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COMBINED TREATMENT OF UNRESECTABLE HILAR CHOLANGIOCARCINOMA WITH SUBSEQUENT LIVER TRANSPLANTATION

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Objective: to demonstrate the experience of unresectable hilar cholangiocarcinoma treatment using neoadjuvant therapy followed by liver transplantation (LT). **Materials and methods**. From 2017 to 2021, six patients were included in the treatment protocol for unresectable Klatskin tumor followed by liver transplantation at Granov Russian Scientific Center for Radiology and Surgical Technology. The neoadjuvant therapy included endobiliary photodynamic therapy (PDT), as well as regional and systemic chemotherapy. Each method was used at least three times for 4 to 5 months with radiological evaluation and measurement of CA 19-9 levels. Patients were placed on the waiting list when the tumor marker reduced, or when there were no radiological signs of disease progression and there was no acute cholangitis. The recipients underwent laparoscopic abdominal revision for carcinomatosis and assessment of lymph nodes in the hepatoduodenal ligament with urgent morphological examination. Where there was no extrahepatic spread, LT was performed according to the classical technique with paracaval, para-aortic and hepatoduodenal lymphodissection, biliodigestive anastomosis by an isolated Roux loop of small intestine. The operation was performed in three patients, all of them were men aged 40 to 55 years (mean 48). The mean time from the start of treatment to transplantation was 9.3 months (range 6 to 14). Mean CA 19-9 level at the time of intervention was 81.3 IU/mL (8 to 212). **Results**. In three patients, CA 19-9 levels more than doubled on average over four months despite treatment. According to data from computed tomography RECIST assessment, two of the patients showed disease progression. In one patient, carcinomatosis was detected by diagnostic laparoscopy. In three patients, CA 19-9 levels decreased more than fourfold. Two of these patients were radiologically confirmed to have the disease stabilized, and one had a partial response. One patient died from sepsis three years after transplantation as a result of secondary biliary cirrhosis and biliary abscesses without signs of progression. Two patients are still alive after 6 and 21 months without signs of tumor progression. **Conclusion**. LT for unresectable Klatskin tumor is effective in controlling the bioactivity of the tumor through the use of neoadjuvant therapy.

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

INTRODUCTION

Hilar cholangiocarcinoma (HCC), or Klatskin tumor, arising from the epithelial cells of the bile duct, is a rare and extremely aggressive disease. It usually manifests in late stages, thus leading to late diagnosis and low survival rate. The best results are achieved by radical surgical intervention in the volume of liver resection with lymphodissection. However, some studies have shown that resectability in HCC is about 30–50%, 5-year survival rate under R0 resection is no more than 30–40% [1], and 5-year recurrence rate reaches 70% [2].

In addition, local recurrence occurs in 50% of cases after radical surgical intervention, and distant tumor metastasis occurs in 30–40% of patients [3]. The high frequency of "positive" surgical margins is down to the lack of detailed understanding of the spread of the process due to extended, predominantly proximal periductal tumor growth with a macroscopically unchanged bile duct wall.

Thus, it should be recognized that resection is currently considered the preferred treatment when technically possible. However, this technique is feasible only for a narrow group of patients, and oncological results, although the best available, are often not enough to achieve >30% 5-year survival rate. Most patients at the moment of referral already have unresectable forms of Bismuth-Corlette type IV, IIIa, IIIb with contralateral damage to vascular structures (branch of hepatic artery or portal vein) and correspond to TNM T4N0M0 stage IIIC. Such tumor spread does not allow for radical surgical intervention (liver resection in various volumes). Meanwhile, the role of palliative therapies and their combinations – systemic chemotherapy (CT), regional CT, photodynamic therapy (PDT), brachial/external beam

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radiation therapy – increases in these cases. Adequate biliary tree drainage and the control of cholangitis with regular bacteriological investigation of bile is of primary importance in the care of these patients due to the high risk of developing septic conditions. In some cases, with proper approach amidst palliative treatment, it is possible to stabilize the disease by reducing the bioactivity of the tumor.

In this situation, liver transplantation (LT) can be considered as an ideal treatment for patients with unresectable HCC due to complete removal of tumor tissue and the whole organ with potential macroscopically invisible micrometastases and substrate for recurrence. However, available studies have shown that the best LT outcomes in Klatskin tumor can be achieved only with proper patient selection and in combination with neoadjuvant therapy [4]. For example, the Mayo Clinic treatment protocol demonstrates an 82% 5-year survival [5].

MATERIALS AND METHODS

From 2017 to 2021, six patients were included in the treatment protocol for unresectable HCC followed by LT (Fig. 1) at Granov Russian Scientific Center for Radiology and Surgical Technology.

