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Diagnosis and Treatment of Klatskin Tumors (KT) Using Interventional Radiology

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Интервенционные радиологические вмешательства в диагностике и лечении опухоли Клатскина

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Introduction. The incidence of Klatskin Tumor (KT) continues to rise worldwide. Despite the development of surgical techniques and the emergence of new drugs, the results of diagnosis and treatment of this disease remain unsatisfactory.

Aim. To evaluate the efficacy of video-assisted intraductal biopsy and intraductal photodynamic therapy (iPDT) in combination with regional chemotherapy (RCT) in patients with KT.

Materials and methods. The results of treatment of 18 patients with KT treated in the Leningrad Regional Clinical Oncological Dispensary and in the Leningrad Regional Clinical Hospital (merged in 2023) from 2021 to November 2024 were evaluated. All patients following percutaneous transhepatic cholangiography (PTC). Bismuth-Corlette classification: IV — 8 (44 %); IIIa — 4 (22 %); IIIb — 5 (28 %) and II — 1 (6 %). 15 patients were examined using the original patented technique of video-assisted intraductal pinch biopsy under fluoroscopic guidance. A total of 45 sessions of iPDT (1 to 7 times) and 34 cycles of RCT (1 to 8 times) were conducted. A cylindrical diffuser was used in the original patented iPDT technique. RCT: chemoinfusion into the common hepatic artery according to the Gemcis or GemOx regimen (lipiodol + oxaliplatin during chemoembolization; n = 8). Three patients with a partial response underwent radical surgery. Three patients underwent stenting. Results were assessed by monitoring CA19-9, MSCT and MRI 4–6 weeks after every two combined cycles. Treatment was repeated after an average of 2.6 months.

Results. There were no complications. Currently, 7 patients (44 %) are alive between 3 and 43 months (mean 22 months) and their treatment is continuing. The actuarial survival rate for the 1-2-3 year period was 89 – 28 – 11 %. Ten (56 %) of 18 patients died between 14 and 24 months, mOS = 17.2 months. OS = 18 months.

Conclusion. Video-assisted intraductal pinch biopsy under fluoroscopic guidance is a safe and simple technique to achieve 100 % verification of the diagnosis of KT. The combination of iPDT and RCT improves survival (OS = 18 months) and

Введение. В мире сохраняется тенденция к росту заболеваемости опухолью Клатскина. Несмотря на развитие хирургической технологии и появление новых лекарственных препаратов, результаты диагностики и лечения этой патологии остаются неудовлетворительными.

Цель. Изучить результаты видеоассистированной внутрипротоковой биопсии и внутрипротоковой фотодинамической терапии в сочетании с регионарной химиотерапией у пациентов с опухолью Клатскина.

Материалы и методы. Оценены результаты лечения 18 больных опухолью Клатскина, получавших лечение в ГБУЗ ЛОКОД и ГБУЗ ЛОКБ (объединение в 2023 г.) с 2021 по ноябрь 2024 гг. Все пациенты после чрескожного чреспеченочного холангиодренирования. Классификация Bismuth - Corlett: IV — 8 (44 %); IIIa — 4 (22 %); IIIb — 5 (28 %) и II — 1 (6 %). 15 пациентам выполнена верификация по оригинальной запатентованной методике видеоассистированной внутрипротоковой щипковой биопсии под рентгеноскопическим контролем. Всего выполнили 45 сеансов внутрипротоковой фотодинамической терапии (от 1 до 7 раз) и 34 цикла регионарной химиотерапии (от 1 до 8 раз). Фотодинамическая терапия выполнялась по запатентованной методике с использованием цилиндрического диффузора. Регионарная химиотерапия: химиоинфузия в общую печеночную артерию по схеме Gemcis или GemOx (липиодол + оксалиплатин при химиоэмболизации; n = 8). Трех больным с частичным ответом выполнены радикальные операции. Еще трем выполнены стентирования. Результаты оценивали, контролируя уровень СА19-9, результаты компьютерной и магнитно-резонансной томографии, спустя 4–6 недель после каждого двух сочетанных циклов. Лечение повторяли через в среднем 2,6 мес.

