

MULTIDISCIPLINARY APPROACH TO TREATMENT OF UNRESECTABLE LIVER METASTASES SEEDED BY LUMINAL BREAST CARCINOMA

Kolomiets KV [✉], Afashagova ZR, Erendzhenova DE, Bashirova AS, Falchari VV, Babayeva NE, Aliyeva AD, Kurmalieva RZ, Fedoseyev YB
Rostov State Medical University, Rostov-on-Don, Russia

Breast cancer (BC) remains the main oncological pathology in the female population. Liver metastases in such cases mean an extremely unfavorable prognosis of the course of the disease. The key predictor of clinical outcome of metastatic BC is the molecular biological subtype of the tumor. The main goals of treatment of metastatic BC are to increase life expectancy, alleviate tumor-related symptoms, and maintain or improve patients' quality of life. Transarterial chemoembolization (TACE) enables new ways of liver metastases control. This article presents a case of application of TACE in combination with hormone therapy and selective inhibitors of CDK4/6 in a patient with unresectable liver metastases seeded by hormone-receptor positive (ER+/PR-) breast carcinoma with an unknown Her2 status (2+). The approach allowed achieving regression of the oncological process in the liver to the point of unclear CT visualizations of metastatic foci, and proper disease control in the course of 28 months.

Keywords: breast cancer, transarterial chemoembolization, hormone therapy, taxanes, selective inhibitors of cyclin-dependent kinases (CDK 4/6), liver metastases

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✉ **Correspondence should be addressed:** Karina V. Kolomiets
Krasnoarmeyskaya st., 198, Novocherkassk, 346400, Russia; karina_kolomiets_99@mail.ru

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МУЛЬТИДИСЦИПЛИНАРНЫЙ ПОДХОД К ЛЕЧЕНИЮ НЕРЕЗЕКТАБЕЛЬНОГО МЕТАСТАТИЧЕСКОГО ПОРАЖЕНИЯ ПЕЧЕНИ ПРИ ЛЮМИНАЛЬНОМ РАКЕ МОЛОЧНОЙ ЖЕЛЕЗЫ

К. В. Коломиец [✉], З. Р. Афашагова, Д. Э. Эрендженова, А. С. Баширова, В. В. Фалчари, Н. Э. Бабаева, А. Д. Алиева, Р. З. Курмалиева, Ю. Б. Федосеев

Ростовский государственный медицинский университет, Ростов-на-Дону, Россия

Рак молочной железы (РМЖ) остается основной онкологической патологией у женского населения. Наличие метастазов в печени при РМЖ определяет крайне неблагоприятный прогноз течения заболевания. Молекулярно-биологический подтип опухоли является главным предиктором клинического исхода при метастатическом РМЖ. Основной целью лечения метастатического РМЖ является увеличение продолжительности жизни, уменьшение симптомов, связанных с опухолью, поддержание или улучшение качества жизни пациентов. Внедрение трансартериальной химиоэмболизации (ТАХЭ) открыло новые возможности контроля над метастатическим поражением печени. В статье представлен клинический случай использования методики ТАХЭ в комбинации с гормонотерапией, а также селективными ингибиторами циклин-зависимых киназ CDK4/6 у пациентки при нерезектабельном метастатическом поражении печени карциномы молочной железы с положительным гормональным статусом (ER+/PR-) и неопределенным Her2-статусом (2+). Подход позволил достигнуть регресса онкологического процесса в печени, вплоть до отсутствия четкой визуализации метастатических очагов в ней при компьютерной томографии органов брюшной полости, а также контролировать течение заболевания на протяжении 28 месяцев.