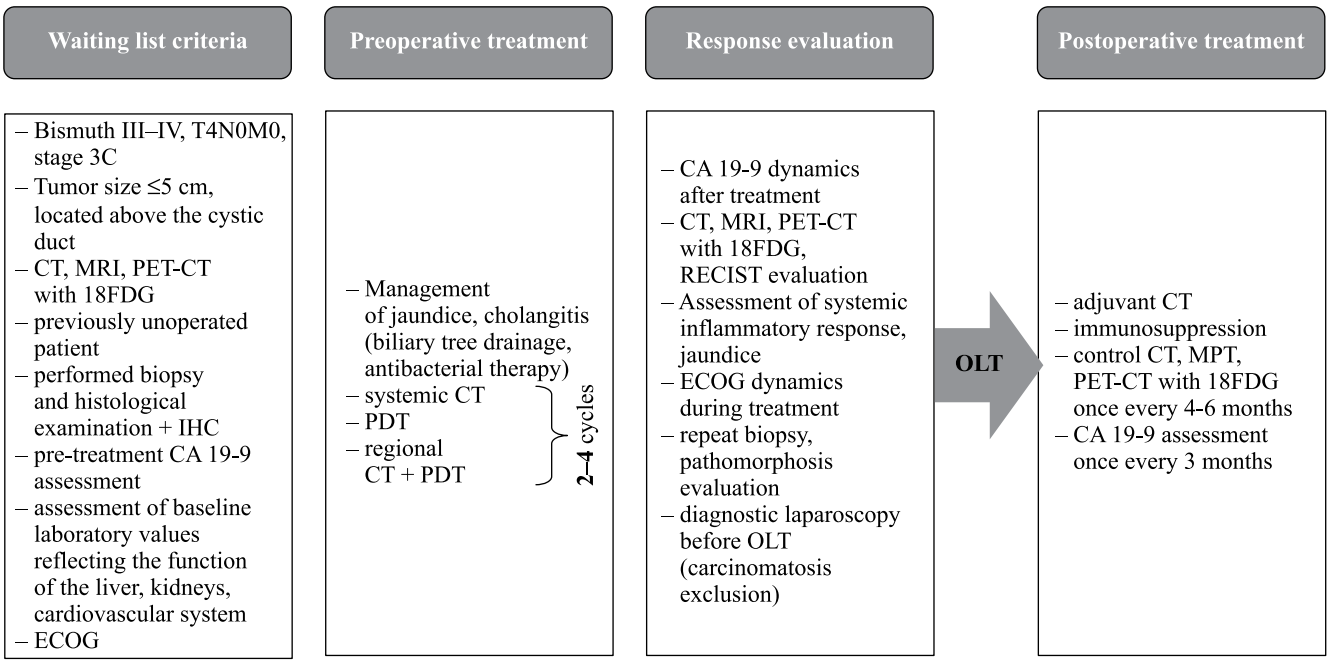

Fig. 1. Brief description of a multidisciplinary protocol for the treatment of unresectable Klatskin tumor with subsequent liver transplantation, developed at Granov Russian Scientific Center for Radiology and Surgical Technology

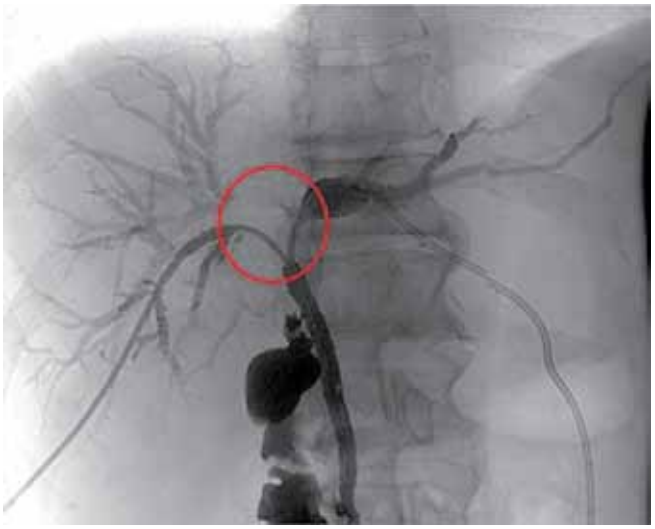

Fig. 2. X-ray picture of a 55-year-old patient with bilaterally installed external-internal cholangiodrainage. The red circle marks the area of confluence of the lobar bile ducts with the tumor stricture

The criterion for unresectability was segmental bile ducts lesion – Bismuth-Corlette type IV or IIIa, IIIb with contralateral lesion of vascular structures (branch of hepatic artery or portal vein). The stage of the disease was established via computed tomography, magnetic resonance imaging (MRI) and direct cholangiography (Fig. 2).