Результаты. Осложнений не было. Живы 7 пациентов (44 %) в сроки от 3 до 43 мес. (в среднем 22); продолжается их лечение. 1-2-3 - летняя актуаральная выживаемость составила 89- 28-11 %. Умерли 10 (56 %) из 18 пациентов в сроки от 14 до 24 мес. Средняя продолжительность жизни составила 17,2 мес. Медиана общей выживаемости 18 мес.

Выводы. Видеоассистированная внутрипротоковая щипковая биопсия под рентгеноскопическим контролем — безопасная и простая методика, позволяющая достичь 100 % верификации диагноза опухоли Клатскина.

may be effective as neoadjuvant therapy prior to extensive liver resection (relapse-free survival 28 months).

Keywords: Klatskin tumor; portal cholangiocarcinoma; intraductal biopsy; videocholangioscopy; intraductal photodynamic therapy; chemoembolisation of hepatic arteries; regional chemoinfusion

For Citation: Aleksei S. Polekhin, Aleksei L. Filonov, Artur Ch. Gapbarov. Diagnosis and treatment of Klatskin tumors using interventional radiology. *Voprosy Onkologii = Problems in Oncology*. 2025; 71(1): 155-162. (In Rus).-DOI: 10.37469/0507-3758-2025-71-1-155-162

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Introduction

Malignant tumors of the bile duct are a current problem in oncology. Cancer of the biliary tract accounts for 15 % of all malignant liver tumors. Of these, Klatskin tumour (KT), or cancer of the proximal part of the bile duct, is the most common (70–80 %). In terms of the frequency of occurrence in the structure of oncological diseases, it is not the leading position (2 %) [1, 2]. However, the incidence of the disease has been increasing year on year. According to official statistical reports in the Russian Federation from 2012 to 2022, the increase was more than 7 %, especially in the male population (more than 18 %) [3]. The peculiarity of this tumor is that it presents with a vivid clinical picture of mechanical jaundice syndrome, which requires urgent surgical intervention in the form of decompression of the biliary tree. The ultrasound, CT and MRI data confirm the dilatation of the intrahepatic bile ducts and the presence of an infiltrate in the region of the hepatic portal vein. Magnetic resonance cholangiopancreatography (MRCPG) can reveal the level and extent of the tumor lesion. KT develops in the extrahepatic part of the bile ducts from the mouths of the lobular ducts, up to the level of the confluence of the vesicular duct. In such localization, percutaneous, puncture drainage is considered the most preferable and effective [4, 5, 6]. The number and type of drains are determined by the Bismuth-Corlette classification [7], which is the primary classification for KT. Surgery remains the most effective treatment for KT. However, radical tumor removal is only possible in 15–20 % of cases from the time of first clinical symptoms [8, 9, 10]. Histologically, KT is a cholangiocarcinoma or ductal adenocarcinoma with infiltrative growth. This is why the small group of patients who have undergone radical surgery are at high risk of early recurrence. According to various authors, 70 % of patients relapse within a year, with an average time to progression of 8.5 months [11, 12]. According to international data, the survival rate of inoperable

Сочетание методик внутрипротоковой фотодинамической терапии и регионарной химиотерапии позволяет улучшить показатели выживаемости, а также может быть эффективным в качестве неoadьювантной терапии перед обширными резекциями печени (безрецидивный период 28 мес.).

Ключевые слова: опухоль Клатскина; воротная холангиокарцинома; внутрипротоковая биопсия; видеохолангиоскопия; внутрипротоковая фотодинамическая терапия; химиоэмболизация печеночных артерий; регионарная химиоинфузия

Для цитирования: Полежаев А.С., Филонов А.Л., Гапбаров А.Ч. Интервенционные радиологические вмешательства в диагностике и лечении опухоли Клатскина. *Вопросы онкологии*. 2025; 71(1): 155-162.-DOI: 10.37469/0507-3758-2025-71-1-155-162

KT without anti-tumor treatment is extremely poor at 6 to 9 months [13]. Histological confirmation of the malignant process is necessary to establish the diagnosis. This has become increasingly important in recent years with the development of molecular genetic technologies and pharmaceuticals. However, histological confirmation of the process is challenging due to the extra-organ location of the tumor and the proximity of the major vessels.

