



КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

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КОМБИНИРОВАННОЕ ЛЕЧЕНИЕ ПРИ МЕСТНОРАСПРОСТРАНЕННОМ ХОЛАНГИОЦЕЛЛЮЛЯРНОМ РАКЕ ПЕЧЕНИ – КЛИНИЧЕСКИЙ СЛУЧАЙ

А.Н.Поляков¹, Ю.И.Патютко¹, А.Ю.Сыслова^{1,2}, К.А.Романова¹, И.С.Базин¹, О.Н.Сергеева¹, Э.Р.Виршке¹, Е.С.Макаров¹, Е.Ю.Антонова^{1,3}, А.А.Киршин⁴, Д.В.Подлужный¹

1. ФГБУ «НМИЦ онкологии им. Н.Н. Блохина» Министерства здравоохранения Российской Федерации, 115478, Российская Федерация, Москва, Каширское шоссе, д. 24
2. ФГБОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Министерства здравоохранения Российской Федерации, 117997, Российская Федерация, г. Москва, ул. Островитянова, д. 1
3. ФGAOU ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет), 119991, Российская Федерация, г. Москва, ул. Трубецкая, д. 8, стр. 2
4. БУЗ УР «Республиканский клинический онкологический диспансер им. С.Г. Примушко» Министерства здравоохранения Удмуртской Республики, 426000, Российская Федерация, г. Ижевск, ул. Труда, д. 3

Резюме

Резекция печени является стандартом лечения больных локальным неосложненным раком внутривисцерального желчного протока. Системная химиотерапия назначается при наличии отдаленных метастазов. Трудности в выборе метода лечения возникают при распространении опухоли на окружающие структуры, множественном поражении печени, признаках вовлечения регионарных лимфоузлов. Свое влияние на тактику оказывает наличие осложнений.

Представленный случай описывает возможности индивидуального мультидисциплинарного подхода при местнораспространенной холангиокарциноме печени, осложненной механической желтухой, холангитом, холангиогенными абсцессами. Хирургический подход выбран основным. Своевременно применены методы интервенционной радиологии, химиотерапии, лучевой терапии. Вышеуказанный подход позволил добиться в этой сложной клинической ситуации хороших результатов: больная жива более четырех лет от момента операции, признаков прогрессирования в настоящее время не определяется.

Ключевые слова:

рак внутривисцерального желчного протока, комбинированное лечение, обширная резекция печени, резекция желчных протоков, интервенционный билиодигестивный анастомоз, послеоперационная химиотерапия, внутривисцеральная лучевая терапия

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Для корреспонденции

Александр Николаевич Поляков, к.м.н., старший научный сотрудник онкологического отделения хирургических методов лечения №7 (опухолей гепатопанкреатобилиарной зоны) ФГБУ «НМИЦ онкологии им. Н.Н. Блохина» Министерства здравоохранения Российской Федерации

Адрес: 115478, Москва, Каширское шоссе, д. 24

E-mail: Dr.alex@gmail.com

ORCID: <https://orcid.org/0000-0001-5348-5011>

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COMBINED TREATMENT FOR LOCALLY ADVANCED CHOLANGIOCELLULAR LIVER CANCER – THE CASE REPORT

A.N.Polyakov¹, Yu.I.Patyutko¹, A.Yu.Syskova^{1,2}, K.A.Romanova¹, I.S.Bazin¹, O.N.Sergeeva¹, E.R.Virshke¹, E.S.Makarov¹, E.Yu.Antonova^{1,3}, A.A.Kirshin⁴, D.V.Podluzhnyi¹

1. N.N.Blokhin National Medical Research Center of Oncology, 24 Kashirskoye sh., Moscow 115478, Russian Federation
2. N.I.Pirogov Russian National Research Medical University (RNRMU), 1 Ostrovityanova str., Moscow 117997, Russian Federation
3. I.M.Sechenov First Moscow State Medical University (Sechenov University), 8/2 Trubetskaya str., Moscow 119991, Russian Federation
4. S.G.Primushko Republican clinical Oncology dispensary, 3 Truda-str., Izhevsk 426009, Russian Federation

Abstract

Liver resection is the standard in the treatment of patients with the local uncomplicated intrahepatic bile duct cancer. Systemic chemotherapy is prescribed in the presence of distant metastases. Difficulties in a choice of the treatment method come up when one or several factors are revealed: the tumor spread towards the surrounding structures, multiple liver lesions, lymph nodes involvement signs. The complications presence manages treatment strategy too. The case describes the possibilities of an individual multimodal approach in a treatment strategy for the patient with locally advanced liver cholangiocarcinoma complicated by obstructive jaundice, cholangitis, cholangiogenic abscesses. The surgical approach was approved as the main one. Methods of interventional radiology, chemotherapy, radiation therapy were applied when necessary. The mentioned above treatment strategy allowed us to achieve good results in this difficult clinical case. The patient is alive for more than four years from the time of surgery, signs of progression are not currently defined.

