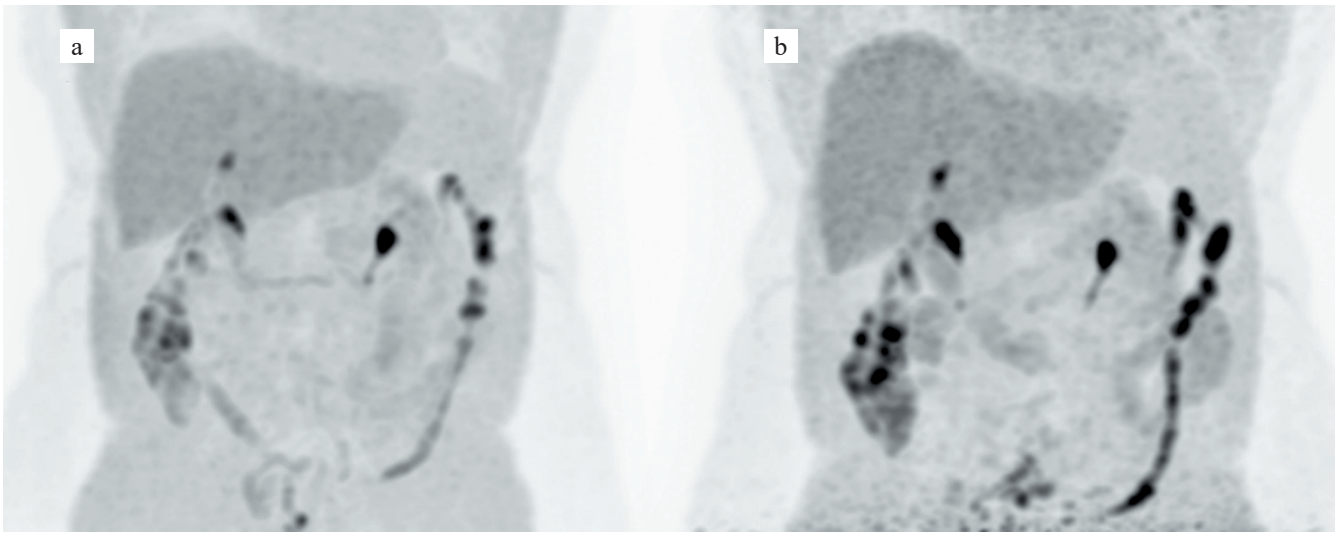

Fig. 1. 3D PET images (maximum intensity projection) with ^{18}F-FMISO: (a) at 90 minutes post-injection; (b) at 180 minutes post-injection. Diffuse tracer uptake is evident in the liver, with higher tracer retention relative to background at 180 minutes compared to 90 minutes. Physiological uptake of ^{18}F-FMISO is also noted in the renal pelvis and calyces, along the colon

