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ORIGINAL ARTICLE

In vivo microcomputed tomography visualization of a hepatocellular carcinoma orthotopic model using a contrast based on LaF_3:Ce(5 %)Tb(15 %) nanoparticles

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ABSTRACT

Purpose of the study. To investigate the effectiveness of a new contrast agent based on LaF_3:Ce(5 %)Tb(15 %) nanoparticles on a hepatocellular carcinoma orthotopic model.

Materials and methods. The experiment was performed on female BALB/c Nude mice. The subcutaneous model was created by injecting Hep G2 tumor cell culture into the right side of the animals. The orthotopic models were obtained by implanting a fragment of a subcutaneous Hep G2 xenograft into the left lobe of the liver of mice. Colloidal water solutions of LaF_3:Ce(5 %) Tb(15 %) nanoparticles were prepared by dispersing the nanoparticle powder in bidistilled water using an ultrasonic tube for 30 minutes. Two samples with different nanoparticle sizes (13 and 60 nm) were administered to mice intravenously in a volume of 200 µl at a concentration of 40 mg/ml. The assessment of changes in radiopacity of the internal organs of animals was carried out at different points in time (before nanoparticle injection, at 5 min, 30 min, 1 h, 2 h, 4 h, 24 h, 48 h, and 7 days after inlection) using microcomputer tomography on a Quantum GX2 device. On the 7th day of the experiment, animals were euthanized by dislocation of the cervical vertebrae, organs (liver and spleen) were collected and fixed in a 10 % solution of neutral formalin. Sections for histological examination and their staining were made according to the standard method.

Results. Microcomputer tomography (micro-CT) results indicated accumulation of both contrast samples in the spleen and healthy liver tissue within 5 minutes after intravenous injection, maintaining X-ray contrast for the 7-days. However, no specific accumulation of nanoparticles in the tumor was observed. Histological analysis revealed minimal impact on the liver structure and cells, with a more pronounced effect in the spleen.

Conclusion. These findings suggest that LaF_3:Ce(5 %)Tb(15 %) metal nanoparticles can be used in *in vivo* experiments for liver and spleen visualization after further investigation of their long-term effects.

Keywords: microcomputed tomography, hepatocellular carcinoma, HepG2, CDX model, mouse model, nanoparticles

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3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Микрокомпьютерная визуализация *in vivo* ортотопической модели гепатоцеллюлярной карциномы с применением контраста на основе наночастиц LaF_3:Ce(5 %)Tb(15 %)

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РЕЗЮМЕ

Цель исследования. Исследование эффективности нового контрастного агента LaF_3:Ce(5 %)Tb(15 %) на ортотопической модели гепатоцеллюлярной карциномы.

Материалы и методы. Эксперимент выполнен на самках мышей линии BALB/c Nude. Подкожная модель была получена введением в правый бок животных опухолевой культуры клеток Hep G2. Модель ортотопической гепатоцеллюлярной карциномы получили путем имплантации в левую долю печени мышей фрагмента подкожного ксенографта Hep G2. Коллоидные водные растворы наночастиц LaF_3:Ce(5 %)Tb(15 %) готовили путем диспергирования порошка нанокристаллов в бидистиллированной воде с помощью ультразвуковой трубки в течение 30 минут. Два образца наночастиц с разными размерами (13 и 60 нм) однократно вводили мышам внутривенно в объеме 200 мкл в концентрации 40 мг/мл. Оценка изменения рентгеноконтрастности внутренних органов животных проводилась в разных временных точках (до введения наночастиц, через 5 мин., 30 мин., 1 ч., 2 ч., 4 ч., 24 ч., 48 ч. и 7 дней после введения) с помощью микрокомпьютерной томографии на приборе Quantum GX2. На 7-й день эксперимента выполняли эвтаназию животных методом дислокации шейных позвонков, забор и фиксацию в 10 % растворе нейтрального формалина органов (печень и селезенка). Изготовление срезов для гистологического исследования и их окрашивание проводилось по стандартной методике.