Keywords:

intrahepatic bile duct cancer, combined treatment, extensive liver resection, bile ducts resection, interventional biliodigestive anastomosis, postoperative chemotherapy, intraductal radiotherapy

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For correspondence

Aleksandr N. Polyakov, MD, PhD, the senior researcher of the oncology department of surgical treatment methods №7 (tumors of the hepatopancreatobiliary zone) N.N.Blokhin National Medical Research Centre of Oncology
Address: 24 Kashirskoye sh., Moscow 115478, Russian Federation
E-mail: Dr.alex@gmail.com
ORCID: <https://orcid.org/0000-0001-5348-5011>

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INTRODUCTION

Liver resection with dissection of regional lymph nodes in compliance with radicalism principles still remains the preferential treatment option for the patients with intrahepatic bile duct cholangiocarcinoma [1]. Extensive liver surgery (70%) is often required to increase radicalism as well as resection of extrahepatic bile ducts (20%) and general vessels (5%). However the frequency of nonradical surgery even in these cases reaches 15% [2]. The involvement of extrahepatic bile ducts and large vessels most often occurs if portal type of liver cholangiocarcinoma is observed, for which, infiltrative periductal growth, presence of mechanical jaundice and a high frequency

of postoperative complications are typical in distinction from peripheral type [3].

In inoperable cases the methods of local or regional impact, radiotherapy or systemic treatment can be applied which may converse the tumor into a resectable condition [4, 5]. The search for optimal schemes and regimen of additional treatment is managed to improve the results of surgical treatment following the radicalism principles [4].

Clinical case

On the 12th of December 2014 patient G., female, 1987 y.b., noted icteric staining of the skin. Complex examination revealed mechanic type of jaundice. Bile hypertension was caused by the tumor located in the

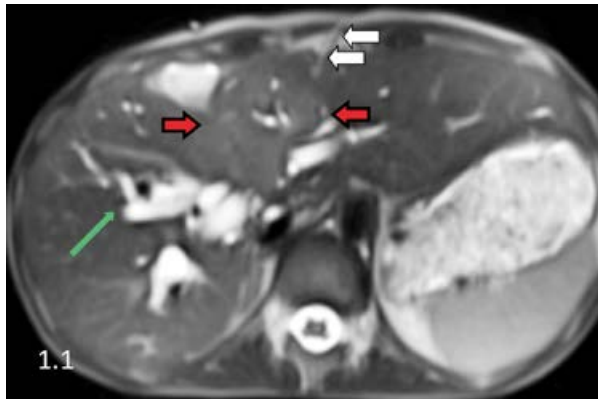


Fig. 1. Abdominal MR-scan data from 02/12/2015

Fig. 1.1. T2-weighted images in axial projection demonstrate a tumor mass in the central part of the liver (56*55*43 mm, red arrows). The tumor invades extrahepatic bile ducts confluence causing significant widening of bile ducts (up to 10 mm, green arrow). In the ducts of the left lobe is introduced a drainage which passes directly through a tumor mass (white arrows)

Рис. 1. МР-томограммы органов брюшной полости от 12.02.15

Рис. 1.1. На Т2-изображениях в аксиальной проекции (рис 1.1) в центральных отделах печени определяется опухолевый узел 5,6х5,5х4,3 см (красные стрелки). Опухоль распространяется на конfluence желчных протоков, вызывая значительное, до 1 см, расширение протоков (длинная зеленая стрелка). В протоках левой доли установлен дренаж, который проходит сквозь опухоль (белые стрелки)

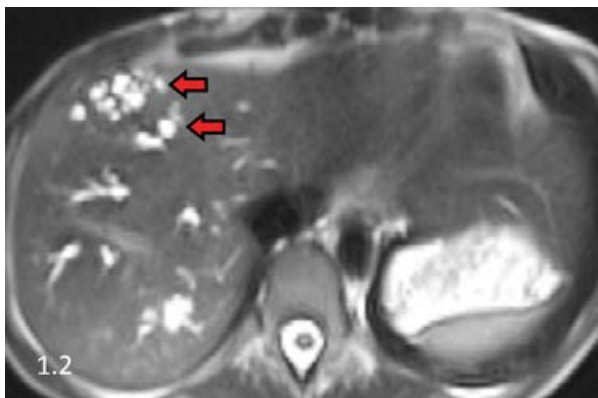


Fig. 1.2. Numerous abscesses up to 15 mm in diameter in the right lobe (red arrows)