Systemic anti-tumor drug therapy, including the use of molecular-guided therapy, is indicated for the inoperable form of KT according to national clinical guidelines. Gemcitabine + cisplatin + durvalumab is considered the most effective combination, with a median duration of 11 months. Existing systemic CT in biliary cancer rarely leads to a significant reduction in the size of the primary tumor and therefore the likelihood of converting an unresectable process into a resectable one is low. Palliative effects can also be achieved with intra-arterial chemoembolization and interventional methods of physical exposure (radiofrequency or microwave ablation), but the advantages of these techniques over chemoradiotherapy have not been proven [14, 15]. The use of cholangiodrainage techniques combined with regional chemotherapy (RCT) significantly improves the quality of life and life expectancy of patients with this pathology [16, 17]. The desire to improve survival rates has led to the development of techniques to physically target the tumor. Intraductal brachytherapy is actively used worldwide. However, this method is not always applicable [18, 19]. In our country, the intraductal photodynamic therapy (iPDT) is a treatment option that is widely used. According to national clinical guidelines, iPDT in combination with stenting and/or drainage has an advantage over stenting and/or drainage alone in terms of survival and quality of life, is feasible in almost all cases, and has similar efficacy to brachytherapy [20]. When KT is detected, the selective delivery and distribution of light specifically to the area of the tumor lesion is relevant [21, 22]. Aim – to investigate our own

outcomes with the use of interventional radiology techniques in the diagnosis and treatment of KT.

Materials and Methods

The study is based on the treatment experience of 18 patients with KT who were treated at the Leningrad Regional Clinical Oncological Dispensary and the Leningrad Regional Clinical Hospital (merged in 2023) from September 2021 to April 2024. All patients underwent percutaneous transhepatic cholangiodrainage: 8 (44 %) in external institutions, 10 (56 %) in the Leningrad Regional Clinical Hospital. To ensure adequate bile flow to the gastrointestinal tract, we performed external internal cholangiodrainage (IICD), including the second stage after external drainage of the bile ducts. 10.2 F external/internal drainage catheters (OOK-Medical) 40 cm long were used in most cases. Due to the high degree of biliary tree involvement, additional drainage holes were often modelled 2–4 cm proximal to the radiopaque marker. We consider this type of dewatering to be necessary for further treatment. According to the Bismuth-Corlette classification, 8 patients (44 %) had type IV, 4 patients (22 %) had type IIIa, 5 patients (28 %) had type IIIb and 1 patient had type II (6 %). Two patients with type IIIb and II had metastatic lesions in the right lobe of the liver.

All patients underwent verification of the oncological process using the original patented technique of video-assisted intraductal pinch biopsy under fluoroscopic control, as previously described in reference [23]. The fundamental principle underlying the method is percutaneous antegrade cholangioscopy, which serves to ascertain the precise location of the tumor. External-internal percutaneous transhepatic cholangiodrainage was performed on the guidewire, then the 10 F introducer was placed over the contrast defect under fluoroscopic guidance and the guidewire was removed. An ultra-thin CMOS endoscope - CM Series 11102 - Karl Storz (Germany; 2.9 mm = 8.7 F) was inserted through an introducer behind the tumor occluded area. After identifying the true location of the tumor, the introducer was brought to the end of the endoscope. The endoscope was then removed and the position of the introducer was fixed. Endoscopic biopsy forceps were then inserted through the introducer at 1.5–2 mm intervals and biopsy was performed under fluoroscopic guidance (fig. 1). In all cases, a sufficient volume of biomaterial was obtained for histological and immunohistochemical examination.

The decision on treatment tactics was made in a multidisciplinary oncology concilium with written consent of all patients. All patients were considered potentially resectable, given the ambiguity in interpreting the results of investigations