Ключевые слова: рак молочной железы, трансартериальная химиоэмболизация, гормонотерапия, таксаны, селективные ингибиторы циклин-зависимых киназ CDK 4/6, метастатическое поражение печени

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✉ **Для корреспонденции:** Карина Викторовна Коломиец
ул. Красноармейская, д. 198, г. Новочеркасск, 346400, Россия; karina_kolomiets_99@mail.ru

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Breast cancer (BC) is the most common neoplasm that remains the main oncological pathology in the female population. In 2022, 2,296,840 new BC cases were registered in the world (first-time oncological diagnoses), and the disease was pronounced cause of death for 666,103 fatalities. As for the Russian Federation (RF), in 2020, there were 75,052 (12.7%) new cases of BC diagnosed there, and 23,130 lethal outcomes caused by it [1]. This is a very heterogeneous disease, with different molecular profiles, which are clinically divided into three main subtypes by the hormone receptors involved (estrogen receptors, ER; progesterone receptors, PR; human epidermal growth factor receptor 2, HER2 or ERBB2), and into luminal

ER-positive and PR-positive, which are further subdivided into luminal A and B, HER2-positive and triple-negative BC. Nuclear protein Ki-67 encoded by the MK167 gene is also regarded as a marker of tumor's proliferation, since neoplasms of the least mature and differentiated cells are the most active in this respect [2]. The mandatory component of a BC treatment protocol is drug therapy: it can significantly increase life expectancy of patients with extensive or metastatic cancer, which prevent full recovery, and up the number of patients that recover from early stages of the disease [3].

The median overall survival (OS) after detection of BC-seeded liver metastases is 18–24 months; five- and ten-year survival

rates in such cases are 27% and 13%, respectively. Without effective treatment of metastatic liver damage, the prognosis is extremely unfavorable, with patients living a maximum of 4 through 8 months [4]. The best OS after detection of such damage is 38 months, peculiar to HER2-positive subtypes with mandatory anti-HER2 therapy in the background. In triple-negative BC cases, the median survival of patients with foci in the liver is only 9 months. For luminal A- and B-subtypes, OS fluctuates within a very large range and depends on the therapy regimen; the median before administration of iCDK is 21 months. These inhibitors significantly increase progression-free survival and OS in metastatic BC patients, even when there are liver metastases. In the placebo group, the median OS of patients without metastatic liver damage was 51.7 months, and metastases reduced this indicator to 36.1 months. Ribociclib allowed prolonging lives of such patients by 10 months, with median OS increasing to 46.5 months. Cyclin-dependent kinases (CDK4 and CDK6) are activated upon formation with D-cyclins; they play a major role in signaling pathways regulating cell cycle and cell proliferation. There are three CDK4/6 inhibitors — palbociclib, ribociclib, and abemaciclib — available for women with advanced or metastatic breast cancer, HR⁺ as well as HER2⁻. Three large-scale randomized trials PALOMA-2, MONALEESA-2, and MONARCH-3 have confirmed the efficacy of including palbociclib, ribociclib, and abemaciclib, respectively, to first-line therapy regimens for menopausal women in combination with aromatase inhibitors. Systemic therapy is the basis of treatment of metastatic BC [5, 6].

Adoption of radiographically controlled endovascular surgery methods, such as TACE, opened new ways to control liver metastases. This technique involves injection of a combination of chemotherapy drugs and microspheres, which slow down and stop supply of oxygen and nutrients to the tumor, into arteries that feed it. This minimally invasive method is applicable to both primary and metastatic cancers. It was developed and first applied in the late 1970s. Currently, the technique is used against tumors of various localizations; in particular, it is a common and effective choice in cases of unresectable liver metastases that originate from neoplasms in the colon, mammary glands, lungs, soft tissue sarcomas and melanomas. Depending on the extent of the lesion, TACE can be palliative treatment, or a procedure in the context of preparation of the patient to surgery, radiofrequency ablation, radiation therapy, etc. [7]. The preferred combinations include doxorubicin (or similar) and 5-fluorouracil, administered simultaneously with taxanes.

There is a systematic analysis of studies investigating application of TACE in cases of BC seeding liver metastases [8].