Результаты. Микрокомпьютерная томография показала накопление обоих образцов контраста в селезенке и здоровой ткани печени уже через 5 минут после его внутривенного введения животным с сохранением рентгенконтраста в течение всех 7 дней эксперимента. Однако не было замечено специфического накопления наночастиц в опухоли. Гистологический анализ показал слабое воздействие на структуру и клетки печени и более выраженное – в селезенке.

Заключение. Наши результаты показывают, что металлические наночастицы LaF_3:Ce(5 %)Tb(15 %) могут быть использованы в экспериментах *in vivo*, где требуется визуализация печени и селезенки, после дополнительных исследований их долгосрочного влияния.

Ключевые слова: микрокомпьютерная томография, гепатоцеллюлярная карцинома, HepG2, CDX-модель, мышиная модель, наночастицы

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Соблюдение этических стандартов: исследование было рассмотрено и одобрено локальным биоэтическим комитетом ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (протокол № 9/219). Все эксперименты на животных были выполнены в соответствии с этическими принципами, установленными Европейской конвенцией по защите позвоночных животных

Финансирование: исследование выполнено при финансовой поддержке Министерства науки и высшего образования Российской Федерации в рамках государственного задания в сфере научной деятельности № FENW-2023-0019

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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INTRODUCTION

In vivo models on small laboratory animals have made a significant contribution to the study of the pathogenesis and development of cancer treatment methods, including liver cancer, which, according to Global Cancer Statistics for 2022, is the third leading cause of cancer death among both sexes [1]. Hepatocellular carcinoma (HCC) is the main histological type of liver cancer characterized by rapid progression and unfavorable prognosis. Despite the fact that new opportunities for screening programs, advanced diagnostic methods and treatments for HCC have emerged over the past decade, morbidity and overall survival rates remain unsatisfactory [2–3].

The creation of new drugs to improve the results of HCC treatment requires easily reproducible adequate models that are created by injecting tumor cell culture or implanting a tumor fragment in immunocompromised mice at a heterotopic (most often subcutaneous) or orthotopic site. The first option is easy to implement, the tumor nodes are available for measurements, which makes it easy and effective to track the response to treatment. The second option has the advantage of simulating the tumor-host interaction, organ-specific conditions, invasion and metastasis, and responses to therapy. However, it is technically more difficult: certain skills are required from the researcher, and tumor growth must be controlled using additional equipment [4].

Over the past decade, the number of publications using microcomputer tomography (micro-CT) in *in vivo* significantly increased. Even though micro-CT initially showed good images of only high-contrast structures, noticeable improvements in spatial and temporal resolution were achieved, which allowed researchers to obtain detailed anatomical images and track the progression of the disease in small laboratory animal models. In addition, contrast agents are used to increase the contrast of soft tissues [5–6].

Metal nanoparticles are a suitable candidate for use as contrast agents for micro-CT. Metal atoms have high atomic numbers and exceptional X-ray attenuation properties, therefore they provide a higher contrast enhancement than iodine preparations used in medical practice at the same concentration [7]. Depending on the purpose of the study, they can be modified: the size of the nanoparticles is changed, they are coated with organic molecules to increase biocompatibility, functional groups are added to increase specificity to certain tissues, which expands the possibility of their use not only in diagnosis, but also in cancer therapy [8–9].

The purpose of the study was to evaluate the effectiveness of a new contrast agent based on nanoparticles – LaF_3:Ce(5 %)Tb(15 %) on an orthotopic model of hepatocellular carcinoma.

MATERIALS AND METHODS

Female Balb/c Nude mice aged 10–12 weeks were taken into the experiment. The animals were kept at a temperature of 22 °C ± 1 °C, humidity 55 % ± 15 % and a 12/12-hour day/night cycle. Food and water were provided to the animals "ad libitum".

The culture of human hepatocellular carcinoma Hep G2 was used in the work. Tumor cells were cultured in DMEM medium (Gibco, Thermo Fisher Scientific), with 10 % veal serum (Gibco, Thermo Fisher Scientific) and 1 % antibiotic (penicillin/streptomycin), in a CO2 incubator (series 8000W, Thermo Fisher Scientific, USA) with a content of 5 % CO2 and a temperature of 37 °C.