at the peak of jaundice. A total of 45 sessions of intraductal photodynamic therapy (1 to 7) and 34 cycles of regional chemotherapy (1 to 8) were performed. Photodynamic therapy was performed according to the original patented technique by antegrade access under fluoroscopic control using a cylindrical diffuser after prior intravenous administration of a photosensitizer (Radachlorin, Photoditazine) [24]. The method involves the use of a cylindrical diffuser. This was not originally designed for intraductal use. The obturator was then removed from the distal part of the diffuser and the gelatinous substance containing the light-optic component was mechanically disrupted to a depth of up to 5 mm. Contrast medium (Omnipak, Ultravist) was injected into the cavity and the obturator was replaced. The obturator was also removed in the proximal part of the diffuser, after which a light guide with a microlens was injected into the optic gel to a depth of 5 mm. In this way, two x-ray contrast marks were created, and the space between them was a working zone for even selective light distribution within the tumor-affected part of the bile duct. After removal of the external-internal cholangiodrainage on the leads through the preserved puncture channels, a plastic catheter with a cylindrical diffuser was inserted into the biliary tree so that the proximal and distal markers were anterior and posterior to the contrast defect (fig. 2). Conductors were removed from this area to ensure even distribution of light. Intraductal photodynamic therapy was performed with the Latus (Atkus) laser device in the mode of dosed light fractionation after prior intravenous administration of photosensitizer. The radiation power at the fibre output was 1 W, the energy density in the tumor lesion zone was 100–300 J/cm². The energy was calculated individually, using a special program, based on the parameters of the cylinder surface area. After completion of the intraductal photodynamic therapy session, the tumor stricture was recanalized and the external-internal biliary drainage was restored with drain replacement. Since the start of intravenous infusion, the patient has adhered to the prescribed light regimen. Regional chemotherapy was performed according to the standard technique: percutaneous femoral puncture, upper mesentericography, celiac and arteriohepaticography. After evaluating the arterial anatomy of the hepatopancreatoduodenal zone and the presence or absence of invasion in the main arteries and veins. Infusion of chemotherapeutic agents into the common or native hepatic artery according to the gemcitabine and cisplatin (Gemcis). The dose of gemcitabine was 1000 mg/m² for 30 minutes, while the dose of cisplatin was 25 mg/m² for 60 minutes. In the presence of liver metastases or parenchymal invasion, regional

chemotherapy was administered according to the GemOx regimen: Gemcitabine - 1000 mg/cm² for 30 minutes and chemoembolization of liver foci (Lipiodol + Oxaliplatin; n = 8). This is due to the fact that cisplatin is a large volume solution which does not allow a stable chemo-oil suspension to be made. Oxaliplatin is also available in the form of a lyophilizate, so a sufficient concentration of the chemotherapeutic agent in a small volume of solvent makes it possible to produce a chemo-oil mixture of acceptable composition. A total of three patients underwent bilateral antegrade stenting, two patients with recurrent cholangitis and one patient with systemic progression.

The interval between cycles of intraductal photodynamic therapy and regional chemotherapy did not exceed 7 days. Treatment outcomes and process dynamics were evaluated by monitoring the level of the oncomarker CA19-9, multispiral computed tomography and MRI (magnetic resonance cholangiopancreatography), 4–6 weeks after each of two combined cycles (intraductal photodynamic therapy

+ regional chemotherapy). Depending on the results of the tests, the cycles were repeated after 1.5–3 (mean 2.1) months. We believe that the most appropriate sequence is as follows: the first stage is intraductal photodynamic therapy, and the second stage is regional chemotherapy or chemoembolization, because this allows the photosensitizer to penetrate the tumour vessels unhindered.

Results

There were no serious complications requiring surgery or intensive care. There were no adverse effects due to non-compliance with the light regime. There were no toxicities from the use of cytostatics.

All 15 patients were successfully diagnosed histologically, demonstrating 100 % efficacy of the technique developed. There were no haemorrhages after video-assisted intraductal pinch biopsy. Our method allowed us to make a diagnosis and start anti-tumor treatment as soon as possible after the manifestation of the disease.