The researchers explored respective papers published from 2000 through 2017, and included only 10 of them into their work, with the total sample comprised of 519 patients. In that sample, only TACE was used in 78.0% of cases, TACE and systemic chemotherapy — in 9.9% of cases, and systemic chemotherapy alone in 12.1% of cases. The analysis has shown that the patients who underwent TACE had higher OS (median of 7.3–47.0 months) and disease-free survival (in the range from 2.9 through 17.0 months) [8].

This study aimed to evaluate the efficacy of a multidisciplinary approach to a case of liver metastases seeded by BC, the said approach involving TACE combined with taxanes (docetaxel), selective CDK4/6 inhibitors, and hormonal therapy.

Case description

A 57-year-old patient was diagnosed with right breast cancer in 2018 (C50), pT2N3M0, st IIIc, cl.gr. 2; the diagnosis was followed by radical mastectomy (RME) on the right side, remote gamma therapy (RGT), hormone therapy (tamoxifen).

Control examination results

Results of chest and abdominal CT, 22.12.2021: lungs without focal and infiltrative changes; density of liver parenchyma uneven, multiple metastatic foci up to 2.6 cm in both lobes (previously undiscovered) (Fig. 1A, B).

Despite multiple liver metastases, biliary tract was not compressed, and the patient's skin and mucous membranes had physiological color. She did not complain of itching, considered her condition satisfactory, and her biochemical indicators were within the reference ranges.

Results of US examination of mammary glands, 22.12.2021: no signs of recurrence and palpable abnormalities.

Results of immunohistochemical (IHC) examination of a liver metastasis sample (trephine biopsy), 29.12.2021: confirmed metastasis seeded by breast carcinoma, ER⁺/PR⁻ and unknown Her2 status (2⁺).

In view of the extent of the process and the results of IHC examination, the patient was recommended hormone therapy: letrozole 2.5 mg per day orally protractedly, ribociclib 600 mg per day orally from the 1st to the 21st days, interval of 7 days.

Diagnosis: (C50) right breast cancer, pT2N3M0, st IIIc, cl. gr. 2, complex treatment in 2018-2019 — RME on the right side, RGT, hormone therapy, December 2021 — progression (HER).

The patient self-referred to the clinic of Rostov State Medical University in December 2021; factoring in the volume of liver damage, the history of the disease and the results of

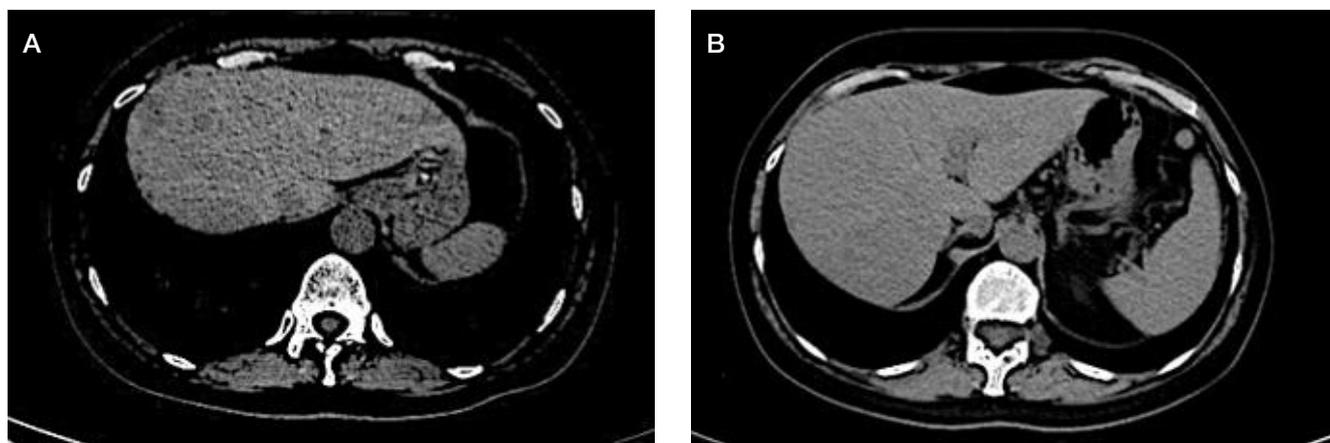


Fig. 1. A, B. Abdominal CT, 22.12.2021. multiple metastatic foci (size up to 2.6 cm) in both lobes