Patients with a tumor size <5 cm and located above the cystic duct were considered. Distant metastases were excluded by radiological methods of investigation. In all cases, histological confirmation by intravesical biopsy, assessment of CA 19-9 levels (in the absence of active cholangitis) before treatment, regular bacteriological examination of bile and appropriate antibacterial therapy were mandatory. Used as neoadjuvant therapy was a combination of endobiliary photodynamic therapy (PDT), regional CT (Fig. 3) and systemic CT.

Each technique was used at least three times for four to five months with radiological evaluation and determination of CA 19-9 levels in order to control tumor growth and bioactivity. Patients were placed on the LT wait list for only when the tumor marker was reduced, there were no radiological signs of disease progression, and there was no acute cholangitis. Prior to orthotopic liver transplantation (OLT), the potential recipient underwent laparoscopic abdominal revision for carcinomatosis and assessment of lymph nodes of the hepatoduodenal ligament with excision of suspicious tissue for morphological examination. Where extrahepatic spread was histologically confirmed, LT was not performed, otherwise, it was performed according to the classical technique with paracaval, para-aortic and hepatoduodenal lymphodissection, biliodigestive anastomosis by an isolated Roux loop of small intestine. All suspicious (enlarged/dense) lymph nodes in the area of hepatoduodenal ligament, ribs, aorta and inferior vena cava were removed. This, according to the classification of the Japanese Research Society for Gastric Cancer (JRSGC), corresponds to anatomic groups 5, 7, 8a, 8p, 9, 12a, 12b, 12p. LT was performed in three patients, all of whom were men. Their age ranged from 40 to 55 years (mean 48). The mean time from the start of treatment to transplantation was 9.3 months (6 to 14). The mean CA 19-9 level at the time of OLT was 81.3 IU/mL (8 to 212). A standard triple immunosuppression (tacrolimus, mycophenolic acid, prednisolone) was used in the postoperative period.

RESULTS

Despite inclusion in the treatment protocol and neoadjuvant therapy, three patients showed a more than twofold increase in CA 19-9 levels over an average of four months. RECIST CT scan showed that one of them had disease progression. Diagnostic laparoscopy demonstrated that one patient had carcinomatosis.

Against the background of a combination of methods (photodynamic therapy, regional chemotherapy, systemic chemotherapy) as neoadjuvant treatment, CA 19-9 was normalized in two patients, while a fourfold reduction of the tumor marker level was achieved in one patient. On follow-up CT scan, two of these patients responded to treatment as the disease stabilized, one patient had a partial response. Diagnostic laparoscopy and biopsy of hepatoduodenal lymph nodes in all patients with decreased CA 19-9 levels did not reveal tumor elements in the examined material, which allowed for OLT (Table). One of the examined specimens of the removed liver showed no macroscopic signs of tumor (Fig. 4).

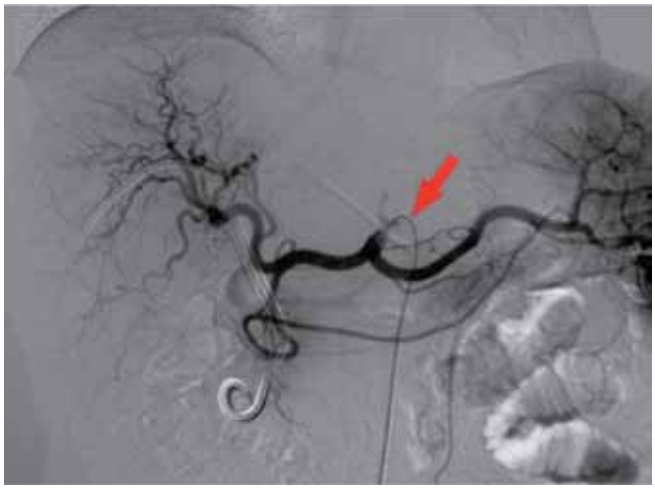

Fig. 3. Angiogram of a 40-year-old patient. Arterial introducer (indicated by red arrow) is inserted into the common hepatic artery for regional chemotherapy

Small single foci of cholangiocarcinoma could be detected only by additional slicing of the microslide (pathomorphosis stage IV) (Fig. 5).