All manipulations were performed under sterile conditions. Two female Balb/c Nude mice were subcutaneously injected with a tumor culture of Hep G2 cells at a concentration of 5×10^6 cells in 200 µl (Fig. 1a) in the right side. When the tumor nodes reached a volume of about 100 mm³, the animals were euthanized by dislocation of the cervical vertebrae, the xenographs were extracted and cut into fragments of 1 mm³ in size. Donor animals (10♀) were anesthetized according to the protocol described earlier [10].

Mice were placed on their backs, the skin and abdominal wall were excised along a white line of the abdomen measuring 30–40 mm and the left lobe of the liver was exposed, into which a previously isolated tumor fragment was implanted (Fig. 1b). Next, the liver was returned to the abdominal cavity, the abdominal wall and skin were sutured with a continuous surgical suture.

Measurement of the linear dimensions of subcutaneous xenografts was performed twice a week. The tumor volume was determined according to the formula:

$V = LW^2/2$,

where *L*, *W*, represent the linear sizes of the tumor nodes.

Two samples of LaF_3:Ce(5 %)Tb(15 %) nanoparticles were used in the work with different sizes (13 and 60 nm), which were obtained by hydrothermal synthesis. To obtain nanoparticles with different average sizes, synthesis was carried out at room temperature (size ~ 13 nm) and at 400 °C (size ~ 60 nm). Colloidal water solutions of LaF_3:Ce(5 %)Tb(15 %) nanoparticles were prepared by dispersing nanocrystal powder in bidistilled water using an ultrasonic tube for 30 minutes. The resulting solutions were administered once intravenously to mice in a volume of 200 µl at a concentration of 40 mg/ml (two groups of 5 animals each).

Microcomputer tomography was performed on a Quantum GX2 microCT device (Perkin Elmer, USA). During the scan, the animals were anesthetized with 2 % isoflurane (Laboratories Karizoo, S.A., Spain) using a RAS-4 anesthesia device (Perkin Elmer, USA). A total of 9 scans were performed for each mouse: before nanoparticle injection, 5 min, 30 min, 1 h, 2 h, 4 h, 24 h, 48 h and 7 days after administration. The scanning parameters were as follows: voltage – 80 kV, current – 90 µA, field of view – 86 mm × 72 mm, voxel size – 140 microns, scanning mode – high resolution, time – 4 min, 360° gentry rotation. The resulting images were analyzed in the Quantum GX2 software (Perkin Elmer, USA). The data was analyzed using Statistica 10 and presented as the "mean ± standard error of the mean".

7 days after the introduction of contrasts and the final scan, the animals were euthanized by dislocation of the cervical vertebrae. Fragments of the spleen and liver with tumor nodules were placed in a 10 % formalin solution for 24 hours. The fixed tissues were then poured into paraffin wax and, using a microtome, sections with a thickness of 5 microns were made onto positively charged specimens. The specimens were stained with hematoxylin and eosin. The finished histological preparations were examined by a pathologist.

STUDY RESULTS

A significant increase in contrast between the spleen and normal liver tissue was observed compared with the results obtained before the administration of the studied substances as early as 5 minutes after the introduction of 60 nm nanoparticles and 30 minutes after the introduction of 13 nm nanoparticles. The following scans, after 1, 2 and 4 hours, show the accumulation of contrasts in these organs (Fig. 2). There was no change in radiopaque contrast in the tumor tissue. After 24 hours, nanoparticles are slightly washed out of the liver,