Рис. 1.2. В правой доле печени – множественные холангиогенные абсцессы размерами до 1,5 см (красные стрелки)

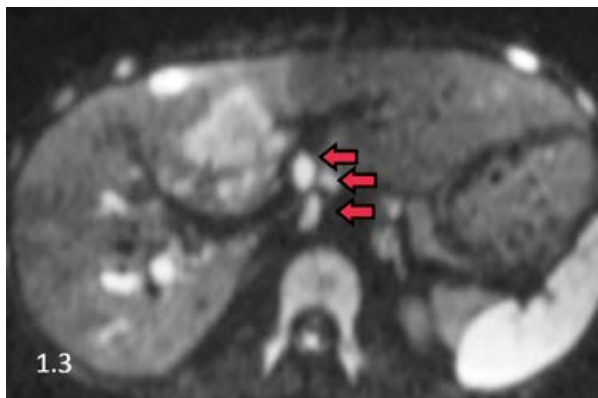


Fig. 1.3. Diffuse-weighted images in addition to the main tumor lesion in the central part of the liver demonstrate hilar lymph nodes enlargement up to 20 mm (red arrows)

Рис. 1.3. На диффузионно-взвешенных изображениях, помимо основной опухоли в центральных отделах печени, в области ворот визуализируются увеличенные лимфатические узлы до 2-х см (красные стрелки)

central part of the liver up to 5 cm in diameter which compressed the external bile ducts confluence. The level of total bilirubin was 346 $\mu\text{mol/l}$.

12/22/2014 transcutaneous transhepatic cholangiostoma was introduced into the left lobe bile ducts under the US-guidance. As soon as biliary decompression was reached on the 19th of January 2015 laparotomy was performed, however high infiltration level of the right and left extrahepatic bile ducts forced to consider the tumor unresectable. The biopsy of the lesion was taken which proved the diagnosis of intrahepatic bile duct cholangiocarcinoma. The patient was directed to the Federal State Budgetary Institution «N.N.Blokhin National Medical Research Center of Oncology» of the Ministry of Health

of the Russian Federation (N.N.Blokhin NMRCO) for further diagnosis and treatment.

On admission: ECOG 1, complaints of weakness, periodical fever up to 38.5 C. Height 154 cm, weight 35 kg, body mass index (BMI) = 14,8. The stomach is soft, painless, without any palpable masses. Approximately 500ml of bile was daily extracting from the external cholangiostoma. Bacteriological examination of the bile obtained the growth of Klebsiella Pneumonia ESBL, which was in vitro sensitive to carbopenems and aminoglycosides. Biochemistry and general blood test parameters as well as coagulogram had no significant deviations. Tumor markers level from 02/12/2015 was: CEA = 2.49 ng/ml, AFP = 1.4 U/ml, CA-199 = 1670 U/ml.

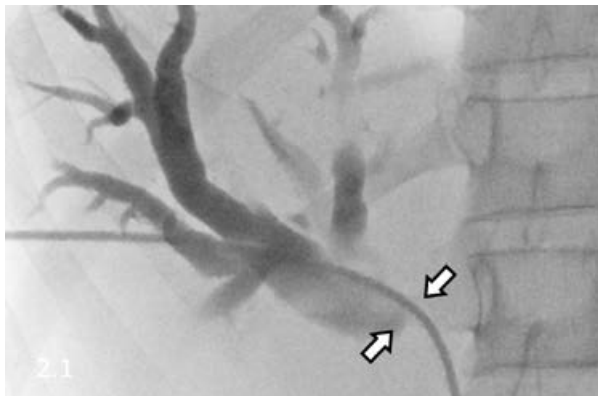


Fig. 2. Preoperational stages of bile ducts draining

Fig. 2.1. Right-hand access transcutaneous transhepatic cholangiogram from 02/26/2015 depicts severe widening of the right lobe bile ducts with hilar block level (white arrows)

Рис. 2. Этапы предоперационного дренирования желчных протоков

Рис. 2.1. Чрескожная чреспеченочная холангиостомия правосторонним доступом 26.02.2015. При холангиографии отмечается расширение желчных протоков правой доли печени с блоком (белые стрелки) на уровне ворот печени

