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Comparative Evaluation of Intraarterial Therapy Methods for Hepatocellular Cancer

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Aim: to compare various methods of intraarterial therapy for hepatocellular carcinoma (HCC) in terms of survival, adverse events, and cost-effectiveness.
Key points. Hepatocellular carcinoma is a malignant liver tumor that originates from hepatocytes. This form of liver cancer is the most common and accounts for 85 % of cases. HCC is the seventh most common cancer and the third leading cause of cancer death worldwide. Unfortunately, the majority of patients with HCC are diagnosed at an advanced stage, when surgical treatment is impossible. Thus, new methods of therapy (including intraarterial) appear, which allow saving the lives of these patients. At present, new intraarterial methods of treatment include transarterial chemoinfusion (TACI), conventional transarterial chemoembolization (cTACE), drug-eluting-beads-TACE (debTACE) and radioembolization (RE).
Conclusion. As a result of studying various sources of world literature about comparing intraarterial methods of HCC treatment, a final table was compiled, which presents the main characteristics of each method. The methods have their advantages and disadvantages, however, according to the criteria of overall survival and progression-free survival, debTACE is in the lead. The most inexpensive method of those presented is TACI, however, in terms of economic efficiency, the method is not a priority, because for treatment with this method, a greater number of cycles is required, compared, for example, with TACE. The radioembolization is associated with the lowest risk of adverse events.
Keywords: hepatocellular carcinoma, chemoembolization, conventional transarterial chemoembolization, radioembolization, transarterial chemoinfusion
Conflict of interest: the authors declare no conflict of interest.

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Сравнительная оценка методов внутриартериальной терапии при гепатоцеллюлярном раке

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Цель: сравнение различных методик внутриартериальной терапии гепатоцеллюлярного рака (ГЦР) по показателям выживаемости, нежелательных явлений и экономической эффективности.
Основные положения. Гепатоцеллюлярный рак — злокачественная опухоль печени, которая исходит из гепатоцитов. Данная форма рака печени является наиболее частой и составляет 85 % случаев. ГЦР находится на седьмом месте по распространенности среди всех видов рака и является третьим по причинам смертности среди онкологических заболеваний во всем мире. К сожалению, у подавляющего большинства пациентов ГЦР диагностируется уже на прогрессирующей стадии, когда хирургическое лечение невозможно. Появляются новые методы терапии (в том числе внутриартериальной), которые позволяют спасать жизни данных пациентов. На настоящий момент к новым внутриартериальным методам лечения относят химиоинфузию в печеночную артерию (ХИПА), масляную химиоэмболизацию (М-ХЭПА), химиоэмболизацию лекарственно-насыщенными микросферами (ХЭПА-ЛНМ) и радиоэмболизацию (РЭ).
Заключение. В результате изучения различных источников мировой литературы на предмет сравнения внутриартериальных методов лечения ГЦР была составлена итоговая таблица, в которой приведены основные

характеристики каждого из методов. Методы имеют свои преимущества и недостатки, однако по критериям общей выживаемости и выживаемости без прогрессирования лидирует метод ХЭПА-ЛНМ. Самый недорогостоящий метод из представленных — ХИПА, однако в аспекте экономической эффективности метод не является приоритетным, так как лечение данным методом предусматривает большее количество циклов по сравнению, к примеру, с методиками ХЭПА. С наиболее низким риском нежелательных явлений сопряжена методика радиоэмболизации.

Ключевые слова: гепатоцеллюлярный рак, химиоэмболизация, масляная химиоэмболизация, радиоэмболизация, химиоинфузия в печеночную артерию

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Introduction

Hepatocellular carcinoma (HCC) is a malignant liver tumor that originates from hepatocytes. This form of liver cancer is the most common and accounts for 85 % of cases [1].

HCC is the seventh most common cancer and the third leading cause of death among cancer diseases worldwide. Men are susceptible to the disease two to three times more often than women [2].

The diagnosis of HCC is established in patients at risk (suffering from viral hepatitis or liver cirrhosis of various etiologies) based on specific pathognomonic signs of laboratory (aimed at assessing liver function), instrumental (aimed at assessing the prevalence of the tumor process) studies, as well as on the basis of the results of pathological examination of biopsy or surgical material [1, 2]. The most commonly used staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC) classification (Fig.). The BCLC classification not only determines the stage of the cancer process but also links it to optimal treatment options and prognosis [3].

Treatment and strategy selection are based on the clinical staging system for cancer patients [4] and determined by a special multidisciplinary HCC team.

Intraarterial therapy methods include transarterial chemoinfusion (TACI), conventional transarterial chemoembolization (cTACE), drug-eluting-beads-TACE (debTACE) and radioembolization (RE). Absolute contraindications to transarterial treatment include decompensated liver cirrhosis, high tumor load, impaired portal blood flow, intractable ascites, severe coagulation disorders, presence of portal shunt, gastrointestinal bleeding in the last three months, and renal failure (creatinine clearance 30 mL/min). Radical treatment includes liver resection, orthotopic liver transplantation, as well as the use of radiofrequency, microwave ablation and other locally destructive ablative methods [1].

Palliative treatment is aimed at improving the quality and increasing the life expectancy. It includes various methods of embolization and systemic chemotherapy [1].

Unfortunately, the majority of patients with HCC are diagnosed at a progressive stage, when the tumor is inoperable. Thus, new methods of intraarterial tumor therapy are emerging, which allow saving the lives of these patients [5–7]. The relevance of the problem allows us to formulate the **aim of the study** — to highlight the data of world literature on the possibilities of endovascular surgery in the treatment of patients with HCC, analysis and comparison of various methods of intraarterial therapy for HCC.