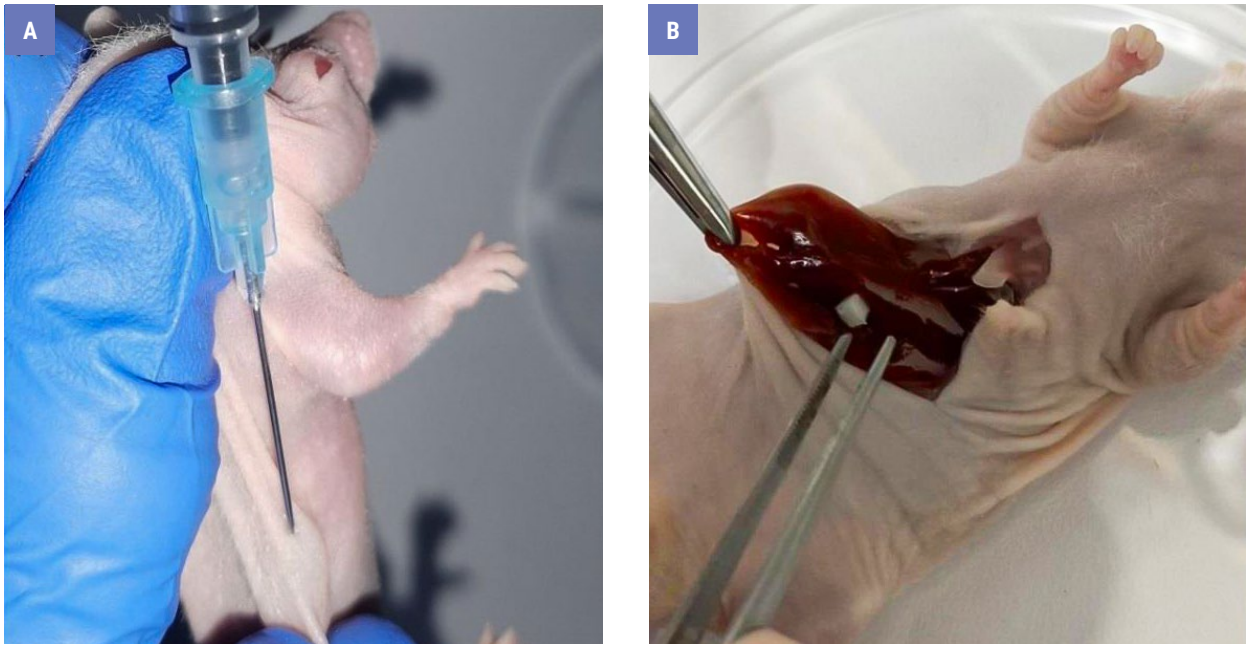

Fig. 1. The stages of an orthotopic HCC CDX model creation: a – subcutaneous injection of the HepG2 cell line with a sterile insulin syringe; b – transplantation of a tumor fragment into the left lobe of the liver

but they continue to accumulate in the spleen. The same dynamics is observed on scans performed after 48 hours and 7 days. There was no significant difference between the measured contrast enhancement of organs such as tumors, heart, and kidneys during the entire experiment.

The weight of the injected animals decreased slightly on the first and second days after the administration of contrasts and stopped after the 3rd day of the experiment (the total weight loss for each mouse was less than 10 %). On day 6, the weight of the mice returned to their initial values. There were no changes in other physical parameters and behavior of the animals during 7 days.

Before organ sampling, a macroscopic examination was performed for histological analysis. The liver of the mice had a red-brown color, and a tumor node was clearly visible in the left lateral lobe. The remaining 3 lobes of the liver – the right inner one with a mastoid process, the right lateral one with a caudate process and the left inner one were unchanged. The spleen of both animals was lighter than normal, enlarged, and free of blotches. No other internal organs were found to have pathological changes caused by the introduction of nanoparticles.

On all histological preparations, the liver retains its histostructure. Hepatocytes are arranged in thin trabeculae separated by sinusoidal vessels. The triads, portal tracts, and central veins are clearly distinguishable (Fig. 3a, b). Histological preparations (Fig. 3b, d) show that the tumor is clearly bounded from the normal liver tissue. Histopathological examination 7 days after the introduction of contrasts (Fig. 3c, d) showed that ectasia of the central veins is observed in the liver, mild inflammation, hepatocytes are slightly enlarged, their nuclei are larger with a finely dispersed chromatin distribution. In all samples, the lymphoid tissue of the spleen was divided by thin trabeculae and had the same density as the follicles in it. Reactive hyperplasia of lymphoid tissue and weak infiltration by macrophages were observed in the spleens of mice injected with contrast (Fig. 3g, h).