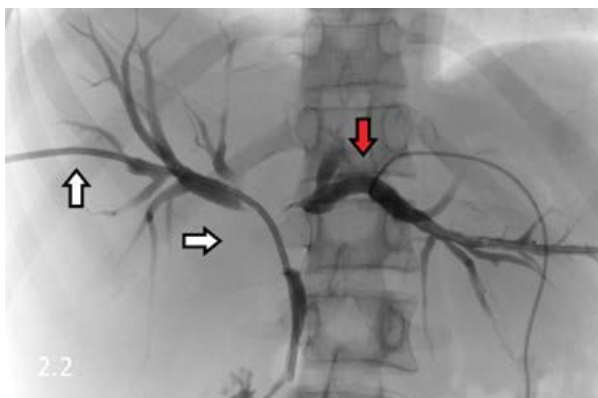


Fig. 2.2. Control cholangiogram from 03/02/2015. Condition after separate drainage of bile ducts. Right-sided catheter 9F (white arrows) is introduced directly through the stricture zone and fixed in the distal portion of choledochus (external-internal pass). Left-sided catheter 7F (red arrow) is fixed in the distal portion of the 3rd segmental duct (external drainage)

Рис. 2.2. Контрольная холангиография 02.03.2015. Состояние после раздельного дренирования желчных протоков обеих долей печени. Холангиостомический катетер 9F (белые стрелки) справа проведен через зону стриктуры с фиксацией его верхушки в дистальном отделе холедоха (наружно-внутреннее дренирование). Слева - наружное дренирование с фиксацией катетера 7F в дистальном отделе 3-го сегментарного протока (красная стрелка)

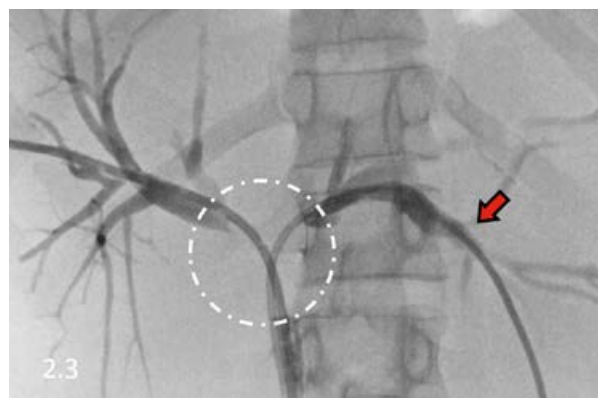


Fig. 2.3. Control cholangiogram from 03/16/2015. Condition after re-drainage of the left intrahepatic bile ducts from 03/12/2015: catheter 8F is introduced through the proximal portion of the 3rd segmental duct (red arrow) and fixed in the distal portion of common hepatic duct. Hilar block level (dotted line); left lobular duct is invaded, right sectoral ducts are spread out and divided

Рис. 2.3. Контрольная холангиография 16.03.2015. Состояние после редренирования слева (12.03.15) через проксимальный отдел (красная стрелка) третьего сегментарного протока с фиксацией верхушки катетера 8F в дистальном отделе общего печёночного протока. Блок на уровне конfluence ЖП - слева распространение на долевого проток, справа – с разобщением секторальных желчных протоков (уровень блока ЖП схематично указан пунктиром)

Abdominal MRI with intravenous enhancement from 02/12/2015 (fig.1) revealed a tumor mass up to 56 mm in the central part of the liver which was infiltrating extrahepatic bile ducts confluence causing biliary hypertension and cholangiogenic abscesses. The enlargement of hilar lymph nodes was also noted which were highly suspicious to be metastatic.

Biopsy probe histological examination depicted tumor cells growth, the structure of which was most appropriate to low-grade cholangiocellular carcinoma. Immunohistochemical examination also revealed cholangiocellular carcinoma.

Complex diagnostic examination showed no sign of distant expansion of the tumor.

The local impact methods were doubtful on the first stage because of suspicion to hilar lymph node metastases. Low frequency of objective response to systemic treatment for cholangiocarcinoma, as well as high risk of the further obstruction of sectoral and segmental bile ducts with progression of cholangitis and cholangiogenic abscesses were taken into the account when it was decided to perform extensive right hemihepatectomy added by resection of extrahepatic bile ducts as the first stage of the combined treatment for this patient. It required to perform additional separate drainage of right and left bile ducts. Firstly, on the 26th of February 2015 — right lobe ducts were drained (fig.2.1) to decrease clinics of cholangitis and

