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LIVER TRANSPLANTATION FOR UNRESECTABLE KLATSKIN TUMOR: FIRST LONG-TERM OUTCOMES – A SINGLE CENTER EXPERIENCE

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Objective: to demonstrate the first long-term outcomes of treatment of unresectable hilar cholangiocarcinoma (HCCA) after combined neoadjuvant therapy followed by liver transplantation (LT). **Materials and methods.** From 2017 to 2023, at the Russian Research Center of Radiology and Surgical Technologies, 10 patients were included in the treatment protocol for unresectable HCCA. Combined neoadjuvant therapy included endobiliary photodynamic therapy (EPDT), regional chemotherapy (RCT) and systemic polychemotherapy (SPCT). Each modality was applied at least three times over a period of four to six months. Patients were placed on the LT waitlist when tumor marker CA19-9 reduced, there was no radiological evidence of disease progression, and there was no evidence of acute cholangitis. Before LT, the recipients underwent diagnostic laparoscopy to exclude carcinomatosis and also evaluation of regional lymph nodes with urgent morphologic examination. In the absence of extrahepatic tumor spread, LT from a deceased donor was performed according to the classical technique with paracaval and hepatoduodenal lymph node dissection, biliodigestive anastomosis using the Roux-en-Y procedure. The operation was performed in six patients. Patient age ranged from 40 to 55 years (mean, 46.3). The mean time from start of treatment to LT was 9.1 months (range 6 to 14). The mean CA19-9 level at the time of LT was 66.5 IU/mL (8 to 212). **Results.** After combined neoadjuvant treatment, the CA19-9 marker normalized in four patients and there was a 3–4-fold decrease in two patients. Radiological evaluation indicated stable disease in five patients, and a partial response in one. Disease progression was noted in four out of 10 patients. Currently, one of the 6 patients is alive with a follow-up of 34 months. Median (Me) overall survival is 28 months; Me overall survival after LT is 22.2 months; Me survival before progression is 27 months. During long-term follow-up of patients after LT, three patients out of six had disease progression: implantation metastasis (n = 2) at 25 and 27 months follow-up (metastasectomy was performed), carcinomatosis (n = 1) at 20 months follow-up. **Conclusion.** LT for unresectable Klatskin tumor is effective when combined neoadjuvant treatment is used and there is no acute cholangitis. However, the use of endobiliary manipulations (drainage change, EPDT) are risk factors for the development of implantation metastasis.

Keywords: Klatskin tumor, hilar cholangiocarcinoma, liver transplantation, photodynamic therapy, regional chemotherapy.

INTRODUCTION

Hilar cholangiocarcinoma (HCCA), also known as Klatskin tumor, is a malignant tumor arising from bile duct epithelium, localized above the confluence of the cystic duct and up to the level of segmental bile ducts outflow. The disease manifests itself as obstructive jaundice, usually in late stages, which leads to late diagnosis and low survival rate. The best outcomes are demonstrated by definitive surgical intervention in bile duct resection with achievement of negative surgical margin (R0), liver resection with lymph node dissection. However, according to some studies, resectability in hilar cholangiocarcinoma is about 30–50%, 5-year survival rate is not more than 43–67% provided that R0 resection is performed and there are no metastases in regional lymph nodes; 5-year survival in patients with lymph node metastasis is 15–22% [1–5]. Recurrence rate within 5 years reaches 70% [6].

In addition, local relapse occurs in 50% of cases after definitive surgery, and distant tumor metastasis occurs in 30–40% of cases [7]. The use of neoadjuvant therapy (chemotherapy, chemoradiotherapy) before resection may increase achievement of negative surgical margins, but there is no convincing evidence of benefits considering postoperative risks [8–10].

Thus, it should be recognized that resection is currently considered the preferred treatment option when technically feasible. However, it is feasible only for a narrow group of patients, and oncologic outcomes are still unsatisfactory. At the time of treatment, most patients already have unresectable Bismuth–Corlette type 4, 3a, 3b with contralateral lesion of vascular structures (branch of hepatic artery or portal vein) and/or presence

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of abdominal lymphadenopathy. Such tumor spread does not allow to perform definitive surgery (liver resection in various volumes). For this category of patients, therapy comes down to the use of palliative treatment methods and their combinations: SPCT, RCT, EPDT, brachytherapy/remote-controlled or stereotactic radiotherapy. In the management of such patients, an integral part of treatment is adequate drainage of the biliary tree and monitoring of cholangitis with regular bacteriological examination of bile due to high risk of septic conditions. In some cases, with a proper approach against the background of palliative treatment, it is possible to stabilize the disease by reducing the biological activity of the tumor (decrease in the level of tumor marker CA19-9).

In this situation, LT can be considered as a definitive treatment option for patients with inoperable HCCA due to complete removal of tumor tissue and the whole organ with potential macroscopically non-visualized micrometastasis and a substrate for relapse. However, based on analysis of available studies, the best outcomes of LT for Klatskin tumor can only be achieved with strict patient selection in combination with neoadjuvant treatment [11]. For example, more recent publications of the Meyo Clinic treatment protocol demonstrate a 5-year survival rate of 72% [12]. Thus, a combination of neoadjuvant therapy with subsequent LT for unresectable Klatskin tumors is a very promising therapeutic option.

MATERIALS AND METHODS

From 2017 to 2023, 10 patients were included in the developed protocol (Fig. 1) for the treatment of unresectable HCCA followed by LT at Russian Research Center of Radiology and Surgical Technologies (Table).