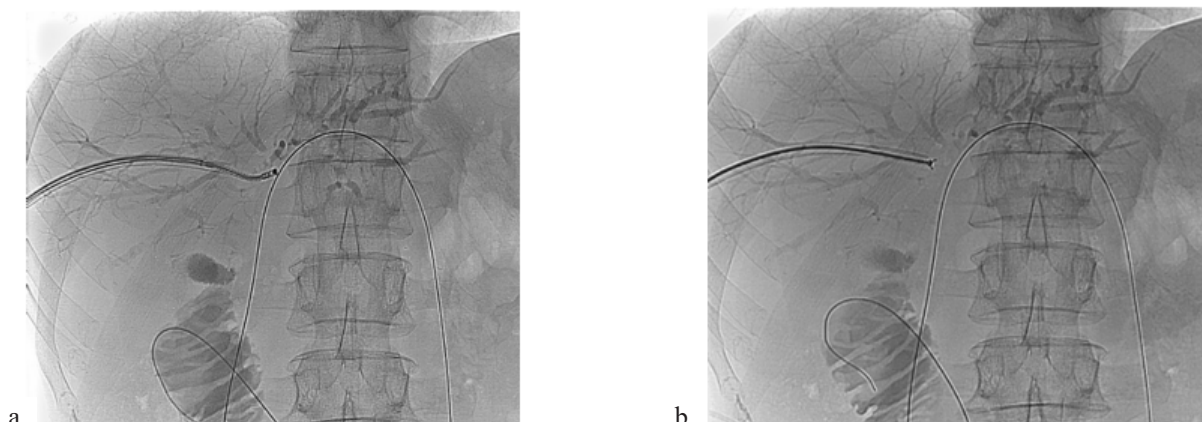


Fig. 1. Video-assisted intraductal pinch biopsy under X-ray guidance.

- a — Radiograph: an ultra-thin endoscope is placed at the site of the tumor at the level of the confluence of the common hepatic duct;
b — Radiograph: targeted intraductal biopsy of a common hepatic duct tumor using biopsy forceps

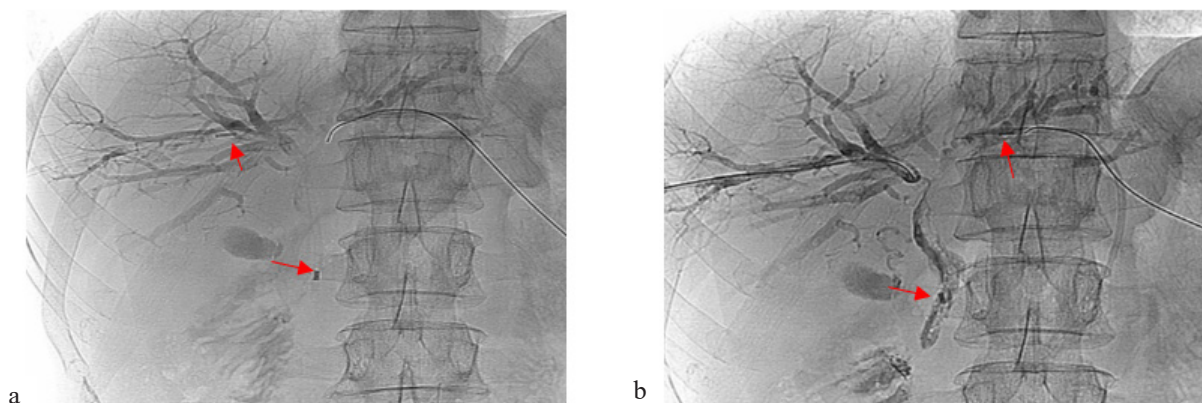


Fig. 2. Intraductal photodynamic therapy under fluoroscopic guidance.

- a — Radiograph: a catheter with a cylindrical diffuser is inserted through the right lobar duct and placed directly at the tumor level, between the distal and proximal radiopaque markers (arrows);
b — Radiograph: a cylindrical diffuser catheter is inserted through the left lobar duct and placed directly at the tumor level, between the distal and proximal radiopaque markers (arrows)