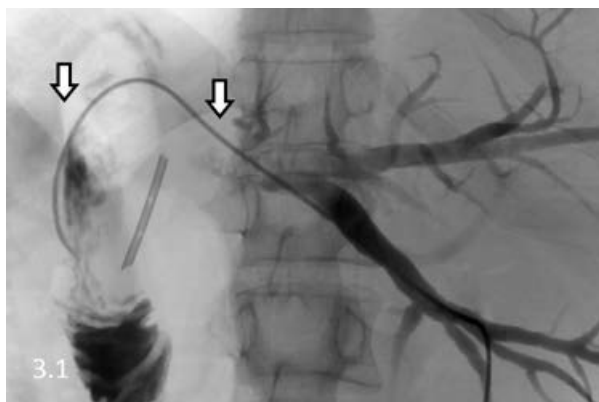


Fig. 3. Performance of the interventional biliodigestive anastomosis and intraductal radiotherapy preparation steps

Fig. 3.1. Cholangiogram from 07/14/2015. Manipulative catheter (white arrows) is installed into the duodenal cavity through the superelastic metal introducer

Рис. 3.1. Манипуляционный катетер (белые стрелки) установлен в полость 12-перстной кишки по суперэластичному металлическому проводнику. 14.07.2015



Fig. 3.2. Cholangiogram from 07/14/2015. Manipulative catheter is replaced by straight 7F drainage (white arrows) which apex is fixed in the duodenal cavity

Рис. 3.2. По проводнику манипуляционный катетер заменен на прямой дренаж 7F (белые стрелки) с фиксацией его верхушки в полости луковицы 12-перстной кишки. 14.07.2015

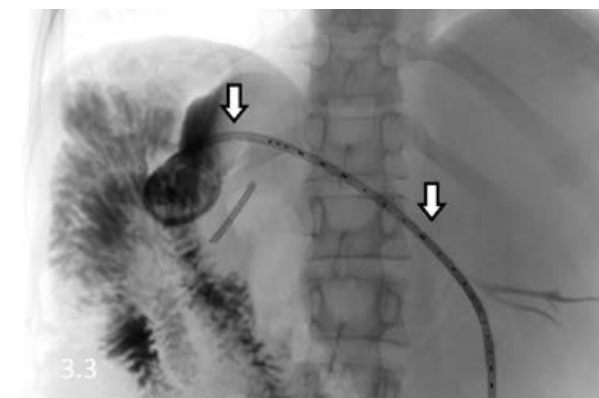


Fig. 3.3. Cholangiogram from 11/02/2015. A source imitator for intraductal radiotherapy (white arrows) is installed into the 12F cholangiostomic drainage

Рис. 3.3. В просвет холангиостомического дренажа 12F установлен имитатор источника (белые стрелки) для выполнения разметки внутрипросветного облучения.02.11.2015

cholangiogenic abscesses. The primary drainage in the left lobe ducts was introduced directly through the tumor (fig.1.1) and had a high risk of migration (fig.2.2). 03/12/2015 transcutaneous transhepatic cholangioscopy was performed through the proximal portion of the 3rd segmental duct which allowed to manage an external-internal passage. The previously introduced catheter was extracted. Control cholangiogram was performed on the 16th of March 2015 (fig.2.3).

After preoperative preparation laparotomy was performed on the 19th of March 2015 which revealed the tumor mass up to 60 mm in the central part of the liver invading the bile ducts starting from the gallbladder duct completely to the liver parenchyma and also enlargement of regional lymph nodes up to 25 mm (hepatoduodenal ligamentum region, behind the pancreatic head, along common hepatic artery). Extensive right hemihepatectomy was performed with 1st segment dissection added by resection of the extrahepatic bile ducts, cholecystectomy, dissection of lymph nodes of hilar zone, along common hepatic artery, behind pancreatic head and around the celiac trunk region. During liver parenchyma resection there was observed pus coming from the cross-section of widened bile ducts. Left extrahepatic bile ducts were resected 2 mm distal to the 2nd and 3rd ducts confluence: duct stump diameter was 4 mm, sectoral ducts diameter was up to 2 mm. In the crossed left lobe ducts there was also observed pus. Express histological exam of the dissected retropancreatic lymph node revealed metastatic adenocarcinoma cells. Microscopy of bile ducts resection borders showed no sign of tumor. It was decided to stitch the bile duct stump tightly because of absence of conditions to create a reliable biliodigestive anastomosis simultaneously according to severe cholangitis clinics and high bile ducts resection level. External cholangiostoma was left to assess biliary decompression. The rear wall of the pyloric portion of the stomach and duodenum bulb were mobilized and attached to liver capsule next to the stitched bile duct stump to perform an interventional biliodigestive anastomosis later.

Hystological conclusion: liver tumor mass up to 50 mm with several satellite nodules up to 5–10 mm is presented by poorly differentiated cholangiocarcinoma cells invading intrahepatic bile ducts; 3 of 11 examined lymph nodes also have metastatic cholangiocarcinoma cells (one node taken from hepatoduodenal ligamentum zone, two — retropancreatic). Microscopy revealed liver resection border invasion near the resected bile duct. 1st segment parenchyma was intact; the proximal and distal borders of the resected bile ducts showed no sign of tumor cells.