The unresectability criterion was lesion of segmental bile ducts – Bismuth–Corlette type 4, 3A, 3B with contralateral lesion of vascular structures (branch of hepatic artery or portal vein). The clinical stage of the disease was established via computed tomography (CT), magnetic resonance imaging (MRI), and direct cholangiography.

Patients with a tumor size <5 cm and localization above the cystic duct were considered. Distant metastases were excluded by radiologic examination methods. In all cases, histological confirmation by intraductal punch biopsy, assessment of CA19-9 level (in the absence of active cholangitis) before treatment, regular bacteriologic examination of bile and appropriate antibacterial therapy were mandatory. A combination of EPDT, RCT and SPCT was used as neoadjuvant therapy (Fig. 1).

Each technique was used at least three times over a period of three to eight months with radiological evaluation and CA19-9 level determination to monitor tumor growth and biological activity. Patients were placed on the LT waiting list only when the tumor marker decreased, no radiologic evidence of disease progression, and

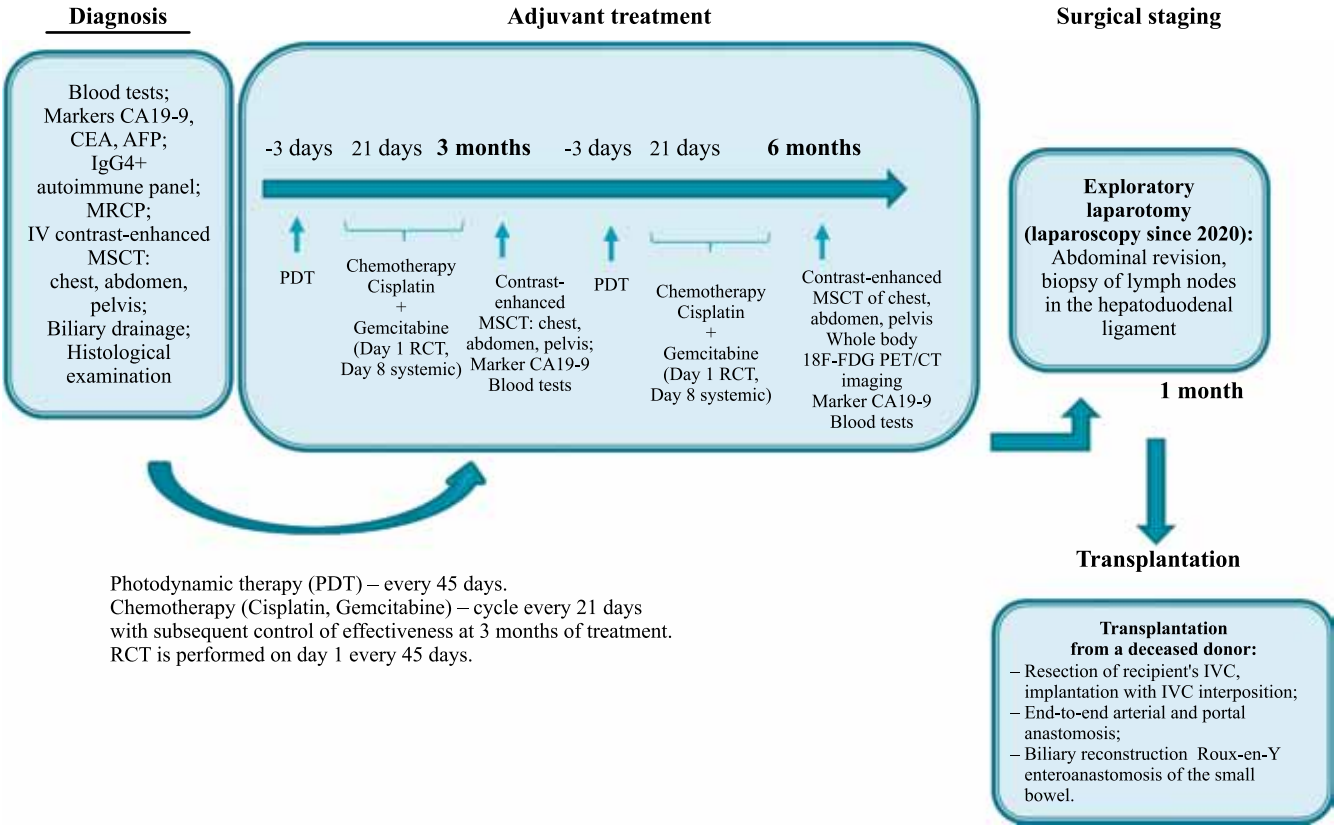

Fig. 1. Brief description of the multidisciplinary protocol for treatment of unresectable Klatskin tumor with subsequent liver transplantation, developed at the Russian Research Center of Radiology and Surgical Technologies

no acute cholangitis. Whole body 18F-FDG positron emission tomography (PET) imaging was performed to monitor tumor metabolic activity and to rule out extrahepatic spread. Before LT, the potential recipient underwent laparoscopic abdominal exploration for carcinomatosis and evaluation of hepatoduodenal lymph nodes with excision of suspicious tissue for morphologic examination. LT was not performed where extrahepatic spread was histologically confirmed. Otherwise, LT was performed according to the classical technique with paracaval and hepatoduodenal lymph node dissection, biliodigestive anastomosis using the Roux-en-Y procedure. All suspicious (enlarged/dense) lymph nodes around the hepatoduodenal ligament, celiac artery, aorta and inferior vena cava, were removed. According to the Japanese Research Society for Gastric Cancer (JRSGC) classification, this corresponds to anatomic groups 5, 7, 8a, 8p, 9, 12a, 12b, and 12p.