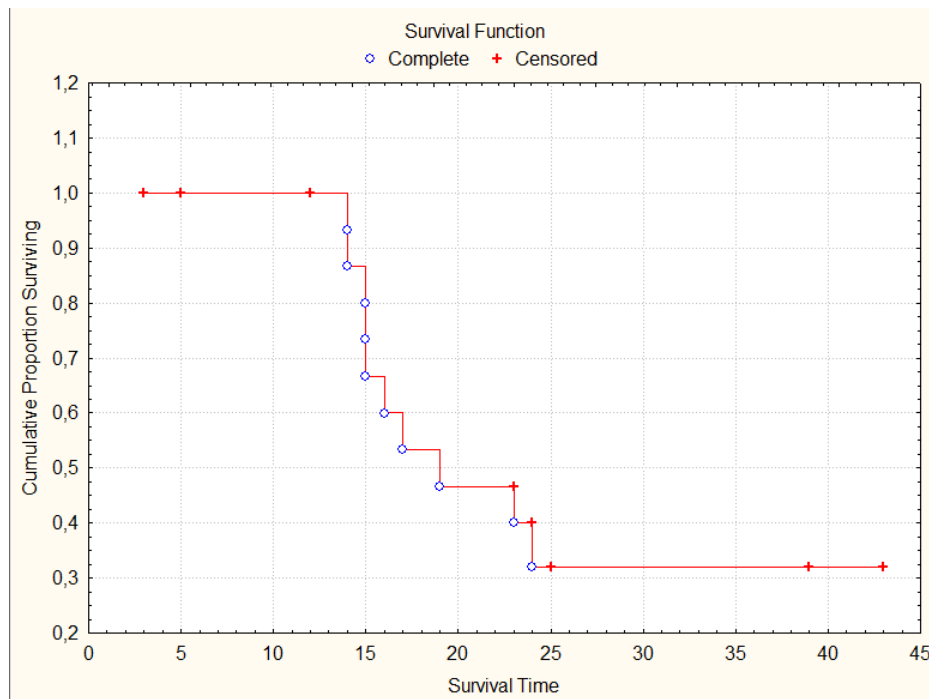


Fig. 3. Calculation of survival in patients with Klatskin tumor according to the Kaplan – Meier method: + — survivors; o — dead

Currently, 8 (44 %) of the 18 patients are alive, ranging from 3 to 43 months (median 22 months), of which 2 patients have shown progression in the form of metastatic disease to distant lymph nodes. They are receiving cycles of palliative chemotherapy (Gemox) combined with intraductal photodynamic therapy between cycles three and four (24 and 23 months - stabilization). Two patients with locally advanced process are treated with combined cycles of intraductal photodynamic therapy + regional chemotherapy with the effect of disease stabilization (3 and 5 months). One patient with poly-resistant cholangitis and dissemination of the tumor process underwent stenting of the common hepatic and common bile ducts. He is currently receiving mono-chemotherapy with capecitabine (Gemox treatment is contraindicated due to diabetic nephropathy and renal failure) and has been alive for 25 months. Two patients underwent extended right hemihepatectomy after two and three courses of intraductal photodynamic therapy + regional chemotherapy and preoperative embolization of the right branch of the portal vein. Both are alive, one at 39 months, under dynamic observation, not receiving any specific anti-tumor treatment. The second was alive for 43 months, but at 28 months local recurrence of the left lobe was noted, without mechanical jaundice, and cycles of intra-arterial chemoembolization of the liver tumor using the Gemox regimen were resumed. This patient had a Bismuth type II bile duct lesion with metastatic involvement of the right lobe of the liver (T2N0M1 - liver; stage IV). One patient underwent left-sided hemihepatectomy after two

cycles of combined treatment, with a recurrence-free period of 6 months.

A total of ten (56 %) of the 18 patients died between 14 and 24 months. Six patients died as a result of tumor dissemination or portal hypertension due to locally advanced disease, while three patients died of cholangitis or sepsis. One patient died of intercurrent disease. Median survival was 17.2 months. One-, two- and three-year actuarial survival rates were 89 %, 28 % and 11 %, respectively. The median overall survival (OS) according to the Kaplan-Meier method was 18 months (fig. 3).

Discussion

In most cases, KT presents with mechanical jaundice and requires decompression of the biliary tree. Diagnostic studies show dilated intrahepatic bile ducts with undilated choledochus and gallbladder. In the context of biliary tree involvement, percutaneous drainage procedures are considered the most preferred and effective treatment option due to the occurrence of what is colloquially known as «high block». After decompression of the biliary tree and determination of the nature of the lesion according to the Bismuth-Corlette classification, the question of surgical treatment arises. The resectability of KT does not exceed 20 % from the first clinical manifestations.

In the context of an inoperable tumor process, histological verification is of paramount importance. This assumption is becoming increasingly relevant with the emergence of new anti-tumor

drugs. Routine histological material, such as percutaneous trepan biopsy, is considered ineffective and extremely risky due to the extra-organ location of the tumor and its proximity to major vessels. Endoscopic methods of obtaining material using the SpyGlass technique are also inefficient (50–70 %) [25]. This is due to the fact that although tumors can be detected by the eye, the endoscope used has a small diameter and a narrow working channel, which allows extremely scarce tissue material to be obtained. This makes histological and immunohistochemical examination impractical in the majority of cases. Bile is prone to sludge and stone formation, especially in the presence of drainage and obstruction. Anterograde techniques are mainly used to identify contrast defects in the biliary tree, which may not always correspond to the actual location of the tumor.