During April till September 2015 according to non-radical surgery type (R1) and lymph node involvement the patient underwent 6 courses of systemic

chemotherapy repeating each 28 days in the following regimen: gemcitabine 1000 mg/m² intravenously at 1st, 8th and 15th day, capecitabine 1600 mg/m² daily on the 1st-14th days. Hematological toxicity of the 3rd grade (thrombocytopenia, neutropenia, anemia) was observed between courses.

Control complex examination after three courses of systemic chemotherapy on the 14th of July 2015 (including abdominal MRI with contrast enhancement and chest x-ray) revealed no sign of progression. Tumor marker levels (CEA, CA-199) were within normal values. It was decided to create an interventional puncture biliodigestive anastomosis. Previously fixed portion of duodenum was punctured through the bile duct stump with 20G needle under fluoroscopic guidance. The confirmation of the needle tip in the cavity of the hollow organ was obtained. After that 0,038 J-conductor was put through the needle by which a manipulative 5F catheter was introduced (fig.3.1). The next step was a 7F cholangiostomic catheter installation (fig.3.2) to manage external-internal pass.

The complex control examination held on the 10/06/2015 (including abdominal MRI with contrast enhancement and chest CT) showed no sign of tumor progression. Inhomogeneity of liver parenchyma was noted with thickening of soft tissue around the bile duct stump. The stump caliber was 6 mm, segmental ducts — 3 mm. Tumor marker levels: CEA = 2,0 ng/ml, CA-199 = 15,0 U/ml. Control cholangiogram from 11/02/2015 demonstrated adequate bile drainage function thus 7F catheter was replaced by 12F one with the source imitator (fig.3.3.) installation to perform intraductal radiotherapy as the next step in combined treatment strategy.

From 11/02/2015 to 11/19/2015 in order to reduce the risk of continued tumor growth in the area of microscopically nonradical surgery (liver parenchyma near the intersection of the left bile ducts) intraductal radiotherapy was performed on the left lateral sectoral and 3rd segmental ducts (from the 1st to the 7th mark, the length of the active line was 50 mm, the distance from the center of the source was 10 mm, fig.3.3). An 18-channel microSelectron HDR device was used for the radiotherapy. Ir192 was a source of radiation with a normal activity of 10 Ci. Twelve sessions of 4 Gy were performed, the course dose was 60 Gy by the isoeffect.

In case of a very high probability of post-beam stricture of biliodigestive anastomosis development as well as tumor relapse risk — cholangiostomic drainage was kept until June 2017 to prevent obstructive jaundice. The drainage was changed each 3 month with checking of its location and correction if necessary. The internal part of the drainage was located in the duodenal bulb cavity, the external end was blocked.

Control complex examination data from 06/06/2017 (including abdominal MRI with contrast enhancement, chest X-ray and cholangiography) showed no evidence of tumor progression. Bile ducts widening was within previous values (up to 6 mm for biliodigestive anastomosis region, 3 mm for segmental ducts). Tumor markers level: CEA = 1.52 ng/ml, CA-199 = 0.63 U/ml.

06/05/2017 (19 months after an interventional anastomosis creation) cholangiostomic catheter was moved under fluoroscopic guidance so that its internal end was placed above biliodigestive anastomosis level. In this condition anastomosis remained completely passable, no stricture signs were observed (fig.4.1). Cholangiostomic drainage was blocked. 4 days later

(06/09/2017) control cholangiogram data depicted complete opening of the anastomosis with no sign of bile ducts widening (fig.4.2.). Cholangiostomic catheter was ejected.

Complex control examination data from 03/14/2018 (including abdominal MRI with contrast enhancement and chest fluoroscopy) showed no sign of tumor progression. Duodenoscopy revealed bile admission through a tiny defect in the upper duodenum bulb wall.

Control examination taken in May of 2019 (MRI data — fig.4.3) revealed no sign of tumor progression or biliary hypertension. Tumor markers level: CEA = 1.26 ng/ml, CA-199 = 0 U/ml.