The combined neoadjuvant treatment protocol initially included 10 patients. LT was performed in 6 patients, including 2 females and 4 males. The age of the patients ranged from 40 to 55 years (mean, 46.3). The mean time from treatment initiation to transplantation was 9.1 months (range, 6 to 14). The mean CA19-9 level at the time of transplantation was 66.5 IU/mL (range, 8 to 212). A standard triple-drug immunosuppression protocol (tacrolimus, mycophenolic acid, prednisolone) was used in the early postoperative period, followed by conversion from tacrolimus to an mTOR inhibitor (everolimus) after one month.

RESULTS

Despite neoadjuvant therapy, three patients showed a more than twofold increase in CA19-9 levels over an average of four months. In two of them, CT revealed disease progression according to the RECIST criterion. In the remaining two patients, carcinomatosis was detected during diagnostic laparoscopy before the planned LT, which was the reason for exclusion from the LT waitlist.

Using a combination of methods (EPDT, RCT, SPCT) as neoadjuvant treatment, we managed to normalize CA19-9 levels in four patients and achieve 3–4-fold decrease of this tumor marker level in two patients. Diagnostic laparoscopy and biopsy of hepatoduodenal lymph nodes in all patients with decreased CA19-9 levels revealed no metastases, which allowed for LT (Table).

During the follow-up period, we analyzed such indicators as overall survival (OS), from the time of neoadjuvant treatment initiation to the time of death in the post-transplant period; OS after LT; and progression-free survival after liver transplantation (PFS after LT).

When analyzing the OS from the moment of neoadjuvant treatment and after LT, one patient out of 6 patients is alive presently, with a follow-up period of 34 months. The median OS was 28 months (Fig. 2).

Median OS after LT was 22.2 months (Fig. 3).

After LT, the disease progressed in three patients out of six (Fig. 4). Two patients had implantation metastasis at 25 and 27 months of follow-up. One patient had carcinomatosis at 20 months follow-up. Median PFS was 27 months.

Two patients with signs of implantation metastasis (right hypochondrium, anterior abdominal wall) were subsequently operated upon (metastasectomy). Detailed description of the clinical cases is presented below.

Case #1

Patient D., 55 years old, in November 2020, the disease manifested with obstructive jaundice; external-internal bile duct drainage was performed. The jaundice

Table

Treatment outcomes with tumor marker dynamics, RECIST and survival rates for all patients included in the developed protocol

Patient	Age (years)	No. of EPDTs	No. of RCTs	No. of SPCT	Ca19-9 before treatment	Ca19-9 after treatment/ at the time of LT	RECIST	Time to progression/LT	Survival after LT	Survival from start of treatment
1	49	7	11	8	986	8	CR	**LT after 14 months**	36 months	50 months
2	40	4	4	5	754	24	SD	**LT after 8 months**	35 months	43 months
3	37	4	4	4	337	754	SD	Carcinomatosis at diagnostic laparoscopy	–	11 months
4	56	2	2	3	3416	7256	PD	Progression after 4 months	–	7 months
5	55	4	3	5	864	212	SD	**LT after 6 months**	28 months	34 months
6	46	5	6	6	789	1456	PD	Progression after 5 months	–	8 months
7	42	3	3	4	62	3.3	SD	**LT after 8 months**	1 months	9 months
8	37	3	3	4	515	150	SD	**LT after 7 months**	22 months	28 months
9	55	2	2	1	420	2	SD	**LT after 12 months**	4 months	16 months
10	34	1	1	1	474	19	SD	Carcinomatosis at diagnostic laparoscopy	–	7 months

was stopped. Based on examination results, unresectable HCCA was diagnosed. Tumor marker CA19-9 before treatment was 864 IU/ml. Cholangiography and intraductal punch biopsy were performed. Cholangiography showed that the tumor involved the right and left hepatic ducts, which corresponded to Bismuth–Corlette type 4. The tumor was histologically verified: moderately differentiated bile duct adenocarcinoma. Given the absence of signs of distant metastasis and lymph node involvement, the patient was considered as a potential LT candidate and was included in the waiting list. Neoadjuvant treatment was performed according to the treatment protocol we developed. The patient received 4 EPDT procedures, 3 RCT cycles and 5 SPCT cycles. After preliminary intraoperative staging, in 6 months from the moment of inclusion in the waiting list, the patient underwent LT from a deceased donor in May 2021. At the time of surgery, tumor marker CA19-9 decreased 4-fold (212 IU/ml). One month after transplantation, there was a clinical and laboratory picture of graft rejection. An ultrasound-guided liver trephine biopsy was performed. Histological conclusion: cholestasis, graft rejection. Blood biochemistry tests dated June 29, 2021 showed increased levels of total serum bilirubin (181.5 μmol/l), alanine aminotransferase 1630 units/L, aspartate aminotransferase 736 units/L, lactate dehydrogenase 426 units/L, and alkaline phos-