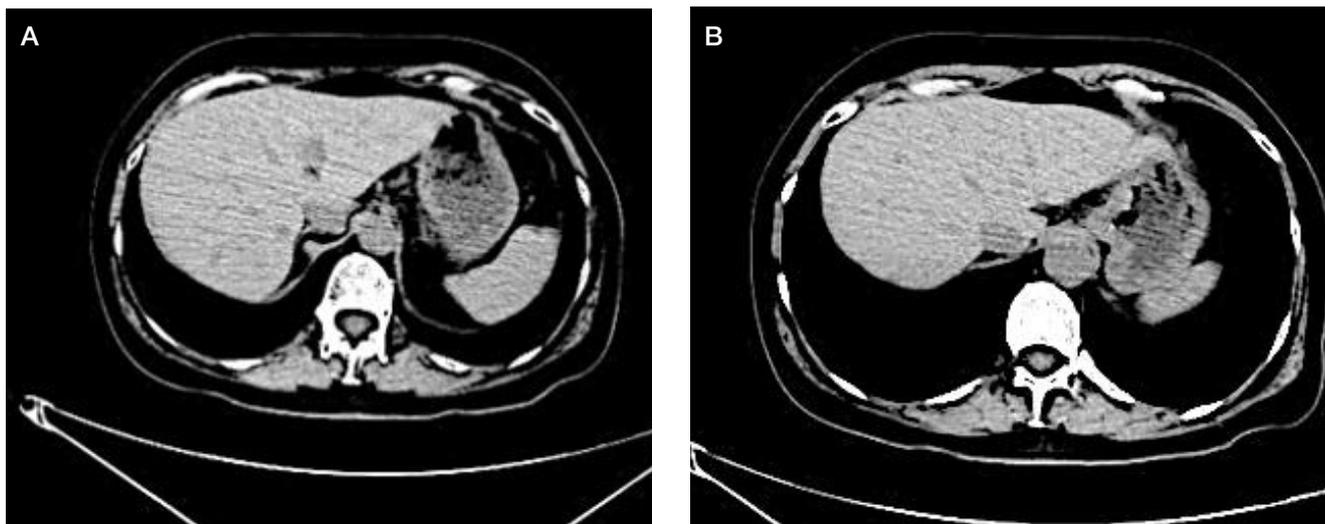


Fig. 2. A, B. Abdominal CT, 04.05.2022. Multiple metastatic foci (size up to 2.6 cm) in both lobes, uneven opacification; no changes since December 2021

instrumental examinations, as well as the extent of the process, the council decided it was expedient to include locoregional therapy (TACE) in the treatment regimen.

On 27.01.2022, the patient underwent TACE aimed at metastatic foci in the liver (docetaxel 150 mg + microspheres). When discharged, the patient assessed her condition as satisfactory, despite the volume of metastatic foci; her body temperature was slightly elevated during the first day after TACE. Further, as per recommendations of the chemotherapist, she received hormone therapy (anastrozole) and CDK4/6 inhibitors.