Application of endovascular techniques in HCC

Transarterial chemoinfusion (TACI)

Since the 1990s, an alternative treatment for HCC, transarterial chemoinfusion (TACI), has become widespread in Japan. The technique involves intraarterial administration of chemotherapy drugs through a port implanted under the skin. This procedure provides direct delivery of the chemotherapy drug through the arteries feeding the tumor and minimizes the toxic effect on the liver, while providing a higher response rate (22–48 %) than with systemic chemotherapy (8–21 %) [8–10]. There are several TACI regimens. The most common ones include cisplatin monotherapy (CDDP); low doses of cisplatin in combination with 5-fluorouracil (5-FU or LFP); interferons in combination with 5-fluorouracil (FAIT) [9]. The antitumor effect of cisplatin is due to the formation of inter- and intra-strand covalent bonds with DNA by direct interaction with guanine or adenine. The response rate from cisplatin administration in advanced HCC varies from 14 to 42 %.

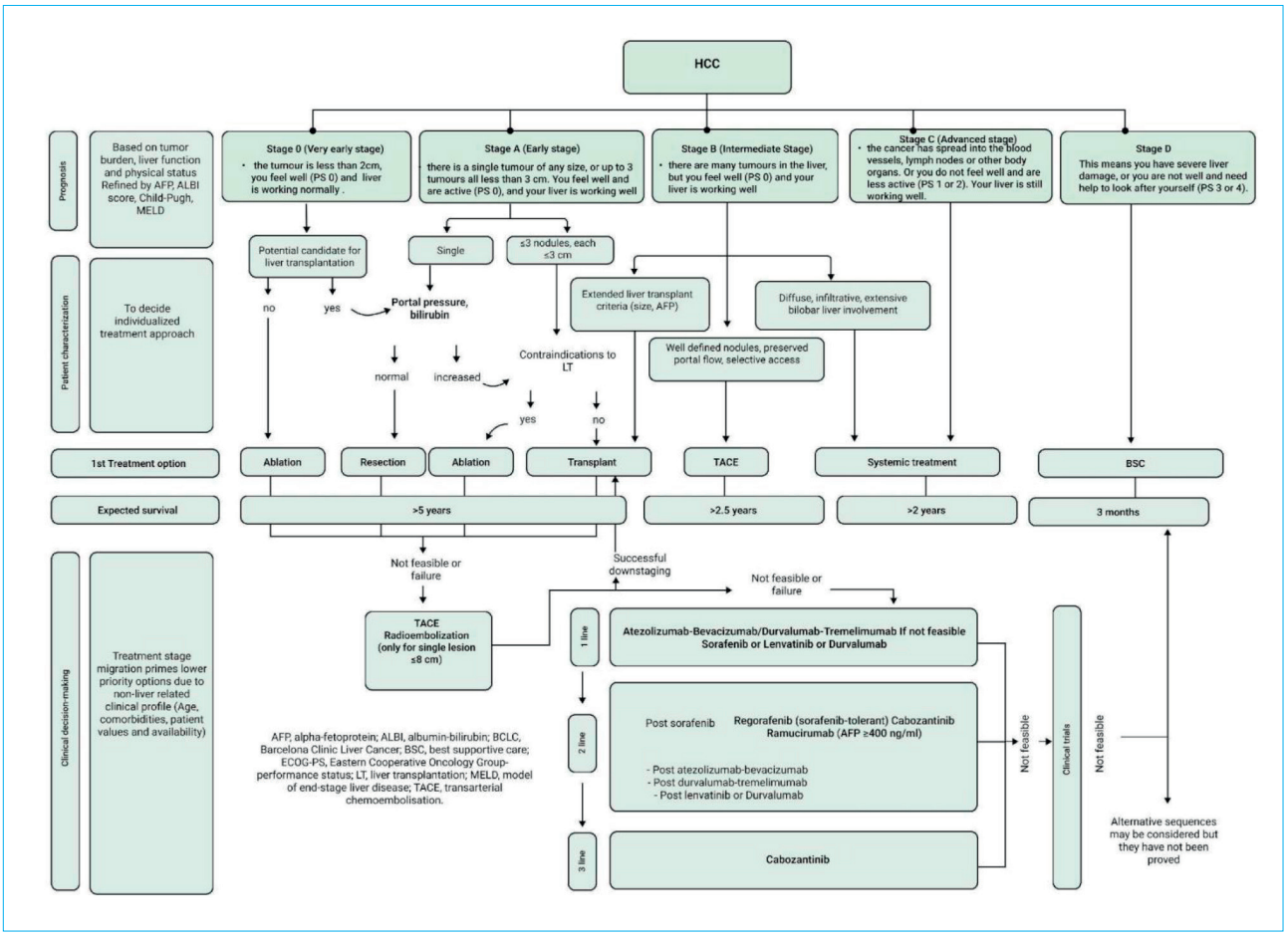

Figure. Barcelona Clinic Liver Cancer (BCLC) classification

Рисунок. Барселонская система стадирования рака печени (Barcelona Clinic Liver Cancer, BCLC)

Low-dose cisplatin (CDDP) in combination with 5-fluorouracil is a regimen in which a small amount of cisplatin (10 mg/m^2 per day, days 1–5) reverses the effects of 5-FU (250 mg/m^2 per day, days 1–5) administered continuously.

In the FAIT regimen, interferons enhance their antitumor effect by directly inhibiting tumor cell proliferation and indirectly affecting angiogenesis [10].

One of the most common drugs for the systemic treatment of HCC is sorafenib. However, treatment with this drug alone has a disappointing prognosis, and the median survival is from 5.5 to 7.2 months [8].

The clinical advantages of TACI include the following points: the ability to perform TACI on patients with class B on the Child — Pugh scale; Child — Pugh scores practically do not decrease as a result of TACI treatment; TACI is a much more effective technique for patients with vascular invasion; TACI has a less systemic effect on non-tumor cells, acting locally. The disadvantages include technical difficulties in installing a catheter with a reservoir; control techniques for checking the catheters; adverse events associated with port migration, catheter dislocation, arterial occlusion, occlusion of the reservoir system, subcutaneous hematomas or infection [10].