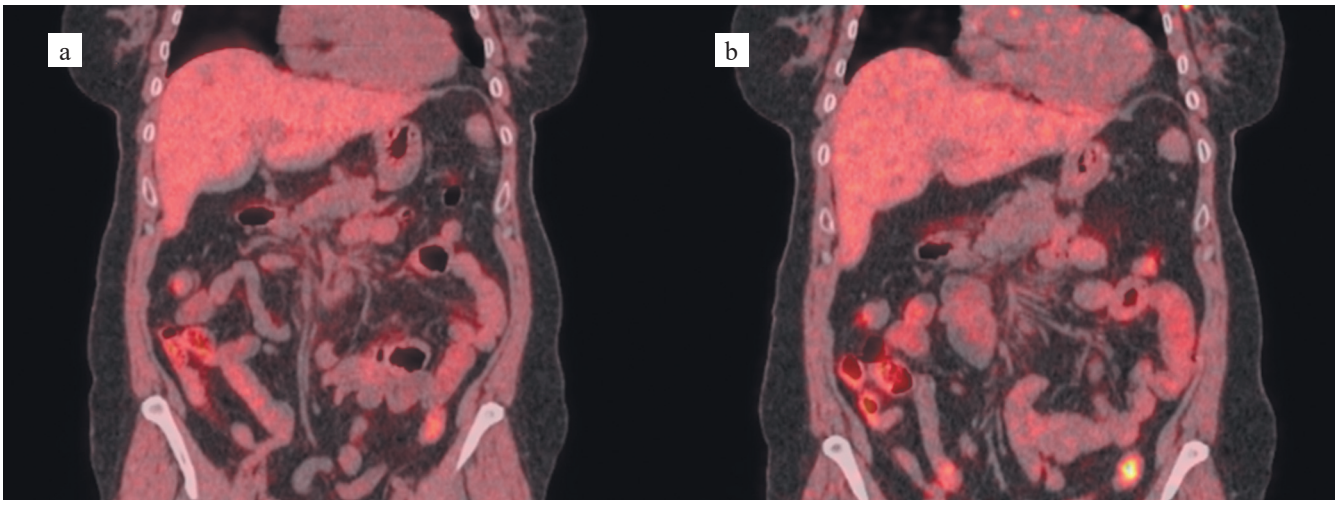

Fig. 2. Coronal fused PET/CT images with ^{18}F-FMISO (native CT): (a) at 90 minutes post-injection; (b) at 180 minutes post-injection. Diffuse tracer uptake is evident in the liver, with higher tracer retention relative to background at 180 minutes compared to 90 minutes. Physiological uptake of ^{18}F-FMISO along the colon is also observed

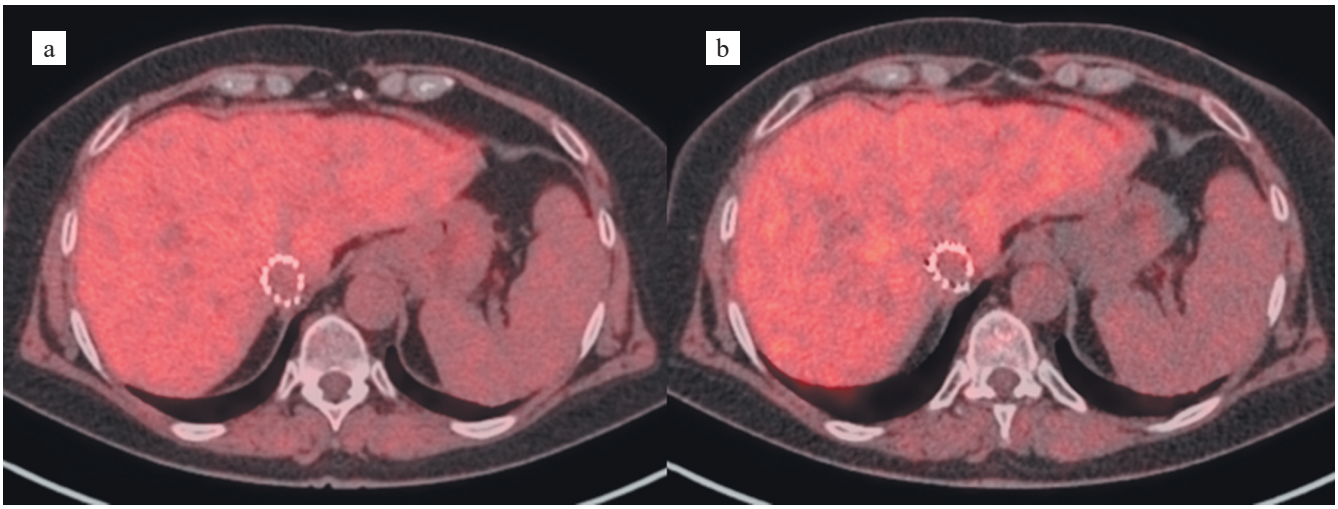

Fig. 3. Axial fused PET/CT images with ^{18}F-FMISO (native CT): (a) at 90 minutes post-injection; (b) at 180 minutes post-injection. Diffuse tracer uptake is evident in the liver, with higher tracer retention relative to background at 180 minutes compared to 90 minutes

maceutical at 180 minutes after injection compared to 90 minutes, supporting the presence of hypoxic changes in the liver graft.

CONCLUSION

Based on the obtained data confirming the presence of hypoxia in the liver graft 27 months after transplantation, the authors consider this method promising for the diagnosis of perfusion-related changes in the liver transplant leading to hypoxia. However, further refinement of the technique and accumulation of additional clinical cases are necessary to validate its effectiveness, both in the early and late post-transplant periods.

The authors declare no conflict of interest.

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