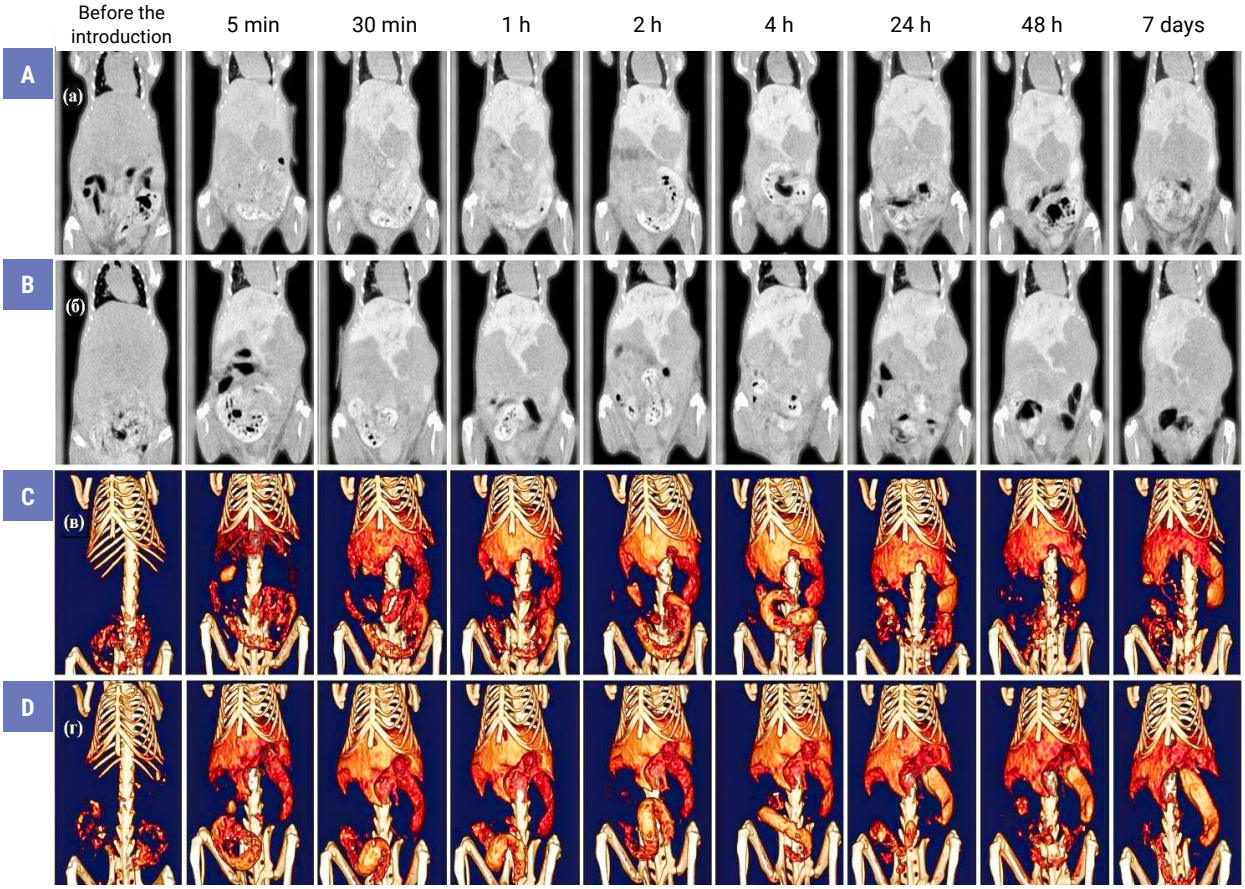

Fig. 2. *In vivo* microcomputer tomography results in 5 min, 30 min, 1 h, 2 h, 4 h, 24 h, 48 h and in 7 days after administration of LaF3: Ce(5 %)Tb(15 %) with nanoparticle size: a, c – 13 nm; b, d – 60 nm. a, b – CT images in coronal projection; c, d – 3D images

DISCUSSION

X-ray microcomputer tomography has gained great importance in recent decades. *In vivo* visualization of soft tissues of small laboratory animal models has become popular due to the introduction of various radiopaque substances that help to circumvent the limitation of low contrast of internal organs [6]. Metal nanoparticles can be used for this purpose, since metals have high X-ray attenuation and high density. Nanoparticles can also provide X-ray contrast for a long time [9].