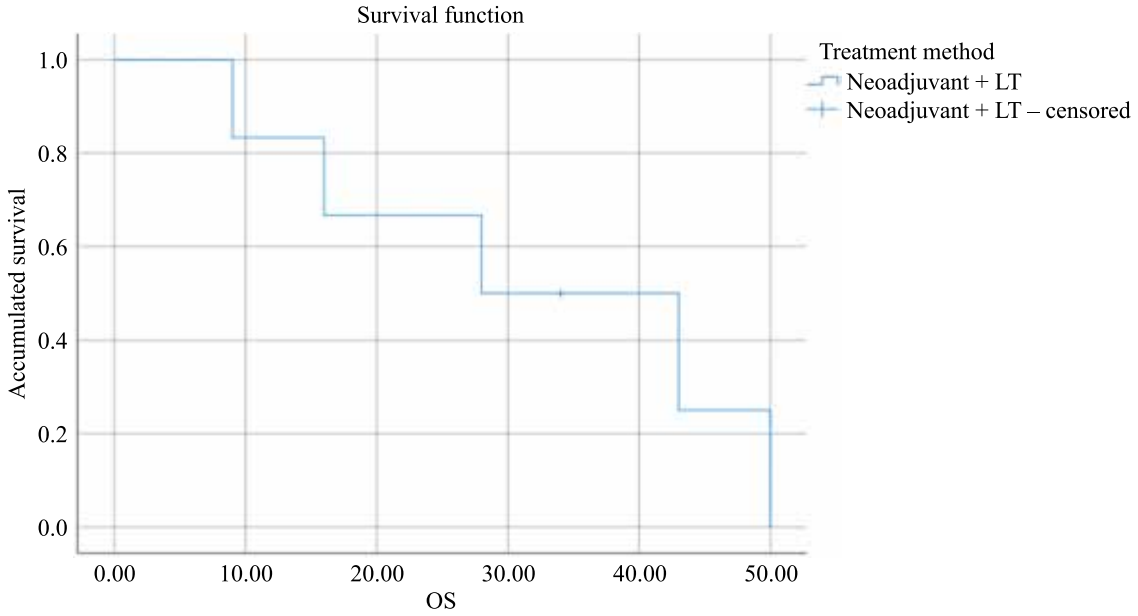

Fig. 2. Overall survival from start of neoadjuvant treatment to time of death in the post-transplant period

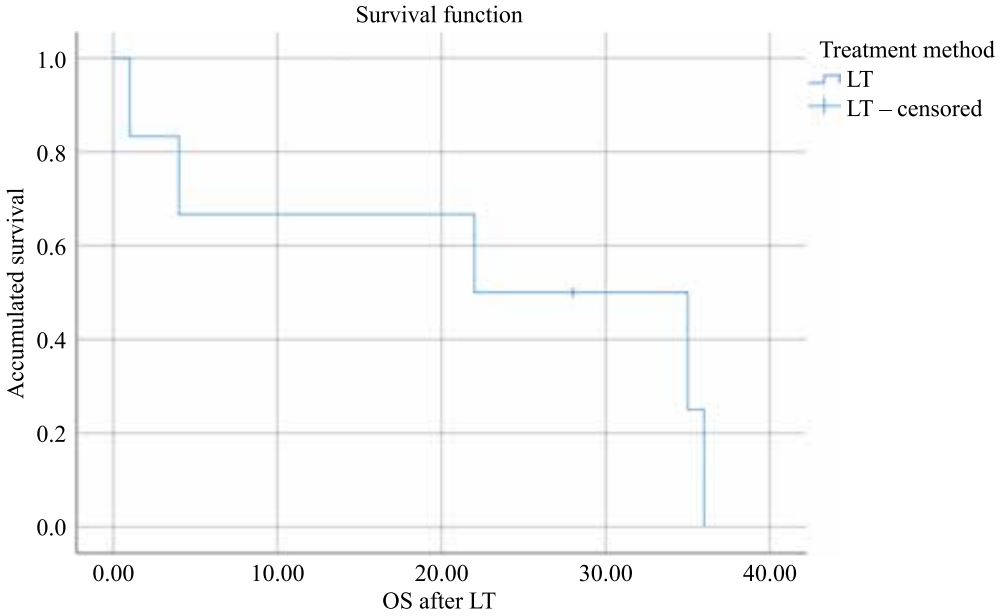

Fig. 3. Overall survival (OS) after transplantation

phatase 225 units/L. Immunosuppressive therapy was corrected (everolimus-to-tacrolimus conversion), pulse methylprednisolone therapy without significant correction of biochemical parameters of the graft. Five sessions of high-volume plasma exchange were performed with positive dynamics – relieving graft rejection signs. Considering the patient's underlying disease, immunosuppression was supplemented with an mTOR inhibitor (everolimus). After 25 months of follow-up after LT, at the next visit to the hospital, the patient was found to have elevated levels of tumor marker CA19-9 (from 38 to 199 IU/mL). Whole body 18F-FDG PET/CT imaging was performed on July 7, 2023. Findings: metabolic active thickening in the 7th intercostal space on the right side, a focus of radiopharmaceutical hyperfixation in the liver at the level of this tumor SUV 4.7, size 22 × 19 × 21 mm (Fig. 5). The finding was considered as an implantation metastasis of HCCA in the area of percutaneous cholangiodrainage previously performed before LT.