In an open randomized phase 3 study, N. Lyu et al. (2022) analyzed and compared TACI treatment with sorafenib [11]. Between May 2017 and May 2020, patients were randomly assigned to either the TACI treatment group (n = 130) or the sorafenib treatment group (n = 132) in a 1 : 1 ratio. Patients in the TACI group underwent arterial biopsy and catheterization before treatment. One cycle was three weeks long, and FOLFOX (oxaliplatin 130 mg/m^2, leucovorin 200 mg/m^2, fluorouracil 400 mg/m^2, and fluorouracil 2400 mg/m^2) was administered each cycle. A total of 406 treatment cycles were completed, with an average of three cycles per patient. The median duration of therapy was 11 weeks. Approximately 13 % of patients had their FOLFOX dose reduced,

and 7 % had their treatment interrupted due to drug toxicity. The main complication during oxaliplatin infusion was acute abdominal pain (in 40.6 % of patients), which was relieved by reducing the rate of drug administration or symptomatic therapy. No patient discontinued treatment due to infusion complications. Non-acute catheter-related complications were observed in 4.7 % of cases.

The average duration of treatment in the sorafenib group was 3.5 months. The average dose of the drug was 614.0 mg. Treatment was interrupted in 93 % of patients for various reasons. Of these, 52.7 % were due to disease progression, 19.4 % were due to adverse drug effects, 9.3 % were due to worsening liver function, 6.2 % were due to worsening ECOG-PS, and 5.4 % were due to the patient's unwillingness to undergo treatment.

The median follow-up time in the TACI group was 17.1 months, while in the sorafenib group it was 19.8 months. The analysis showed longer survival of patients receiving TACI (overall survival — 13.9 months) compared to sorafenib treatment (8.2 months). The median progression-free survival in the TACI group was 7.8 months compared to 4.3 months in the sorafenib group.

Thus, in this study, the TACI technique showed longer overall survival and progression-free survival of patients compared to sorafenib therapy.

The first studies on TACI demonstrated that the technique leads to uniform distribution of the chemotherapy drug in the capillary network of both the tumor location and the regional metastasis zones, but researchers needed to improve treatment results. In this regard, ideas about a combination of intraarterial and systemic chemotherapy began to appear.

Currently, there is evidence that TACI in combination with sorafenib gives the most favorable results, which are demonstrated by various clinical studies. In 2019, a randomized open-label phase 3 study by M.K. He et al. was conducted, which involved 247 patients [12]. The observation was carried out for 10 months. Patients were randomly assigned to two groups: a group receiving sorafenib (n = 122) and a group receiving sorafenib in combination with TACI (sorafenib + TACI) (n = 125). Treatment was divided into 3-week cycles. Patients in both groups received sorafenib 400 mg orally twice a day from day 1 to day 21, TACI was performed every 3 weeks. In the sorafenib + TACI group, femoral artery puncture and catheterization were performed on the first day of each cycle. The TACI regimen was as follows: oxaliplatin 80 mg/m^2 (hours 0 to 2 on day 1), leucovorin 400 mg/m^2 (hours 2–3 on day 1), fluorouracil 400 mg/m^2 bolus on the third hour and 2400 mg/m^2 over 48 hours on days 1 and 2. Before each new TACI cycle, a new catheterization was performed. On average, there were four TACI cycles per patient. The duration of sorafenib treatment was longer in patients in the group receiving sorafenib with TACI, but the doses were the same. The median survival in the group of patients receiving sorafenib with TACI was 13.37 months, in contrast to the group receiving sorafenib only (7.13 months).

The median progression-free survival in the sorafenib + TACI group was 7.03 months, in the sorafenib group — 2.6 months.

Adverse events from treatment occurred in 10 % of the total sample and were approximately equal in each of the groups (118 in the sorafenib + TACI group and 109 in the sorafenib group). Adverse events of grade 3–4 were most common in patients in the sorafenib + TACI group. Also, abdominal pain was noted in 34 patients in the sorafenib + TACI group, which was relieved by reducing the infusion rate or stopping TACI. Thirty days after stopping the study treatment, 3 deaths related to treatment and not dependent on disease progression occurred (two in the sorafenib + TACI group and one in the sorafenib group) [8]. Thus, this study showed the advantages of sorafenib therapy in combination with TACI in terms of overall survival and progression-free survival, and the percentage of adverse events remained approximately equal for both groups.

The number of studies devoted to the analysis of the efficacy and safety of combined intraarterial and systemic chemotherapy also included an open-label randomized multicenter study by M. Ikeda et al. (2016), which assessed and compared the treatment of patients with sorafenib and a combination of sorafenib with TACI [13]. From June 2011 to December 2013, 108 patients took part in the study, who were randomly distributed into two groups with 1 : 2 ratio: group 1 — patients receiving sorafenib (n = 42), group 2 — patients receiving sorafenib + TACI with cisplatin (n = 66). Patients in both groups were administered sorafenib orally at a dose of 400 mg twice daily. Patients in the sorafenib + TACI group received cisplatin at a dose of 65 mg/m^2 throughout the cycle through a catheter placed in the native left or right hepatic artery or another feeding artery for 4–6 weeks. The average number of cisplatin administrations was 2 times, and the average drug concentration was 222 mg. The dose intensity of sorafenib was 488 mg/day in the sorafenib only group and 540 mg/day in the sorafenib + TACI group. Over time, the dose of sorafenib was required to be reduced by 49.2 % and 63.4 % in groups 1 and 2, respectively. For patients in the sorafenib group, treatment lasted 86 days on average (range: 6–449 days), and for patients in

the sorafenib + TACI group — 75 days (range: 4–881 days).

According to the results of the study, 37 and 49 patients died in the sorafenib group and the sorafenib + TACI group, respectively. The median survival in each group was 8.7 months in group 1 and 10.2 months in group 2.

HCC progression was observed in 39 patients in group 1 and in 61 patients in group 2, and the average progression time was 2.8 months and 3.1 months, respectively.

Adverse events from treatment (neutropenia, leukopenia, hypohemoglobinemia, hyponatremia, thrombocytopenia, nausea) were more common in patients in the sorafenib + TACI group. However, these adverse events were not serious, and this therapy can be considered well tolerated.