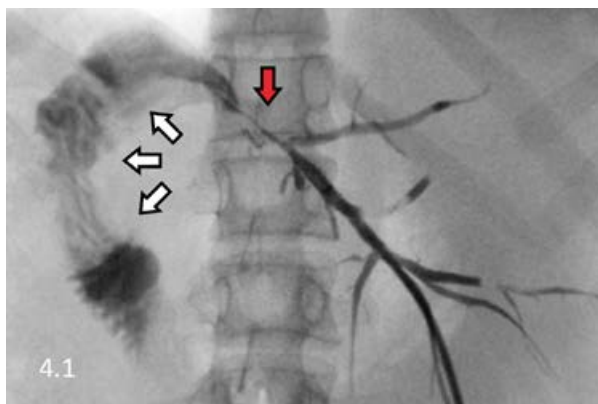


Fig. 4. Steps of cholangiostomic drainage ejection and dynamic abdominal MRI data

Fig. 4.1. Control cholangiogram data from 06/05/2017 depict the location of the apex of direct 10F drainage is proximal to biliodigestive anastomosis. Contrast agent (white arrows) admission into duodenal cavity through the formed channel (red arrows) is complete and fluent

Рис. 4. Фистулохолангиография перед удалением холангиостомического дренажа и МРТ при динамическом наблюдении

Рис. 4.1. Контрольная холангиография 05.06.2017, верхушка прямого дренажа 10F установлена проксимальнее билиодигестивного соустья. Контрастное вещество (белые стрелки) свободно поступает по сформированному каналу (красные стрелки) в просвет 12ПК

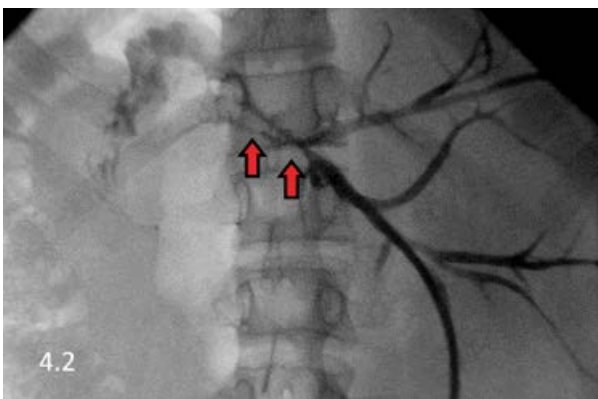


Fig. 4.2. Cholangiogram data from 06/09/2017 shows the absence of left lobe bile ducts widening. Contrast agent fluently admits duodenal cavity by the formed channel (red arrows)

Рис. 4.2. Контрольная холангиография 09.06.2017 (на 4 сутки после перекрытия холангиостомы). Желчные протоки левой доли печени не расширены. Контрастное вещество свободно по сформированному каналу (красные стрелки) поступает в просвет 12ПК



Fig. 4.3. Abdominal MRI data from 05/07/2019. T2-weighted images, frontal projection. Liver resection border shows no sign of tumor regrowth. Minimal widening of bile ducts in the remaining liver parenchyma remains stable (white arrows)

Рис. 4.3. МР-томограммы при динамическом наблюдении от 07.05.19. Т2-изображения, фронтальная проекция: по краю резецированной печени - без видимых патологических образований, сохраняется минимальное расширение желчных протоков оставшейся печени (белые стрелки)

DISCUSSION

Surgical treatment is a potentially radical method for intrahepatic bile duct cancer patients. It is reasonable to value the use of local destruction methods or radiotherapy variety, as well as chemoinfusion or hepatic artery chemoembolization, and, finally, — systemic chemotherapy in case if surgery is impossible [4].

In case of little tumor size with isolated liver lesion the usefulness of surgery usually leaves no doubt. The prevalence of systemic chemotherapy in case of hematogenous or implant metastases is also obvious. Treatment strategy for patients with no sign of distant tumor metastases but having such negative prognostic factors as lymph node metastases, multiple liver lesions, vessel and/or extrahepatic bile ducts invasion with obstructive jaundice development still remains discussable [1].

In such cases the current conservative treatment strategies with application of radiotherapy, systemic and regional chemotherapy attract firstly by their relative safety and by increasing effectiveness [6, 7, 8]. Combination of gemcitabine, cisplatin and nab-paclitaxel allowed to reach a partial answer to therapy in 45% of cases [9]. For some of the previously inoperable patients (12.5–36.4%) liver resection can be performed after induction chemoradiotherapy is applied and then, in R0-surgery cases it can help to achieve survival results comparable to the ones for primary resectable cases [5, 10].

Taking a review of the presented case it's worth noting that the usefulness of preoperational therapy was also discussed. Such factors as reasonable doubt in surgery radicalism and lymph node enlargement revealed by MRI pushed to use preoperative therapy however, there was no confidence that chemotherapy would be provided completely taking in account BMI < 15 and a source of infection existence (cholangitis and cholangiogenic abscesses) which was significantly hard to sanitize. It is also important to underline that the actual chemotherapy regimen for cholangiocarcinoma patients in 2014th year was gemcitabine and cisplatin combination: in case of its usage only 19% of objective answer was expected and less than half of patients included in the cited study managed to finish the complete course [11].