Description of the surgical intervention

Under aseptic conditions of the operating room with radiographic control equipment, following the required surgical field treatment, the patient, supine, had her left radial artery punctured in a typical location (angiographic needle 18G), using the Seldinger technique (introducer 5F 11 cm). Through a 035" 180 cm hydrophilic conductor, an H1 125 cm catheter was sequentially inserted into the left brachial, axillary, subclavian arteries, descending thoracic aorta. Removal of the conductor was followed by aortography, which established that the celiac trunk deviates at the L1 level. Celiac trunk's mouth was selectively catheterized: cranial position, splenic artery not dilated, convoluted, gastric branches (anastomoses) not found hypertrophied. The common hepatic artery could not be visualized; left hepatic artery branches from the celiac trunk, and in the middle section, the gastroduodenal artery branches off it. Selective catheterization of the superior mesenteric artery yielded visualization of the right hepatic artery extending from the proximal part of the superior mesenteric artery. The left and then the right hepatic arteries were selectively catheterized; angiography visualized hypervascular lumps in the projection of both lobes of the liver. Afferent tumor arteries were superselectively catheterized using a 1.98F microcatheter in a 014" 165 cm microconductor. Falciform ligament artery was embolized with a Concerto 5 × 15 cm spiral (protection against inappropriate embolization). Saturated with a chemotherapy drug (docetaxel 150 mg), 150–200 nm HepaSphere microspheres (Merit Medical; USA) were injected to achieve chemoembolization of arteries supplying blood to metastatic foci. Then microcatheter was removed. Control angiography revealed a significantly slower opacification in segmental branches of hepatic artery that deliver blood to multiple tumor foci. There were no signs of inappropriate embolization. The

catheter was withdrawn into the aorta; control angiography revealed right and left hepatic, gastroduodenal, and superior mesenteric arteries to be uncompromised. The instruments were removed sequentially, with introducer pulled out last. Hemostasis by compression — 8 min (stable). The operative field was treated with alcohol and covered with an aseptic pressure bandage.

The postoperative pharmacotherapy included:

- analgesia: ketoprofen 100 mg IM twice a day for 5 days; drotaverine 40 mg IM twice a day for 5 days;
- prevention of thromboembolic complications: parnaparin sodium 0.3 ml SC once a day for 7 days;
- infusion therapy: for hepatoprotective purposes — remaxol 400 ml IV once a day for 3 days, for prevention of ulcerative complications — NaCl 0.9% 500 ml + 40 mg omeprazole IV once a day for 3 days.

Results of chest and abdominal CT, 04.05.2022: no focal and infiltrative changes in the lungs, liver parenchyma density uniform, multiple metastatic foci (size up to 2.6 cm) in both lobes accumulate contrast (Omnipak) unevenly, no changes since December 2021. Given the extent of damage to the liver, process dispersion and dynamics, in was decided to keep liver TACE in the treatment plan (Fig. 2A, B).

The decision to repeat TACE was made on 18.05.2022.

The patient underwent chemoembolization of metastatic foci in the liver and parenchymal chemoembolization of arteries supplying the foci (lipiodol 10 ml + docetaxel 150 mg). A hemostatic sponge suspension was used for arterial embolization. After surgery, the patient was prescribed pharmacotherapy as recommended earlier, after the first TACE of 27.01.2022, and subsequent therapy with hormones (anastrozole) and CDK4/6 inhibitors.

Control examination of 18.07.2022 included CT of the brain, chest and abdominal organs. Conclusion: no pathological changes discovered in the brain, neck, chest organs; multiple metastatic foci (size up to 2.1 cm) identified in both lobes of the liver (Fig. 3A, B).

Given the extent of damage to the liver, process dispersion and dynamics, in was decided to keep liver TACE in the treatment plan.

The decision to repeat TACE was made on 26.07.2022. Metastatic foci in the liver were chemoembolized. After superselective catheterization, right gastric artery was embolized (to prevent inappropriate embolization) using Amplatzer Vascular Plug II 9-AVP2-016 vascular occluder (Abbot; USA).



Fig. 3. A, B. Abdominal CT, 18.07.2022. Multiple metastatic foci (size up to 2.1 cm) in both lobes of the liver; positive dynamics compared to 04.05.2022

Chemoembolization (docetaxel 150 mg + hemostatic sponge suspension) was performed after superselective catheterization of afferent tumor arteries. After surgery, the patient was prescribed pharmacotherapy as recommended earlier, after the first TACE of 27.01.2022.

Following studies were conducted to verify the results achieved.