In our work, we used LaF_3:Ce(5 %)Tb(15 %) nanoparticles of different sizes in orthotopic tumor models of HCC. The Hep G2 tumor cell line was used to create them. However, when trying to create a HCC model using the injection method, negative consequences arise: leakage of cell suspension from the puncture site and ingress into the abdominal cavity and, as a result, the formation of tumor nodules in other tissues and organs of the animal [11]. Therefore, in our work, we first obtained a subcutaneous xenograft from a cell line, and then it was used to create an orthotopic model of HCC.

Basic images (before contrasting) of xenographs were made on micro-CT for further visual and quantitative assessment of the effectiveness of the tested contrasts. After the introduction of LaF_3:Ce(5 %)Tb(15 %) nanoparticles showed rapid distribution in the tissues of the spleen and nor-

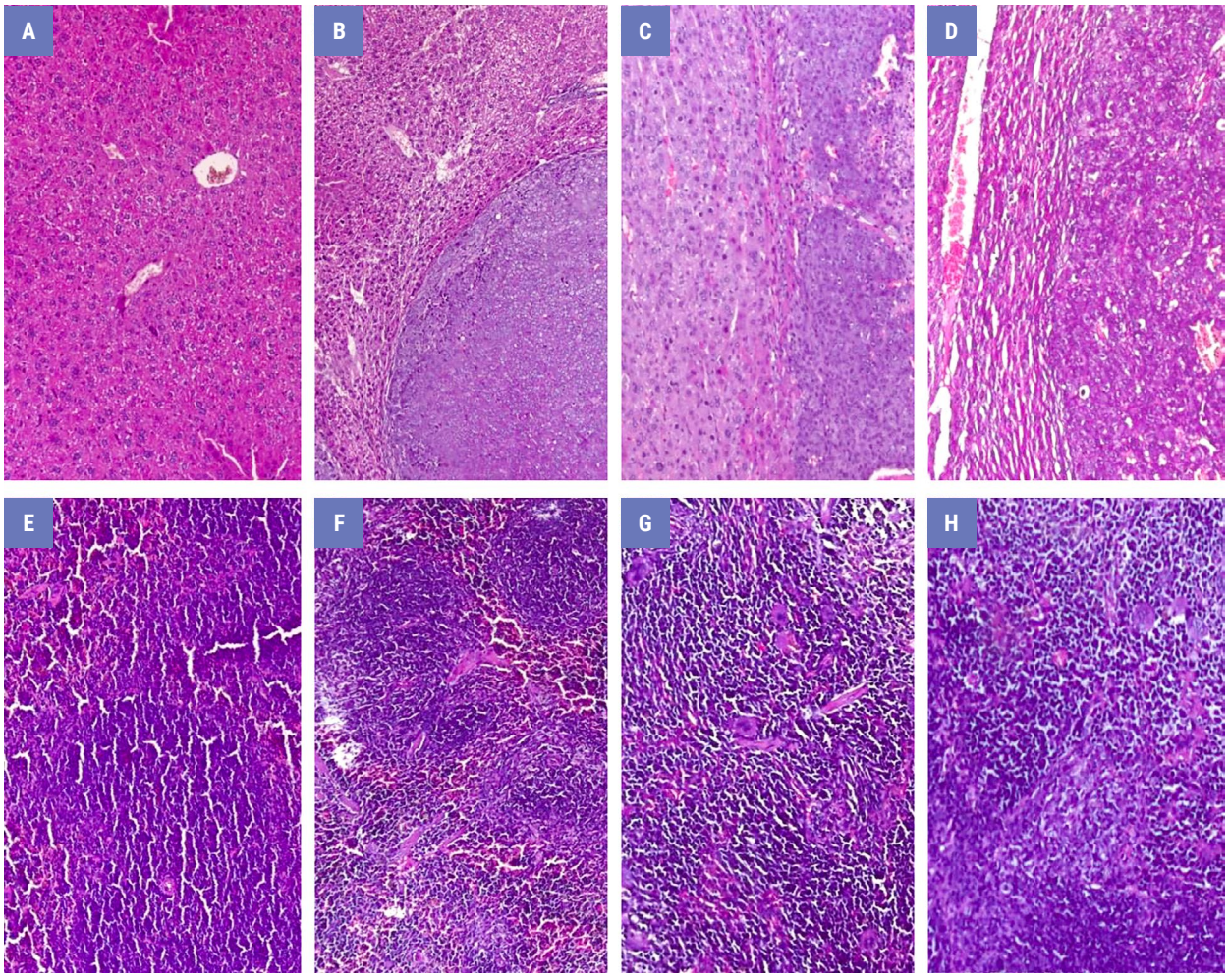

Fig. 3. Histopathological examination of the liver and spleen (100x): a – normal liver; b – liver with tumor without exposure; c – liver with tumor 7 days after administration of LaF3 nanoparticles: Ce(5 %)Tb(15 %) with a size of 13 nm; d – liver with a tumor 7 days after administration of LaF3: Ce(5 %)Tb(15 %) nanoparticles 60 nm in size; e – normal spleen; f – spleen taken from a mouse with a tumor in the liver, without exposure; g – spleen 7 days after administration of LaF3: Ce(5 %)Tb(15 %) nanoparticles with a size of 13 nm; h – spleen 7 days after administration of LaF3: Ce(5 %)Tb(15 %) nanoparticlessize 60 nm

mal liver tissue, high absorption in the X-ray range, and provided X-ray contrast during 7 days of the experiment. Nanoparticles with a size of 13 nm reached their maximum accumulation in the liver (241.18 ± 6.07 HU) 4 hours after their administration. Then there was a slow weakening of the radiopaque contrast in the organ. Accumulation in the spleen occurred gradually, and the maximum value of HU units was obtained on the last day of the experiment (272.4 ± 9.9 HU). A similar dynamic was observed for the second sample with a nanoparticle size of 60 nm. The maximum accumulation in the liver (230.19 ± 8.84 HU) was reached 30 minutes after the introduction of contrast, after which the radiopaque contrast in the organ weakened. For the spleen, the maximum value of HU units was also obtained on the last day of the experiment, but it was higher than the results obtained from the first sample (311.95 ± 9.36 HU).