From an economic point of view, this combination with TACI in treatment is relatively advantageous and amounted to approximately 2000 USD per procedure [13]. Thus, the study showed the advantage of the sorafenib + TACI group over the sorafenib group in terms of overall survival. At the same time, the percentage of cases of HCC progression in the sorafenib + TACI group was almost twice as high as the number of cases in the sorafenib group.

Thus, it can be said that the TACI gives relatively good survival results, compared with classical methods of systemic chemotherapy. The combination of systemic chemotherapy and TACI also has an advantage in survival over classical systemic chemotherapy. The summary data of the studies presented are contained in Table 1.

Transarterial chemoembolization (TACE)

Transarterial chemoembolization is a standard method of treating inoperable hepatocellular carcinoma [14].

Drug-eluting-beads-TACE (debTACE) and conventional transarterial chemoembolization (cTACE)

The debTACE technique involves the introduction of spherical microspheres into the hepatic artery that release drugs with an antitumor agent [15].

The exact size of the microparticles plays a decisive role in the effectiveness of vascular embolization. Thus, there is evidence that for occlusion of the distal branches of the hepatic artery, the optimal size of the microspheres should be

Table 1. Comparison of the results of the TACI studies
Таблица 1. Сравнение результатов исследований ХИПА

Authors *Авторы*	Aim of the study *Цель исследования*	Subject groups *Группы пациентов*	Results *Результаты*
Lyu N. et al. [11]	Comparison of TACI and sorafenib *Сравнение ХИПА с сорафенибом*	TACI / *ХИПА* *n* = 130	OS — 13.9 months PFS — 7.8 months *ОВ — 13,9 мес.* *ВБП — 7,8 мес.*
		Sorafenib / *Сорафениб* *n* = 132	OS — 8.2 months PFS — 4.3 months *ОВ — 8,2 мес.* *ВБП — 4,3 мес.*
He M.K. et al. [12]	Comparison of sorafenib + TACI combination and sorafenib *Сравнение комбинации «Сорафениб + ХИПА» с сорафенибом*	Sorafenib + TACI *Сорафениб + ХИПА* *n* = 125	OS — 13.37 months PFS — 7.03 months *ОВ — 13,37 мес.* *ВБП — 7,03 мес.*
		Sorafenib / *Сорафениб* *n* = 122	OS — 7.13 months PFS — 2.6 months *ОВ — 7,13 мес.* *ВБП — 2,6 мес.*
Ikeda M., Shimizu S., Sato T., et al. [13]	Comparison of sorafenib + TACI combination and sorafenib *Сравнение комбинации «Сорафениб + ХИПА» с сорафенибом*	Sorafenib + TACI *Сорафениб + ХИПА* *n* = 66	OS — 10.2 months Progression — 61 patients *ОВ — 10,2 мес.* *Прогрессирование — 61 чел.*
		Sorafenib / *Сорафениб* *n* = 42	OS — 8.7 months Progression — 39 patients PT — 2.8 months *ОВ — 8,7 мес.* *Прогрессирование — 39 чел.* *ВП — 2,8 мес.*

Note: *TACI — transarterial chemoinfusion; OS — overall survival; PFS — progression-free survival; PT — progression time.*
Примечание: *ХИПА — химиоинфузия в печеночную артерию; ОВ — общая выживаемость; ВБП — выживаемость без прогрессирования; ВП — время прогрессирования.*

40–100 μm, and for embolization of the proximal branches of the hepatic artery, the optimal size is 300 μm [16].

One of the advantages of debTACE is the creation of a comparatively high concentration of the drug within the tumor with a relatively lower systemic concentration than cTACE [17]. However, due to the fact that the antitumor agent penetrates and blocks the sinusoids, portal vein, and hepatic arterial microanastomoses, ischemia may also affect non-tumor surrounding tissues. Thus, the treatment may cause liver damage [14].

cTACE was developed in the 1980s and is the standard of treatment for intermediate-stage HCC and remains one of the most widely used intraarterial methods for the treatment of HCC [16,18,19]. This procedure is performed by administering a mixture of epirubicin and lipiodol to concentrate the drug within the tumor. This is achieved using a gelatin sponge, which creates occlusion of the tumor-feeding arteries in order to lead to infarction and necrosis of tumor tissue. cTACE is widely used due to the high penetration of embolic agents into capillaries and good diffusion capacity [20]. However, due to tissue clearance and blood purification, the drug can be easily excreted without providing stable embolization. Disadvantages also include a high risk of adverse events, such as pulmonary and cerebral embolism, hypersensitivity reaction, and decompensation of chronic liver failure [16, 19]. The oil suspension enters both tumor and healthy tissues. However, the muscular layer of arteries of tissue unaffected by the tumor removes the oil drug, and tumor vessels, which do not have a muscular apparatus, retain the chemoembolizate in the tumor for a long time [21]. A number of studies have been devoted to the issue of the effectiveness of the cTACE technique in comparison with other methods of HCC therapy. Thus, a randomized phase 3 study by Q.J. Li et al. (2022) was devoted to a similar goal, where the effectiveness of cTACE and TACI techniques was analyzed and compared [22]. From October 2016 to November 2018, 315 patients were selected and randomly assigned to the TACE group (n = 156) and the TACI group (n = 159). Eight patients from the TACI group transferred to the TACE group, while 20 people from the TACE group transferred to the TACI group.

For chemoembolization, 50 mg of epirubicin and 50 mg of lobaplatin in a mixture with lipiodol were used. Then, embolization was performed with the introduction of polyvinyl alcohol particles. In this case, the TACE cycles were repeated every 6 weeks.

For the implementation of TACE, oxaliplatin 130 mg/m^2 from hours 0 to 2 on day 1, leucovorin 400 mg/m^2 from hours 2 to 3 on day 1, and fluorouracil 400 mg/m^2 continuously for 3 hours on day 1, 400 mg/m^2 for 24 hours were used. TACE cycles were repeated every 3 weeks up to 6 cycles.