The patient underwent surgical intervention (August 30, 2023), which included excision of metastatic lesion of intercostal muscles of the anterior chest wall on the right side, diaphragm, marginal atypical liver resection, drainage of the right pleural cavity using the Bülau

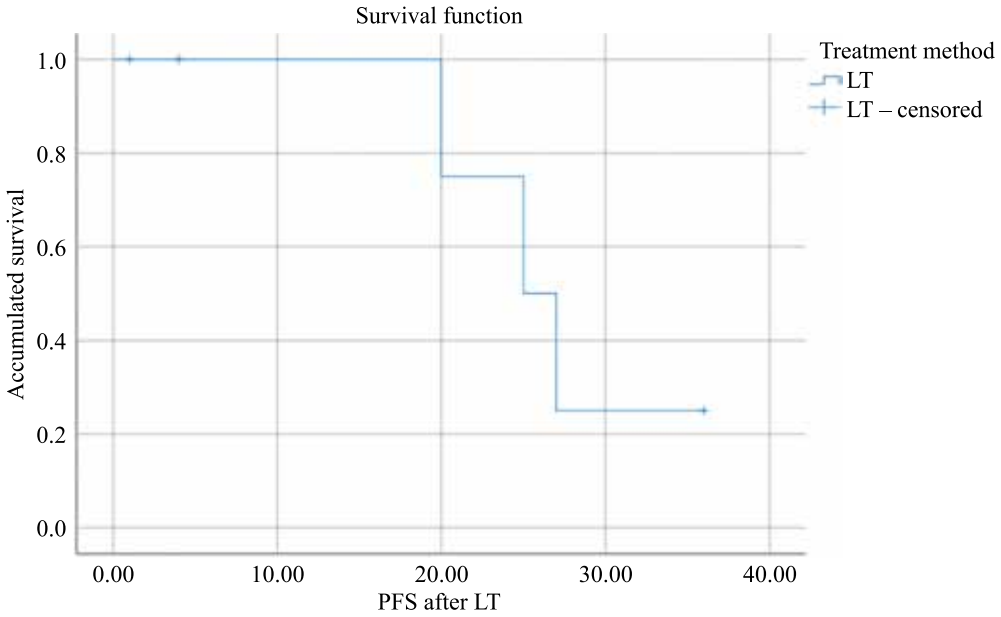

Fig 4. Progression-free survival (PFS)

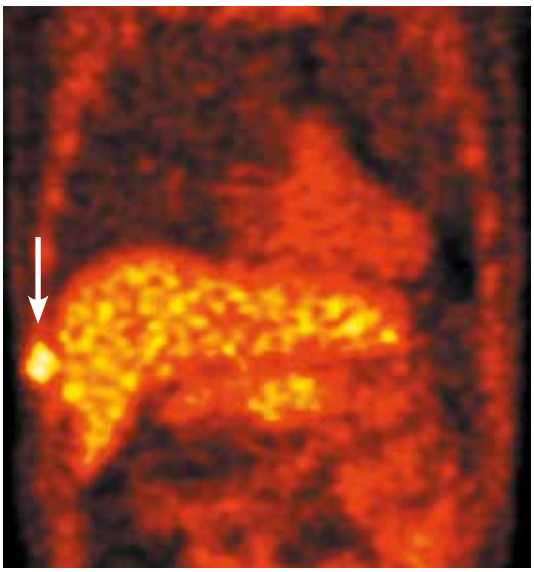

Fig. 5. Whole body 18F-FDG PET/CT imaging at 25 months of LT (study dated July 7, 2023). The CT scan shows a metastatic focus with active accumulation of radiopharmaceuticals (marked with a white arrow)

drain procedure (Fig. 6). The postoperative period was uneventful. Histological study of postoperative material: metastasis of poorly differentiated adenocarcinoma into subcutaneous fatty tissue and transverse striated muscle tissue. Liver fragments were with pronounced artificial changes without convincing signs of tumor growth. Considering the definitive nature of the surgical intervention, absence of tumor spread to the liver, it was decided not to perform systemic chemotherapy and radiotherapy. The patient continues to be monitored. Indicators of tumor markers as of November 13, 2023 are within normal values (CA19-9 23.7 IU/mL, carcinoembryonic antigen 7.3 ng/mL).

Case #2

Patient Y., 40 years old, the disease manifested with obstructive jaundice, fever, acute cholangitis in February 2017. Percutaneous external-internal drainage of bile ducts was performed. After additional examination, CT

magnetic resonance imaging revealed a 30 × 40 mm tumor in the porta hepatis.

In March 2018, after stopping the infectious-inflammatory process and obstructive jaundice, surgical treatment was undertaken, exploratory laparotomy was performed during which the tumor process was considered as unresectable – invasion of the native hepatic artery, Bismuth–Corlette type 4. A biopsy was performed. Histological conclusion – highly differentiated pancreaticobiliary adenocarcinoma. Given the unresectable nature of the tumor, absence of distant metastasis and regional lymph node involvement, the patient was included in the LT waitlist. The CA19-9 level at the moment of treatment initiation was 754 IU/ml. The patient received neoadjuvant treatment according to the protocol we developed. The patient received 4 EPDT procedures, 4 RCT cycles and 5 SPCT cycles. After 8 months from the moment of inclusion in the waiting list, the patient underwent LT from a deceased donor in February 2020. At the time of surgery, tumor marker CA19-9 was normalized (24 IU/ml). The postoperative period was uneventful, the patient was regularly observed in the hospital. In 27 months after LT, during the next visit, a CT scan revealed a tumor on the anterior abdominal wall on the right side in the projection of the postoperative scar, measuring up to 51 × 56 × 75 mm, with invasion of the anterior abdominal wall muscles over the entire thickness, the tenth rib, the S6 liver capsule throughout 10 mm, involving the ascending colon (Fig. 7).