Abdominal CT, 26.09.2022: the contours of the liver are smooth, clear, the liver not enlarged, parenchyma's density uniform, multiple metastatic foci (size up to 2.1 cm) in both lobes of the liver (unchanged since 18.07.2022) (Fig. 4A, B).

Abdominal CT, 30.11.2022: parenchyma's density uniform, multiple metastatic foci (size up to 1.5 cm) in both lobes of the liver. Positive dynamics, size and number of foci reduced since 26.09.2022. The effectiveness of TACE was evaluated a month later using CT/MRI scans with intravenous contrasting, relying on RECIST 1.1 (Response evaluation criteria in solid tumours); the evaluation confirmed a partial response, regression: >30% of the sum of the largest sizes (long axes) of foci. Given the extent of damage to the liver, process dispersion and dynamics, in was decided to keep liver TACE in the treatment plan (Fig. 5A, B).

The decision to repeat TACE was made on 05.12.2022. The patient was hospitalized on 05.12.2022, and on 06.12.2022 she underwent 4th TACE procedure, aimed at liver metastases. Chemoembolization (docetaxel 150 mg + hemostatic sponge suspension) was performed after superselective catheterization of afferent tumor arteries.

After surgery, the patient was prescribed pharmacotherapy as recommended earlier, after the first TACE of 27.01.2022.

Further, as per recommendations of the chemotherapist, she received hormone therapy (anastrozole) and CDK4/6 inhibitors.

On 01.03.2023, a control abdominal CT has shown the following: parenchyma's density uniform, single metastatic foci (size up to 0.9 cm) in both lobes, smaller compared to 30.11.2022; positive dynamics confirmed with RECIST 1.1 (Fig. 6A, B).

On 03.06.2023, the patient visited chemotherapist as scheduled; positive dynamics, satisfactory haematological parameters and absence of somatic contraindications allowed recommending continuation of hormone therapy: CDK4/6 inhibitors — ribociclib 600 mg or palbociclib 125 mg orally from day 1 to day 21, with an interval of 7 days, protractedly, a cycle of 28 days, plus aromatase inhibitors — letrozole 2.5 mg or anastrozole 1 mg daily, protractedly.

Results of chest and abdominal CT, 03.10.2023: metastatic foci in the liver not visualized clearly since 01.03.2023; parenchyma's density uniform, without localized condensation or rarefaction spots (Fig. 7A, B).

Given the positive dynamics, satisfactory haematological parameters and absence of somatic contraindications, it was recommended to continue with the combined therapy: CDK4/6 inhibitors — ribociclib 600 mg or palbociclib 125 mg orally from day 1 to day 21, with an interval of 7 days, protractedly, a cycle of 28 days, plus aromatase inhibitors — letrozole 2.5 mg or anastrozole 1 mg daily, protractedly.

Results of CT, 15.01.2024: no pathological changes discovered in the brain, neck, chest organs; metastatic foci in the liver not visualized clearly since 03.10.2023;



Fig. 4. A, B. Abdominal CT, 26.09.2022. Multiple metastatic foci (size up to 2.1 cm) in both lobes of the liver; no changes since 18.07.2022