The median overall survival in the TACE group was 23.1 months, which is longer than in the TACE group (16.1 months). The median progression-free survival was 17.9 months in the TACI group and 10.4 months in the TACE group. The frequency of increased aspartate aminotransferase, alanine aminotransferase and hyperbilirubinemia was recorded more often in the TACE group. Abdominal pain was the most common adverse event in the TACI group (37 patients). Catheter displacement occurred in 12 patients in the TACI group; gastric ulcers were observed in 4 patients in this group, and one patient developed gastrointestinal bleeding. In the TACI group, 16 % of patients received a dose reduction of oxaliplatin due to specific abdominal pain.

Thus, in this study, TACI showed the highest overall survival and progression-free survival compared to the TACE group. At the same time, adverse events in the form of abdominal pain became the most common in the TACI group. The possibility of effectively combining intraarterial methods of HCC therapy has also been actively studied by researchers. Thus, in a randomized study by B. Li et al. (2021), the effectiveness of cTACE in combination with transarterial chemoinfusion was studied in comparison with cTACE without chemoinfusion [23]. A total of 83 patients were included in the study, who were randomly divided into cTACE (n = 42) and cTACE + TACI (n = 41) groups. The cTACE included 30 mg/m^2 epirubicin, 200 mg/m^2 carboplatin and 4 mg/m^2 mitomycin C mixed with 2–5 mL lipiodol. After that, 20 mL of additional lipiodol was injected into the target artery to stasis of blood flow in the artery feeding the tumor. Repeated TACE sessions were performed at intervals of 4 weeks.

Chemoembolization in the cTACE + TACI group was performed with 30 mg/m^2 of epirubicin with 2–5 mL of lipiodol, then lipiodol was administered without the mixture. Then, a catheter was inserted into the target artery for FOLFOX TACI: 85 mg/m^2 oxaliplatin infusion for 2 hours, 400 mg/m^2 leucovorin infusion for 2 hours, and 400 mg/m^2 5-FU bolus and 2400 mg/m^2 continuous infusion for 48 hours (high-dose 5-FU, received by 24 patients, from August 2017 to November 2018) or 1200 mg/m^2 continuous infusion for 23 hours (low-dose 5-FU, received by 17 patients, from December 2018 to June 2019).

The cTACE + TACI procedure was performed every 4 weeks. The average follow-up period was 27.6 months (cTACE — 47.8 months, cTACE +

TACI — 19.6 months). Overall survival was 13.5 months in the cTACE group and was unknown in the cTACE + TACI group. Median survival to progression was 9.2 months in the cTACE group and was not available for analysis for the cTACE + TACI group. It turned out that 48.8 % received conversion resection in the cTACE + TACI group, while this figure was only 9.5 % of patients in the cTACE group.

Thus, within the limits of this study, it can be concluded that combination therapy allowed to obtain conversion liver resection to a significantly higher extent than cTACE. The optimal criteria for choosing between cTACE and debTACE are not completely clear, so there are currently a relatively large number of studies analyzing and comparing the effectiveness of debTACE with cTACE [14]. Thus, according to a multicenter prospective randomized controlled study by M. Ikeda et al. (2022), the effectiveness of debTACE and cTACE was compared in patients with inoperable HCC [14]. All subjects (199 patients) were randomly divided into two groups with 1 : 1 ratio, receiving debTACE (n = 98) and cTACE (n = 101), respectively. debTACE was performed using microspheres saturated with epirubicin (75 mg) mixed with a non-ionic contrast agent. Particles of 100–300 μm were used, no more than two injections per TACE session. The maximum dose of epirubicin was no more than 150 mg per session. The TACE procedure was successful in both groups. The concentration of epirubicin was approximately the same in both groups (22.5 mg in the debTACE group, 25 mg in the cTACE group). Seven patients in the debTACE group received additional microspheres unloaded with the drug.

One month after treatment, tumor response was assessed using CT and MRI. According to the results, after one month, the tumor response rate was 35.7 % in patients in the debTACE group and 84.2 % in patients in the cTACE group, and after three months — 27.6 and 75.2 %, respectively. Adverse events associated with post-embolization syndrome (fever, fatigue, nausea, abdominal pain, increased liver enzymes) were observed more often in the cTACE group: loss of appetite — 28.7 % in the cTACE group, 12.2 % in the debTACE group; abdominal pain — 23.8 % in the cTACE group, 8.2 % in the debTACE group;, hypoalbuminemia — 69.4 and 4.4 %, respectively; increased aspartate aminotransferase — 81.2 and 35.7 %, respectively; increased alanine aminotransferase — 77.2 and 35.7 %, respectively.

Thus, cTACE has proven to be the most effective method: a higher tumor response rate was observed within the study. However, at the same time, adverse events in the form of post-embolization syndrome were observed significantly more often in the cTACE groups than in the debTACE group.

The issue of comparing TACE methods was also addressed in the work of Q. Shi et al. (2022). A retrospective study was conducted to evaluate the clinical results of cTACE and debTACE [24].

The sample included 312 patients (140 in the debTACE group and 172 patients in the cTACE group). The groups were compared according to the criteria of overall survival (OS), progression-free survival (PFS). Thus, according to the results of the analysis, the PFS rate in the debTACE group was 11.5 months vs. 9 months for cTACE, and the OS rate in the debTACE group was 24 months vs. 19.2 months in the cTACE group.

Thus, the analysis of the methods according to survival criteria showed that debTACE can be an effective method for the treatment of inoperable HCC (Table 2).

Radioembolization

Radioembolization (RE) of the hepatic artery involves the introduction of radioactive microspheres into the artery feeding the tumor for subsequent irradiation [25]. Thus, unlike chemoembolization, which is based on ischemia due to vascular occlusion and the delivery of chemotherapy drugs, in radioembolization the key role in antitumor effectiveness is played by selective irradiation of tumor cells using isotopes. Also, microparticles for radioembolization have a much smaller diameter compared to microspheres used in TACE (35 μm compared to 300 μm). As a rule, yttrium-90 (^{90}Y) is used for radioembolization, which is a high-energy source with a short half-life (64.1 hours) and a sufficient range to penetrate tissue (2.5 mm). At the same time, such a range allows for a decrease in the radiation load on tissues [26]. The mechanism of action of microspheres for RE is the generation of free radicals due to the ionization of water molecules. Thus, free radicals irreversibly disrupt the structure of DNA and cause apoptosis of tumor cells. Within two weeks after injection, more than 95 % of the radiation passes into the tissues surrounding the vessels embolized with microparticles [25].