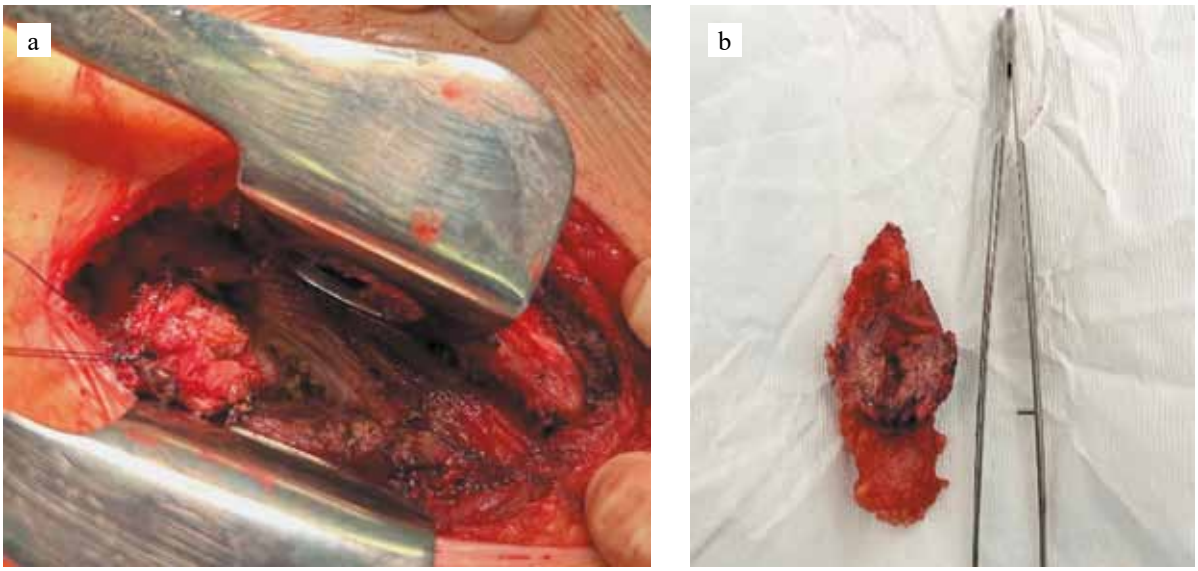

Fig. 6. Intraoperative photograph: a, the tumor node is taken on a holder; b, macroscopic specimen of the removed metastasis

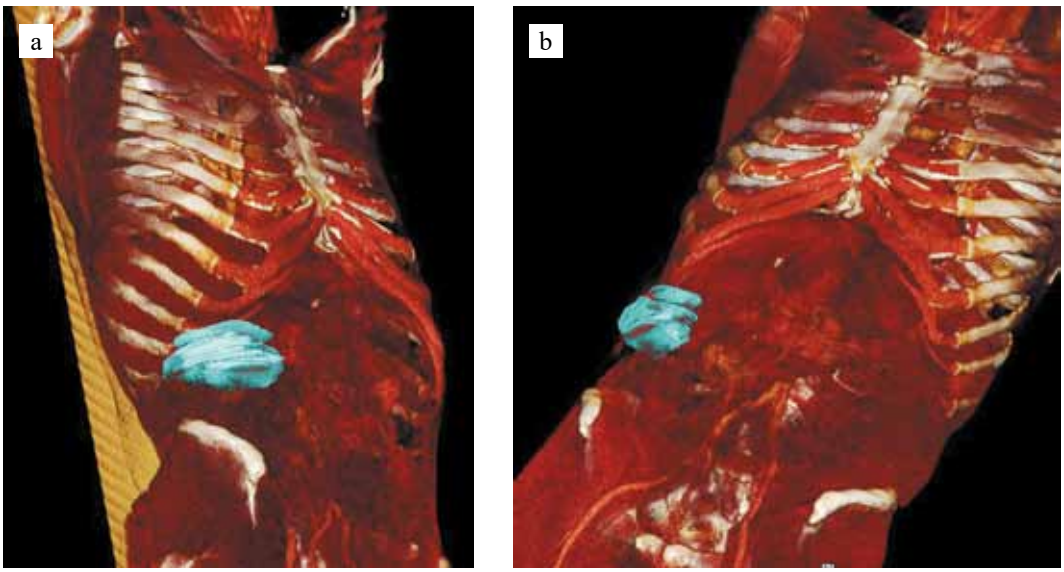

Fig. 7. Preoperative 3D reconstruction of CT tumor images with assessment of invasion of deep tissues and structures (turquoise)

The operation was performed on May 27, 2022, and included: removal of tumor from the anterior abdominal wall, resection of the tenth and eleventh ribs on the right side, marginal atypical liver resection, right hemicolectomy, reconstruction of the anterior abdominal wall with plasty using a Permacol biological implant (Fig. 8). The removed tumor conglomerate is shown in Fig. 9.

Histological examination of the removed tumor: moderately differentiated adenocarcinoma without signs of dMMR/MSI-H. Testing positive to PMS2, MLH1, MSH2, and MSH6 in the tumor. In the postoperative period after wound healing, the patient received 3 SPCT cycles based on the GemCis regimen. Four months after metastasectomy, the patient died of a stroke and autopsy showed no signs of progression. Overall survival after LT was 35 months, and from the time of neoadjuvant treatment 43 months.