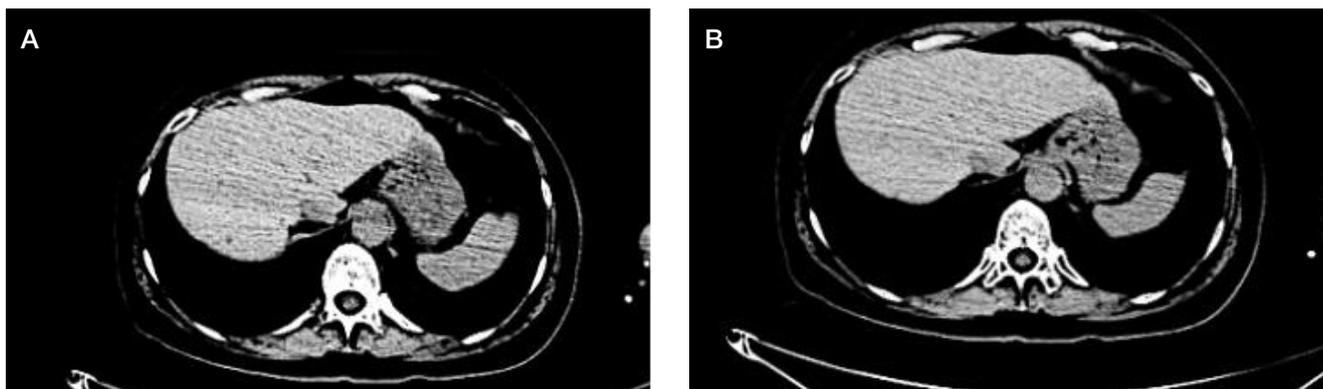


Fig. 5. A, B. Abdominal CT, 30.11.2022. Metastatic foci (size up to 1.5 cm) in both lobes of the liver; positive dynamics compared to 26.09.2022

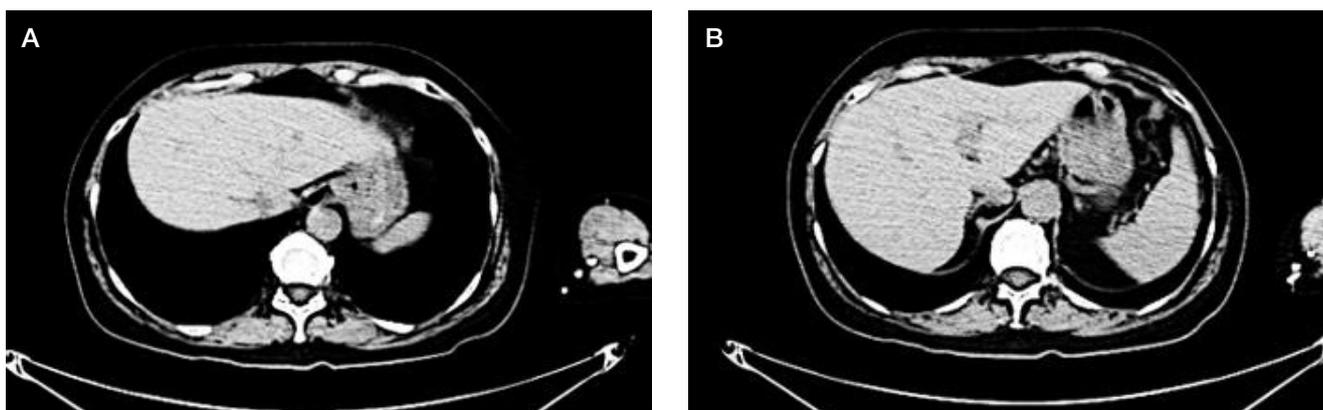


Fig. 6. A, B. Abdominal CT, 01.03.2023. Singular metastatic foci (size up to 0.9 cm) in both lobes of the liver; size of the foci decreased compared to 30.11.2022

Positive dynamics allowed suggesting continuation of the combined therapy; with the aim at preventing osteoporosis and mitigating the recurrence risk, the following was recommended:

- bisphosphonates (zoledronic acid 4 mg IV, once in 6 months);
- colecalciferol 400–800 IU/day orally, daily, plus calcium carbonate 500–1000 mg/day orally, daily, protractedly;
- densitometry (bone mineral density control) once a year.

Results of CT, 16.04.2024: no pathological changes discovered in the brain, neck, chest organs; metastatic foci in the liver not visualized clearly since 15.01.2024 (no negative dynamics).

It was recommended to continue combined therapy.

The therapy did not cause significant toxic effects, dose adjustment was not required; ALT and AST values spiked periodically. Currently, the patient follows the recommendations of the chemotherapist. She considers her condition to be

satisfactory, has no active complaints. The treatment does not affect her quality of life.