The advantages of this technique include minimal post-embolization syndrome, delivery of high doses of radiation without relative harm to healthy liver parenchyma [25, 27]. One of the disadvantages of the technique is the high cost of the procedure [28].

A number of studies have been devoted to the research of factors affecting the survival of patients with HCC. One of such works is the study of F. Kolligs et al. (2023), which analyzed 422 patients with HCC who received RE with ^{90}Y microspheres

Table 2. Comparison of the results of TACE studies
Таблица 2. Сравнение результатов исследований ХЭПА

Authors *Авторы*	Aim of the study *Цель исследования*	Subject groups *Группы пациентов*	Results *Результаты*
Li Q.J. et al. [22]	Comparison of cTACE and TACI *Сравнение методик М-ХЭПА и ХИПА*	cTACE / *М-ХЭПА* *n* = 156	OS — 16.1 months PFS — 10.4 months *ОВ — 16,1 мес.* *ВБП — 10,4 мес.*
		TACI / *ХИПА* *n* = 159	OS — 23.1 months PFS — 17.9 months *ОВ — 23,1 мес.* *ВБП — 17,9 мес.*
Li B. et al. [23]	Comparison of cTACE + TACI and cTACE *Сравнение комбинации М-ХЭПА + ХИПА и М-ХЭПА*	cTACE + TACI *М-ХЭПА + ХИПА* *n* = 41	OS — unknown PFS — unknown Conversion resection — 48.8 % *ОВ — неизвестна* *ВБП — неизвестна* *Конверсионная резекция — 48,8 %*
		cTACE / *М-ХЭПА* *n* = 42	OS — 13.5 months PFS — 9.2 months Conversion resection — 9.5 % *ОВ — 13,5 мес.* *ВБП — 9,2 мес.* *Конверсионная резекция — 9,5 %*
Ikeda M. et al. [14]	Comparison of cTACE and debTACE *Сравнение методик М-ХЭПА и ХЭПА-ЛНМ*	debTACE *ХЭПА-ЛНМ* *n* = 98	Tumor response rate: after 1 months — 35.7 % after 3 months — 27.6 % Adverse events: loss of appetite — 1.2 % abdominal pain — 8.2 % hypoalbuminemia — 4.4 % *Уровень ответа опухоли:* *через 1 мес. — 35,7 %* *через 3 мес. — 27,6 %.* *Нежелательные явления:* *потеря аппетита — 1,2 %* *боли в животе — 8,2 %* *гипоальбуминемия — 4,4 %*
		cTACE / *М-ХЭПА* *n* = 101	Tumor response rate: after 1 months — 84.2 % after 3 months — 75.2 % Adverse events: loss of appetite — 28.7 % abdominal pain — 23.8 % hypoalbuminemia — 69.8 % *Уровень ответа опухоли:* *через 1 мес. — 84,2 %* *через 3 мес. — 75,2 %.* *Нежелательные явления:* *потеря аппетита — 28,7 %* *боли в животе — 23,8 %* *гипоальбуминемия — 69,8 %*
Shi Q. et al. [24]	Comparison of cTACE and debTACE *Сравнение методик М-ХЭПА и ХЭПА-ЛНМ*	debTACE *ХЭПА-ЛНМ* *n* = 140	OS — 24 months PFS — 11.5 months *ОВ — 24 мес.* *ВБП — 11,5 мес.*
		cTACE / *М-ХЭПА* *n* = 172	OS — 19.2 months PFS — 9 months *ОВ — 19,2 мес.* *ВБП — 9 мес.*

Note: *cTACE — conventional transarterial chemoembolization; TACI — transarterial chemoinfusion; debTACE — drug-eluting-beads-TACE; OS — overall survival; PFS — progression-free survival.*
Примечание: *М-ХЭПА — масляная химиоэмболизация печеночной артерии; ХИПА — химиоинфузия в печеночную артерию; ХЭПА-ЛНМ — химиоэмболизация лекарственно-насыщенными микросферами; ОВ — общая выживаемость; ВБП — выживаемость без прогрессирования.*

in the period from January 2015 to December 2017 [29]. The mean follow-up time was 11.1 months, and the mean age of patients was 67 years. The statistical analysis showed that the median overall survival for HCC treatment was 16.5 months, and the progression-free time was 6.1 months. A total of 36.7 % of patients experienced one or more adverse events. Based on the relatively good survival data and adverse event rate in this study, it can be concluded that RE is an effective treatment for HCC.

To determine the duration of response and objective response rate among patients with solitary inoperable HCC, a multicenter, single-case retrospective study was conducted [30]. The study included 162 patients who received radioembolization with TheraSphere glass microspheres from January 2014 to December 2017. As a result of statistical analysis, the best and confirmed objective response rates were 88 and 72 %, respectively. The average time to achieve the best confirmed response was 3.9 months. The average duration of response was 11.8 months. Overall survival of the entire sample was 94.8 % at 24 months and 86.6 % at 36 months. Thus, the observed indicators suggest that tumors respond well to yttrium-90 radioembolization.

To compare the efficacy and safety of the TACE and RE techniques, E. Dhondt et al. (2022) conducted a prospective, single-center, randomized, controlled study [31]. From September 2011 to March 2018, 487 patients were examined, and 72 of them were included in the study. Of the total sample, 38 patients were included in the radioembolization (RE) group and 34 in the debTACE group. Six patients from the RE group did not undergo the prescribed treatment.

debTACE was performed using microspheres of 100–300 μm, 300–500 μm in size using doxorubicin. Blood test monitoring was performed two weeks after each treatment and three months later. Liver MRI or CT was performed at three-month intervals. Thus, the participants were followed for 2 years. The median time to tumor progression was 17.1 months in the RE group and 9.5 months in the debTACE group, with a subgroup analysis of BCLC stage B HCC showing a median time to progression of 12.8 months in the RE group and 9.6 months in the debTACE group. 41 % of participants in the RE group and 53 % of participants in the debTACE group underwent postoperative treatment.