For a long time, the main method of obtaining histological material remained surgical. Often, when attempting to remove the tumor, a dense tumor infiltrate was found in the liver gate, its biopsy was performed and the operation was terminated at the diagnostic stage. The advent of laparoscopic technology has reduced the degree of surgical trauma associated with this type of biopsy. However, the underlying principle of surgery for diagnostic purposes remains unchanged. The method of obtaining a biopsy specimen from KT, using an ultra-thin endoscope under fluoroscopic control, allows an adequate amount of tumor tissue to be obtained in a safe and minimally invasive manner. All cases underwent histological and immunohistochemical examination. This method of biopsy can be performed after a period of 10 to 14 days from the time of biliary drainage. We consider this period to be sufficient for the formation of the puncture channel and the safe performance of repeated endobiliary procedures.

Once the diagnosis of KT has been confirmed, it is imperative to initiate targeted anti-tumor therapy. Even in cases where the biliary tree has been adequately decompressed without intervention, the median overall survival (OS) does not exceed 6–9 months. The efficacy of anti-tumor drug therapy is similarly unsatisfactory, with median OS remaining below 11 months even when monoclonal antibodies are employed. This is due to the inability to adhere to the prescribed treatment regimen, as this patient population often experiences complications related to biliary drains, including drain dysfunction and dislodgement, as well as chronic catheter cholangitis. Regional chemotherapy results in a higher concentration of cytostatic agents in the tumor due to the primary passage effect, with reduced systemic toxicity. This allows the interval between cycles to be safely extended from 3 weeks to 6–8 weeks, in line with the postulates

of locoregional therapy. Finally, without the use of implantable arterial port systems, it is impossible to maintain the same drug delivery regimen as with systemic chemotherapy. If there is evidence of tumor invasion into the liver parenchyma or metastatic lesions, chemoinfusion can be used in combination with intra-arterial chemoembolization, allowing long-term fixation of the cytostatic agent within the tumor under conditions of ischemia.

In our opinion, the most promising treatment option for this disease is the introduction of intraductal photodynamic therapy in combination with endovascular treatment. Photodynamic therapy itself is a versatile method of anti-tumor treatment based on intracellular phototoxic and photochemical reactions. The way in which light is delivered to such an inaccessible area is fundamental to the treatment of KT. The method we have developed, using a catheter with a cylindrical diffuser, allows not only the selective delivery of light at the required wavelength, but also the uniform distribution of this light within the bile duct affected by the tumor. Cholangiodrains are changed after each cycle of intraductal photodynamic therapy (on average every 2.6 months). This allows the biliary tree to be cleaned in a timely manner and prevents the exacerbation of chronic catheter cholangitis, which is significant in this patient population.

The combination of intraductal photodynamic therapy and regional chemotherapy in two cases (16.6 %) allowed us to achieve a partial response to the treatment regimen and to perform radical resection in a process that was initially considered unresectable. This approach to the choice of treatment tactic is therefore particularly useful in borderline resectable cases.

Conclusion

Video-assisted intraductal biopsy under fluoroscopic guidance is a safe and simple technique that allows 100 % verification of the diagnosis of KT. The combination of iPDT and RCT techniques can improve survival rates (OS = 18 months) and can also be effective as neoadjuvant treatment, allowing a recurrence-free period of up to 28 months.

Conflict of interest

The authors declare no conflict of interest.

Compliance with patient rights and principles of bioethics

All included patients received treatment in routine clinical practice after obtaining informed consent for treatment. No patients' personal data were used in the study.

Financing

The work was performed without external funding.

Authors' contributions

The authors declare that their authorship is in accordance with the international ICMJE criteria.

All authors made a substantial contribution to the design of the work, acquisition and analysis of data, drafting and editing of the manuscript, and revising and final approval of the version to be published.

All authors approved the final version of the article before submission for publication and agreed to assume responsibility for all aspects of the work.

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Received / 24.06.2024

Reviewed / 29.10.2024

Accepted for publication / 07.11.2024

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