One patient died from sepsis 3 years after OLT as a result of secondary biliary cirrhosis and biliary abscesses without signs of progression. It should be noted that the patient did not comply, had an episode of chronic rejection in the first six months after surgery due to violation of the medication regimen. Also, ischemic bile

Table

Neoadjuvant treatment with tumor marker dynamics and RECIST response for all patients included in the protocol. Treatment results

Patient	Age (years)	Number of PDT	Number of RCT	Number of SCT	CA 19-9 level before treatment	CA 19-9 level after treatment / at the time of OLT	RECIST response	Time to progression/OLT	Survival after OLT	Survival from initiation of treatment
1	49	7	11	8	986	8	CR	**OLT at 14 months**	36 months	50 months
2	40	4	4	5	754	24	SD	**OLT at 8 months**	21 months	29 months
3	37	4	4	4	337	754	SD	Carcinomatosis in diagnostic laparoscopy	–	11 months
4	56	2	2	3	3416	7256	PD	Progression at 4 months	–	7 months
5	55	4	3	5	864	212	SD	**OLT at 6 months**	6 months	12 months
6	46	5	6	6	789	1456	PD	Progression at 5 months	–	8 months

duct injury resulting from arterial insufficiency of blood supply to the graft cannot be ruled out. Two patients are still alive for 6 and 21 months without signs of cancer progression.

DISCUSSION

The use of LT as a treatment option for HCC patients has been attempted since the 1980s. Despite the reasonable potential advantage of complete removal of the affected organ with the achievement of a "negative" resection margin, the outcomes have left much to be desired. At the dawn of attempts to solve this problem, clinics performing LT in HCC reported a 3-year survival rate of about 30% [6]. Such results have led the global medical community to the conclusion that providing radical surgery by unilaterally hepatectomizing the recipient cannot significantly improve long-term outcomes. Moreover, immunosuppression is known to increase the risk of tumor progression and can lead to rapid patient death. However, a careful analysis of the accumulated materials revealed that cohorts of patients with "negative" resection margins and no metastases in regional lymph nodes had much better survival rates. Besides, a small group of patients at the Mayo Clinic who received only chemoradiotherapy without subsequent surgical treatment had a 22% 5-year survival rate [7]. Unsatisfactory outcomes of standard HCC treatment methods and the success of individual studies were the trigger for the active use of combined methods. With data indicating the effectiveness of chemoradiotherapy for HCC and the knowledge that disease progression is usually associated with local recurrence rather than distant metastases [8], a Nebraska transplant team first developed a strategy – high dose-rate neoadjuvant brachytherapy in combination with 5-fluorouracil (5-FU) chemotherapy and subsequent LT [9]. Of course, there were biliary, infectious and vascular complications associated with the use of high dose-rate brachytherapy and peculiarities of the course of the disease. However, early results were promising with regard to the development of local recurrences. Subsequently, the Mayo Clinic adopted this concept, developing a similar protocol for neoadjuvant therapy followed by LT in 1993. The protocol combined the benefits of radiation therapy, chemotherapy, and LT with appropriate selection of patients with localized, unresectable HCC. Preliminary results for 11 patients reported in 2000 were encouraging, and an update in 2004 reported an 82% 5-year survival rate in 28 patients [5].

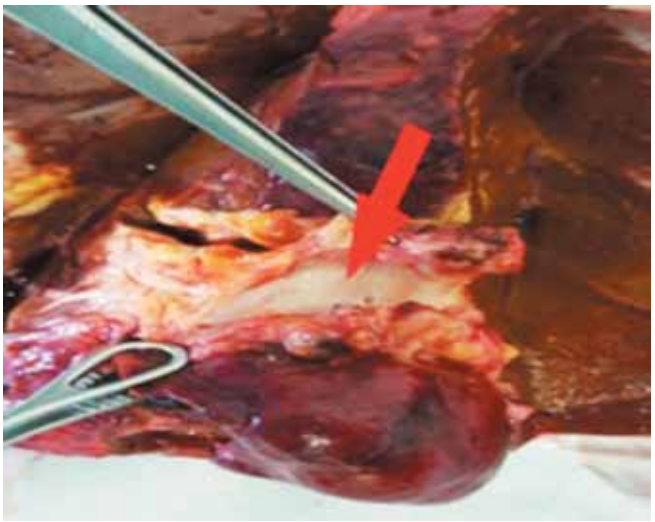

Fig. 4. Photo of a macroscopic specimen (removed recipient's liver). No macroscopic signs of tumor (indicated by red arrow) in the bile duct lumen