Adverse events of grade 3 or higher were observed in 39 % of patients in the RE group and in 53 % of the debTACE group. Within 6 months after the last treatment, 6 deaths occurred (5 in the debTACE group and 1 in the RE group).

A meta-analysis of studies aimed at comparing the efficacy and safety of TACE and RE [32] included 17 studies involving 2465 patients. Twelve of the studies were retrospective cohort studies, one randomized and four prospective cohort studies. BCLC stage B was the most common (42.1 %), the second most common was stage A (30 %), and stage C was 29.0 %.

Eight of the 17 studies used cTACE. Five studies used debTACE and three studies used both. One study used DSM, a microsphere composed of hydrolyzed starch.

In terms of overall survival, no significant differences were found between TACE and RE. However, in two studies, the time to progression was significantly higher in the RE group than in TACE (17.5 months and 9.8 months, respectively).

The individual meta-analysis included 311 patients. The TACE group included 143 patients and 168 patients in the RE group. Cohort characteristics did not differ significantly between the two groups, but the proportion of patients with BCLC stage A was higher in the TACE group. The analysis of overall survival did not show significant differences between the two groups. Adverse events according to different studies were observed in 10–73 % of TACE patients and in 10–44 % of RE patients, and the incidence of grade 3–4 complications was approximately equal in both groups (around 4–30 %). The incidence of complications such as nausea and vomiting in one study was 55 % in the RE group compared to 16.5 % in the TACE group. In two studies, severe abdominal pain was noted as an adverse event in 73–83 % of patients in the TACE group and in 5–33 % of patients in the RE group. Diarrhea was observed in 21 % of the TACE group compared to 0 % in the RE group in one study.

Thus, data from various studies show that radioembolization can be a fairly effective and safe method for the treatment of HCC.

Comparison of intraarterial techniques with radioembolization has also found a place in other studies. Thus, in an open randomized prospective single-center phase 2 study, cTACE techniques were compared with RE [33]. Of 179 patients, only 45 agreed to be randomized. Thus, patients were randomly assigned to groups receiving chemoembolization (control group) and radioembolization (experimental group). The observation time in the cTACE group was 15.7 months, and in the RE group – 21 months. The results revealed the best indicators of time to progression in the RE group: in the cTACE group it was 6.8 months, in the RE group it was not reached (i. e., more than 21 months). The overall survival was 17.7 months and 18.6 months for the cTACE and RE groups,

Table 3. Comparison of the results of RE studies
Таблица 3. Сравнение результатов исследований РЭ

Authors ***Авторы***	**Aim of the study** ***Цель исследования***	**Subject groups** ***Группы пациентов***	**Results** ***Результаты***
Kolligs F. et al. [29]	Study of factors influencing survival after RE *Изучение факторов, влияющих на выживаемость после РЭ*	*n* = 422	OS — 16.5 months PFS — 6.1 months AE — 36.7 % *ОВ — 16,5 мес.* *ВБП — 6,1 мес.* *НЯ — 36,7 %*
Salem R. et al. [30]	Study of RE as a treatment option for inoperable HCC *Изучение РЭ как способа лечения неоперабельного ГЦР*	*n* = 162	OS: 24 months — 94.8 % 36 months — 86.6 % Average response time — 11.8 months *ОВ:* *24 мес. — 94,8 %* *36 мес. — 86,6 %* *Среднее время продолжительности ответа — 11,8 мес.*
Dhondt E. et al. [31]	Comparison of debTACE and RE *Сравнение методик ХЭПА-ЛНМ и РЭ*	debTACE *ХЭПА-ЛНМ* *n* = 34	Average time to progression — 9,5 months 3rd degree AE — 53 % *Среднее время прогрессирования — 9,5 мес.* *НЯ 3-й степени — 53 %*
		RE / *РЭ* *n* = 388	Average time to progression — 17,1 months 3rd degree AE — 39 % *Среднее время прогрессирования — 17,1 мес.* *НЯ 3-й степени — 39 %*
Duran R. et al. [33]	Comparison of cTACE and RE *Сравнение методик М-ХЭПА и РЭ*	*n* = 179	cTACE: Average time to progression — 6.8 months OS — 17.7 months М-ХЭПА: *Время до прогрессирования — 6,8 мес.* *ОВ — 17,7 мес.*
			RE: Time to progression — not reached (> 21 months) OS — 18.6 months *РЭ:* *Время до прогрессирования — не достигнуто (> 21 мес.)* *ОВ — 18,6 мес.*

Note: *RE — radioembolization; HCC — hepatocellular cancer; debTACE — drug-eluting-beads-TACE; cTACE — conventional transarterial chemoembolization; OS — overall survival; PFS — progression-free survival; AE — adverse events.*
Примечание: *РЭ — радиоэмболизация; ГЦР — гепатоцеллюлярный рак; ХЭПА-ЛНМ — химиоэмболизация лекарственно-насыщенными микросферами; М-ХЭПА — масляная химиоэмболизация печеночной артерии; ОВ — общая выживаемость; ВБП — выживаемость без прогрессирования; НЯ — нежелательные явления.*

Table 4. Comparison of intraarterial methods of treating HCC
Таблица 4. Основные характеристики методик внутриартериальной терапии для пациентов с ГЦР