DISCUSSION

LT as a therapeutic option for HCCA patients was attempted earlier (1980–1990); despite the reasonable potential advantage of definitive removal of the affected organ with achievement of a negative resection margin, its outcome left much to be desired. In the early days of attempts to address this problem, hospitals performing LT for HCCA reported a 3-year survival rate of about

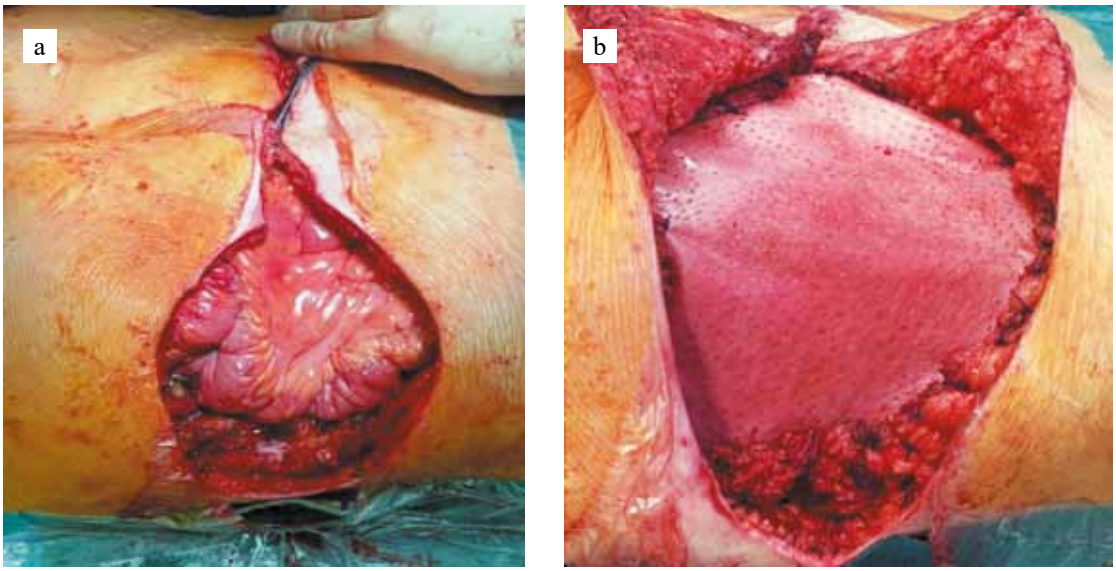

Fig. 8. Photograph after tumor removal: a, there is a defect in the anterior abdominal wall; b, photograph after repair of the anterior abdominal wall defect with biological implant Permacol. The synthetic material is sewn using single interrupted sutures to the edges of the muscles and anterior abdominal aponeurosis

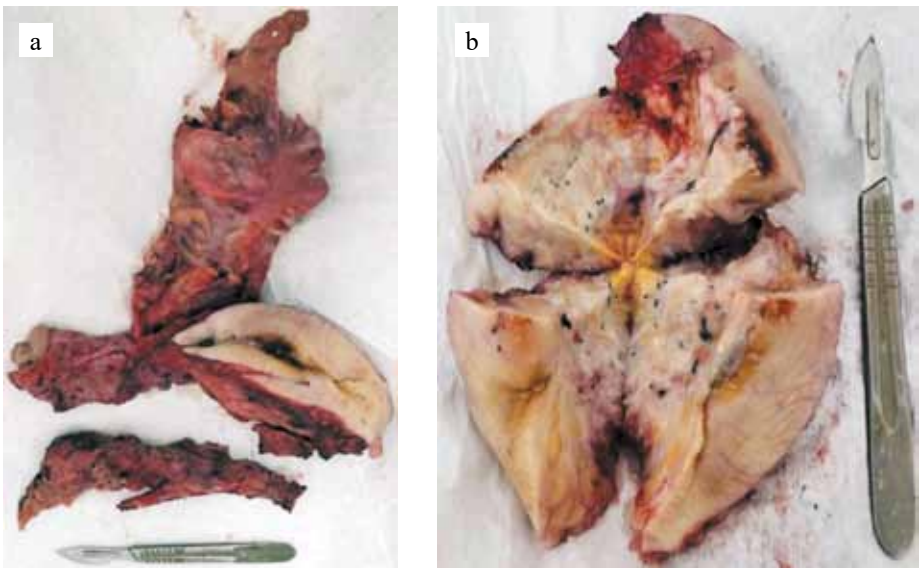

Fig. 9. Photograph of removed tumor: a, general view of the removed tumor with resected structures: anterior abdominal wall, rib, colon segment; b, view of the anterior abdominal tumor after incision

30% [11]. These results led to the conclusion that LT alone does not improve long-term treatment outcomes. Moreover, immunosuppression is known to increase the risk of tumor progression and may lead to rapid patient death. However, careful analysis of accumulated data has revealed that the cohort of patients with negative resection margins and no metastases in regional lymph nodes had much better survival rates. In addition, a small group of patients at the Mayo Clinic who received only chemoradiotherapy without subsequent surgical treatment had a 22% 5-year survival rate [13]. Unsatisfactory outcomes of standard methods of HCCA treatment and the success of individual studies were the reason for the active application of combined methods of treatment. Given evidence on the efficacy of chemoradiotherapy for HCCA and the predominant progression of the disease in the form of local recurrence rather than distant metastasis, a group of Nebraska transplant surgeons first developed a strategy for neoadjuvant high-dose-rate (HDR) brachytherapy in combination with chemotherapy with 5-fluorouracil (5-FU) and subsequent LT [12, 14]. The use of HDR brachytherapy increased the incidence of biliary, infectious and vascular complications. Still, early results were promising with respect to reducing local recurrence. The Mayo Clinic subsequently adopted this concept, developing a similar protocol for neoadjuvant therapy followed by LT in 1993. The protocol combined the benefits of radiotherapy, chemotherapy, and LT while carefully selecting patients with localized, unresectable HCCA. Preliminary results for 11 patients, which were reported in 2000, were encouraging, and an update in 2004 reported an 82% 5-year survival rate in 28 patients [7]. However, the survival rate fell to 72% as the patient sample increased [12].