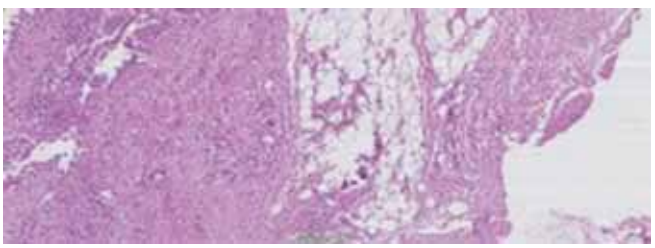

Fig. 5. Photo of a macroscopic specimen. Single foci of cholangiocarcinoma detected by additional slicing. Grade 4 pathomorphosis

Unfortunately, the domestic practice of LT in HCC appears to be extremely scarce and unsystematic, judging by the absence of a significant volume of publications. Treatment of technically unresectable HCC is palliative, and its results and prognosis differ little from those of disseminated process and, as a rule, are caused by rapidly progressing biliary obstruction and cholangitis. The primary task in treatment of such patients is biliary decompression in order to relieve mechanical jaundice and purulent cholangitis [10]. For this patient cohort, biliary decompression involves percutaneous transhepatic cholangiostomy due to the impossibility of performing retrograde drainage in more than a half of cases with proximal extrahepatic bile duct strictures [11].

The standard anti-tumor treatment for unresectable HCC, as well as for any form of inoperable locally disseminated or metastatic cholangiocellular carcinoma based on Russian and foreign clinical guidelines, is systemic polychemotherapy according to GemCis (gemcitabine/cisplatin) or GemCap (gemcitabine/capecitabine) scheme, as well as high-precision stereotactic conformal chemoradiotherapy with fluoropyrimidines [12, 13] or other options of chemotherapy and radiotherapy, depending on the patient's somatic status, individual intolerance and developing complications.

At the same time, according to the combined statistics of the effectiveness of these treatment methods for all inoperable malignant tumors of biliary structures, the median overall survival is 8–10 months [14]. Some of the best results achieved by chemoradiotherapy demonstrate a 30% 4-year survival rate [15].

Endobiliary PDT is a relatively new progressive treatment for unresectable HCC. The efficacy of PDT in combination with biliary decompression has been confirmed by numerous studies, some of which have shown a fivefold difference in life expectancy [16–19].

Being engaged in hepatobiliary and endovascular surgery and oncology in general, as well as HCC and LT in particular, we have been trying to use the entire arsenal of available options for this nosology for a long time. Like most of our colleagues, for biliary decompression we perform percutaneous transhepatic cholangiodrainage with mandatory evaluation of the bile microbial landscape and antibacterial therapy. The presence of percutaneous transhepatic drainage in the biliary tree in HCC patients implies that delivery of the emitter to the affected area is relatively easy and that multiple repetition of PDT procedure is possible, which has been confirmed by our own experience.

The ideological similarity between the world-renowned Mayo protocol and the treatment protocol developed by us is the stopping of tumor growth, reduction of biological activity of the tumor until radical treatment. Our neoadjuvant treatment includes PDT and no radiation therapy (RT). The efficacy of LT in unresectable Klatskin tumor is beyond doubt. However, as the authors themselves admit, implementation of external beam and intraductal brachytherapy is often accompanied by severe cholangitis, biliary abscesses, sepsis and vascular complications [5, 9], which, in our opinion, is manifested as pronounced proliferation of connective tissue and formation of rough cicatricial structures in the hepatoduodenal ligament. This cannot but affect the intraoperative precision of dissection of anatomical structures and formation of anastomoses, which significantly complicates vascular reconstruction during LT. The need to maintain a balance between the benefits and possible complications makes it necessary to keep the issue of RT use open. However, with regard to chemotherapy, we believe that in addition to the use of systemic chemotherapy, implementation of transarterial chemoinfusion (TAI) allows to create a high concentration of chemotherapy drug in a limited anatomical area, thereby increasing the cytostatic effect. In addition, direct angiographic examination allows to clearly assess the degree of involvement of vascular structures in the tumor process. In our opinion, alternating systemic chemotherapy and TAI with endobiliary PDT sessions is the best option for neoadjuvant therapy.

An additional advantage of the neoadjuvant protocol is the "test of time", as a cohort of patients with aggressive tumor biology experience disease progression despite ongoing treatment [20]. In such cases, LT is not indicated.

CONCLUSION

Indications for LT and its success in unresectable Klatskin tumor are determined by the effectiveness of palliative treatment for at least 3–4 months by reducing the tumor biological activity (assessment of tumor marker, size, metastatic lesion, extrahepatic spread) and control of acute cholangitis.

The authors declare no conflict of interest.

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