Characteristics ***Характеристики***	**TACI** ***ХИПА***	**debTACE** ***ХЭПА-ЛНМ***	**cTACE** ***М-ХЭПА***	**Radioembolization** ***Радиоэмболизация***
Advantages *Преимущества*	1. Possibility of performing TACI in patients with class B according to the Child — Pugh scale. 2. Child — Pugh indices practically do not decrease as a result of TACI treatment. 3. Effective for patients with vascular invasion. 4. Anticancer agents act more locally, low systemic toxicity *1. Возможность проводить ХИПА пациентам класса В по шкале Чайлда — Пью.* *2. Показатели по шкале Чайлда — Пью практически не снижаются вследствие лечения ХИПА.* *3. Эффективна для пациентов с сосудистой инвазией.* *4. Противораковые агенты действуют более локально, низкая системная токсичность*	1. Comparatively higher concentration of the drug within the tumor with a relatively low systemic concentration than cTACE. 2. Low systemic toxicity *1. Сравнительно большая концентрация препарата в пределах опухоли с относительно низкой системной концентрацией, по сравнению с М-ХЭПА.* *2. Низкая системная токсичность*	1. High penetration of embolic agents into capillaries. 2. Good diffusion capacity *1. Высокая степень проникновения эмболических агентов в капилляры.* *2. Хорошая способность к диффузии*	1. Minimal post-embolization syndrome. 2. Delivery of high doses of radiation without causing relative harm to healthy liver parenchyma *1. Минимальный постэмболизационный синдром.* *2. Доставка высоких доз радиации без относительного причинения вреда здоровой паренхиме печени*
Disadvantages *Недостатки*	1. Technical difficulties with placement of a reservoir catheter. 2. Control procedures for checking catheters. 3. Adverse events associated with port migration, catheter dislocation. 4. Arterial occlusion, occlusion of the reservoir system. 5. Subcutaneous hematoma or infection *1. Технические трудности установки катетера с резервуаром.* *2. Контрольные приемы для проверки катетеров.* *3. Нежелательные явления, связанные с миграцией порта, дислокацией катетера.* *4. Артериальная окклюзия, окклюзия резервуарной системы.* *5. Подкожные гематомы или инфекция*	1. Possible ischemia of healthy tissues around the tumor. 2. Post-embolization syndrome *1. Возможная ишемия здоровых тканей вокруг опухоли.* *2. Постэмболизационный синдром*	1. High risk of adverse events: pulmonary and cerebral embolism, hypersensitivity reaction, and decompensation of chronic liver failure. 2. Easy elimination of the drug (stable embolization is not ensured) *1. Высокий риск нежелательных явлений: легочной и церебральной эмболии, реакции гиперчувствительности, а также декомпенсации хронической печеночной недостаточности.* *2. Легкое выведение препарата (не обеспечивается стойкая эмболизация)*	1. High cost of the procedure. 2. Radiation load on the body. 3. Leukopenia, stage 3 thrombocytopenia. 4. Fatigue. 5. Dyspeptic symptoms — nausea, vomiting, anorexia, abdominal discomfort *1. Высокая стоимость процедуры.* *2. Радиационная нагрузка на организм.* *3. Лейкопения, тромбоцитопения 3-й степени.* *4. Утомляемость.* *5. Диспептические явления — тошнота, рвота, анорексия, дискомфорт в животе*

End of Table 4.
Окончание табл.цы 4.

Overall survival *Общая выживаемость*	16.5 months* *16,5 мес.**	18.36 months** *18,36 мес.***	16.6 months*** *16,6 мес.****	14.5 months**** *14,5 мес.*****
Progression-free survival *Выживаемость без прогрессирования*	8.5 months* *8,15 мес.**	11.2 months** *11,2 мес.***	10.25 months*** *10,25 мес.****	9.75 months**** *9,75 мес.*****
Cost (per cycle, USD) *Стоимость (за цикл, в долларах)*	1850	2100	2100	7000

Note: *TACI – transarterial chemoinfusion; debTACE – drug-eluting-beads-TACE; cTACE – conventional transarterial chemoembolization; * median values are calculated based on data from studies [11, 22, 35, 36]; ** median values are calculated based on data from studies [24, 37–41]; *** median values are calculated based on data from studies [22–24, 32, 40, 41]; **** median values are calculated based on data from studies [30, 34, 42–44].*

Примечание: *ХИПА – химиоинфузия в печеночную артерию; ХЭПА-ЛНМ – химиоэмболизация лекарственно-насыщенными микросферами; М-ХЭПА – масляная химиоэмболизация печеночной артерии; * медианные значения рассчитаны на основании данных исследований [11, 22, 35, 36]; ** медианные значения рассчитаны на основании данных исследований [24, 37–41]; *** медианные значения рассчитаны на основании данных исследований [22–24, 32, 40, 41]; **** медианные значения рассчитаны на основании данных исследований [30, 34, 42–44].*

respectively. Thus, according to the results of the comparative study, it can be concluded that RE can provide high-quality tumor control and increase survival (Table 3).

Currently, studies are also being conducted to study the quality of life of patients, the efficacy and safety of RE using TheraSphere ^{90}Y glass microspheres. Thus, the large multicenter prospective French study PROACTIF [34] currently includes more than 1000 patient participants from more than 30 centers. The endpoints of the study are the overall survival rate, tumor response, and assessment of adverse events. The results are expected in 2025.

Thus, as a result of studying various data from the world literature on the comparison of intraarterial methods of treating HCC, a final table was compiled, which presents the main characteristics of each method (Table 4). The methods have their advantages and disadvantages, but according to the criteria of overall survival and survival without progression, the debTACE method is in the lead. The least expensive method of those presented is TACI ($1850 per cycle), but in terms of economic efficiency, the method is not a priority, since treatment with this method requires a larger number of cycles, compared, for example, with TACE methods. The radioembolization is associated with the lowest risk of adverse events.

Conclusion

Endovascular treatment methods are safe methods that have shown high efficiency in primary liver cancer in a short period of time.

The use of intraarterial options in various algorithms for the treatment of HCC can improve survival rates in patients of this category. Most of these methods are currently in the clinical study stage, and therefore there are still many questions that we have to answer. In particular, the optimal schemes for combining intraarterial treatment methods with systemic therapy, as well as the combination of endovascular methods with ablative technologies. In addition, despite the huge steps in studying the issue of selecting patients for a particular method of endovascular surgery (which is quite clearly defined in the BCLC classification), today this issue remains open for further study and improvement of survival rates in patients with hepatocellular carcinoma.

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