Case discussion

Liver metastases shorten life expectancy of breast cancer patients significantly: the median OS, according to the SEER registries, is 20 months [9].

Surgery prescribed in connection with liver metastases seeded by hormone-receptor positive BC with unknown Her2 status (2+) involved TACE and injection of microspheres, with two effects: firstly, prolonged ischemia caused by microspheres blocking arterial flow to the tumor, and secondly, gradual release of high-concentration docetaxel from those microspheres pre-saturated therewith, which occurred in the immediate vicinity of the metastases, thus minimizing systemic side effects.

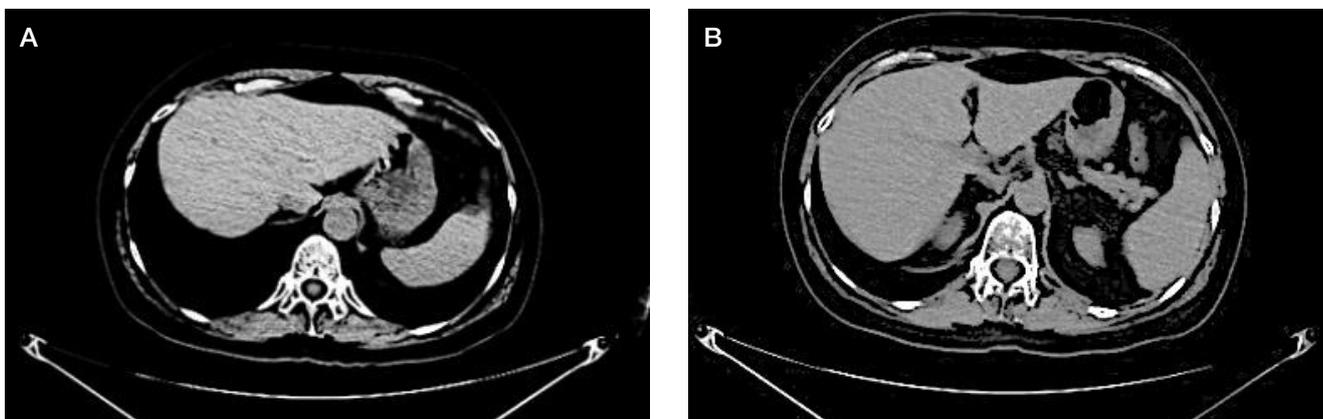


Fig. 7. A, B. Abdominal CT, 03.10.2023. Metastatic foci in the liver not visualized clearly since 01.01.2023 (positive dynamics)

Hormone therapy and selective CDK4/6 inhibitors (ribociclib) underpin significant achievements in the treatment of tumors and demonstrate encouraging results (as part of the first line regimens, they help overcome the five-year threshold), which significantly improves respective prognoses. In the context of MONALEESA-3 randomized trial, tested both as a first and a second line regimen drug, ribociclib proved to be highly effective in the cohort of patients with metastatic liver damage (poorest prognoses), contributing to the increase of their life expectancy to 1 year, and in a heterogeneous population of patients, it enabled growth of OS to 36.1 months (median value).

CONCLUSION

The combination of contemporary methods of treatment, such as TACE, and classic approaches to BC-seeded liver

metastases requires further investigation, since it helps to improve the patients' quality of life and increase disease-free and overall survival.

Effective multidisciplinary approach that involved TACE, selective CDK4/6 inhibitors (improved progression-free survival, increased life expectancy, preserved high quality of life), and hormone therapy, was practiced in treatment of a patient with unresectable liver metastases seeded by hormone-receptor positive BC (ER⁺/PR⁻) with unknown Her2 status (2⁺), and yielded regression of the oncological process in the liver and rendered CT visualization of metastatic foci there unclear. When this report was prepared, the patient has been receiving therapy for metastatic breast cancer for 28 months. Absence of clearly visualized metastatic foci in her liver can be an important indicator of the effectiveness of combination therapy in this patient.

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