Unfortunately, domestic experience with LT in HCCA is very limited, judging by the lack of significant publications. Treatment of technically unresectable HCCA is classified as palliative, and its outcomes and prognosis do not differ much from those of disseminated process and, as a rule, are caused by rapidly progressing biliary obstruction and cholangitis. The primary task in the management of such patients is biliary decompression to stop obstructive jaundice and purulent cholangitis signs [15]. Transhepatic percutaneous cholangiostomy is the method of choice for biliary decompression for this patient category due to the impracticability of retrograde drainage in more than a half of cases with proximal extrahepatic bile duct strictures [16].

The standard of antitumor treatment for unresectable HCCA, as well as for any form of inoperable locally advanced or metastatic cholangiocarcinoma according to Russian and foreign clinical guidelines is SPCT based on GemCis (gemcitabine plus cisplatin) or GemCap (gemcitabine plus capecitabine) regimens, as well as stereotactic precision conformal chemoradiotherapy with fluoropyrimidines [17, 18] or other chemotherapy and radiotherapy variants depending on the patient's somatic status, individual intolerance and developing complications.

Moreover, according to combined statistics on the effectiveness of these methods of treatment for all inoperable malignant biliary tumors, the median overall survival rate is 8–10 months [19]. Some of the best outcomes achieved using chemoradiotherapy demonstrate a 4-year survival rate of 30% [20].

EPDT is a relatively new progressive treatment option for unresectable HCCA . The efficacy of EPDT in combination with biliary decompression is confirmed by numerous studies, some of which showed a five-fold difference in life expectancy [15, 21–25].

Having a wide enough experience in hepatobiliary surgery and oncology in general, as well as in HCCA therapy in particular, we tried to use the whole available arsenal of possibilities in relation to this pathology. Like most colleagues, we actively perform percutaneous transhepatic cholangial drainage for biliary decompression, with compulsory assessment of the bacteriologic flora of bile and antibacterial therapy according to sensitivity. The presence of percutaneous transhepatic drains in the biliary tree in HCCA patients implies the relative ease of EPDT delivery to the lesion area and the possibility of repeating the procedure many times, which confirms our own experience [15, 16].

The ideological similarity between the world-renowned protocol of the Mayo Clinic and the treatment protocol we have developed is stopping tumor growth, reducing the biological activity of the tumor until the time of definitive treatment. Our neoadjuvant treatment includes EPDT and no radiotherapy. Undoubtedly, the effectiveness of LT in unresectable Klatskin tumor is beyond doubt, however, as the authors themselves admit, remote-controlled radiotherapy and intraductal brachytherapy is often accompanied by severe cholangitis, biliary abscesses, sepsis and vascular complications [7, 12], which, in our opinion, is due to the pronounced connective tissue overgrowth and formation of rough scar structures in the hepatoduodenal ligament. This cannot but affect the intraoperative precision of dissection of anatomical structures and formation of anastomoses, which can significantly complicate the vascular reconstruction procedure during LT. Thus, after our combined neoadjuvant treatment, there were no postoperative vascular and biliary complications. However, it is necessary to recognize that multiple endobiliary interventions (the need to change drains, multiple EPDT procedures) are risk factors for implantation metastasis. Thus, in our study, two patients developed implantation metastases in the projections of previously installed biliary drains during the long-term follow-up period. The necessity to maintain a balance between the benefit and possible complications leaves open the question of using radiotherapy/brachytherapy. Most likely, the use of simultaneous bile duct drainage and brachytherapy at the first stages of

neoadjuvant treatment can reduce the likelihood of implantation metastasis [26]. With regard to chemotherapy, in our opinion, in addition to using SPCT, transcatheter arterial chemotherapy infusion (TACI) allows to create a high concentration of chemotherapy drug in a limited anatomical area, thereby increasing cytostatic effect and reducing overall toxicity. In addition, direct angiographic examination allows one to visually assess the degree of involvement of vascular structures in the tumor process. Alternating SPCT and TACI with EPDT sessions, in our opinion, seems to be the most optimal option for neoadjuvant therapy, considering the resulting decrease in tumor biological activity, absence of an increase in the risks of biliary and vascular complications in the post-transplant period.

An additional advantage of a neoadjuvant protocol is the "test of time", as a cohort of patients with aggressive tumor biology experience disease progression despite treatment [27]. In such cases, LT is not indicated.

CONCLUSION

Based on our own and foreign experience, we conclude that indications for LT and its success in unresectable Klatskin tumor depend on careful selection of patients according to strict inclusion and exclusion criteria, on effectiveness of combined treatment methods for at least 3–4 months through reduction of the biological and metabolic activity of the tumor, reduction of the size, as well as assessment of metastatic involvement of lymph nodes, assessment of extrahepatic spread and monitoring of acute cholangitis.

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The authors declare no conflict of interest.

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