There were no changes in the contrast ability of the other organs of the animals during the entire observation period. There was also no accumulation of contrast in tumor tissues, as, for example, in a study where gold nanoparticles with an average size of 50 nm were used, which were injected intravenously into a mouse model of breast cancer at a concentration of 4.8 mg/kg and a mouse model of fibrosarcoma at a concentration of 9.6 mg/kg [12]. The researchers noted the accumulation of nanoparticles in the tumor tissue of both models. The biodistribution could be influenced by the difference in the metals included in the nanoparticles, the presence of polyethylene glycol (PEG) coating on gold nanoparticles, the use of different tumor models, etc. We assume that the non-penetration of nanoparticles into the tumor nodes was due to their low vascularization. Therefore, additional studies using other *in vivo* tumor models are required.

Histological analysis revealed that both samples did not affect tumor cells, but caused mild inflammation in the liver and reactive hyperplasia in the spleen. As a rule, nanoparticles are removed from the bloodstream mainly by Kupffer cells of the liver and macrophages of the spleen [13], which explains the presence of the latter on histological preparations.

CONCLUSION

Both samples of LaF_3:Ce(5 %)Tb(15 %) nanoparticles have proven to be effective contrast agents for micro-CT imaging. Depending on the size of the nanoparticles, the time of their maximum accumulation in the liver and the maximum value of HU units in the spleen varied. Further work is required to study their safety profile and study the effects on the liver and spleen with a longer follow-up period. It is also promising to study possible modifications of some characteristics of nanoparticles, which will increase their accumulation directly in the tumor tissue.

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