The presence of enlarged lymph nodes suspicious to be metastatic in liver hilar region, behind pancreatic head and along common hepatic artery made the usefulness of local or regional therapy methods very doubtful. Persistence of infection in the undrained liver segments leading to cholangiogenic abscesses formation also significantly reduced the safety of these methods. During surgery lymph node metastases were proved as well as persistence of purulent cholangitis in spite of separate bilateral bile ducts drainage performed. According to mentioned above reasons it was

decided not to perform reconstructive step on site of surgery which required further creation of an interventional biliodigestive anastomosis.

Because of poor results of surgical treatment for cholangiocarcinoma patients, the search for effective methods of additional therapy is justified. Preoperative therapy in inductive variety was discussed above while neoadjuvant treatment in case of deliberately resectable tumors is not recommended [12]. Standard adjuvant chemotherapy for biliary cancer patients is presented by capecitabine usage in monoregimen after BILCAP work is published [13]. There are no randomized trials which demonstrate the advantages of other schemes in adjuvant regimen compared to common cohort [14], but their usage can be justified in case of unfavorable factors are revealed [15, 16].

By the way, we could not rely on the above-mentioned modern sources at those time, however, taking into account nonradical surgery results the usefulness of postoperative treatment was doubtless; besides that, Murakami et al. suggested that addition of adjuvant chemotherapy improves the long-term survival results in lymph node invasion patient group [17]. In order to reduce the risk of distant progression chemotherapy was performed for 6 month in combination of gemcitabine and capecitabine. Intraductal radiotherapy was performed on the left lateral sectoral and 3rd segmental ducts (the area of maximum local relapse risk) after the systemic treatment and exception of further tumor progression according to abdominal MRI and chest CT data were finished. This type of radiotherapy was chosen for its maximum safety and accuracy of impact.

By the time of publication (4 years after the surgery) the patient is alive and has no complaints. ECOG 0, weight 42 kg, BMI = 17.7. Clinical and diagnostic examination data show no sign of tumor progression.

CONCLUSION

Reported clinical case demonstrates the result of successful use of individual combined treatment strategy for the patient with cholangiocellular liver cancer with extrahepatic bile ducts and regional lymph nodes invasion. Interventional methods were used to reduce the clinics of jaundice and cholangitis, biliary reconstruction and radiation source admission. Surgical stage was presented by R1-extensive resection. Systemic chemotherapy scheme selected in account with available at the time information sources and drugs as well as intraductal radiotherapy use allowed to reach good results in the difficult clinical condition: by the time of the article preparation (May of 2019) the patient was alive and had no sign of tumor progression.

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Информация об авторах:

Поляков Александр Николаевич, к.м.н., старший научный сотрудник онкологического отделения хирургических методов лечения № 7 (опухолей гепатопанкреатобилиарной зоны) ФГБУ «Национальный медицинский исследовательский центр онкологии им. Н.Н. Блохина» Министерства здравоохранения Российской Федерации. ORCID: <https://orcid.org/0000-0001-5348-5011>

Патютко Юрий Иванович, д.м.н., профессор, главный научный сотрудник онкологического отделения хирургических методов лечения № 7 (опухолей гепатопанкреатобилиарной зоны) ФГБУ «Национальный медицинский исследовательский центр онкологии им. Н.Н. Блохина» Министерства здравоохранения Российской Федерации. ORCID: <https://orcid.org/0000-0001-9254-1346>

Анна Юрьевна Сысцова, аспирант кафедры онкологии и лучевой терапии лечебного факультета ФГБОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Министерства здравоохранения Российской Федерации. Проходит обучение в онкологическом отделении хирургических методов лечения № 7 (опухолей гепатопанкреатобилиарной зоны) ФГБУ «Национальный медицинский исследовательский центр онкологии им. Н.Н. Блохина» Министерства здравоохранения Российской Федерации. ORCID: <https://orcid.org/0000-0001-7163-2089>

Романова Ксения Александровна, к.м.н., научный сотрудник рентгенодиагностического отделения, научно-исследовательский институт клинической и экспериментальной радиологии ФГБУ «Национальный медицинский исследовательский центр онкологии им. Н.Н. Блохина» Министерства здравоохранения Российской Федерации. ORCID: <http://orcid.org/0000-0002-8938-3313>

Базин Игорь Сергеевич, д.м.н., старший научный сотрудник отделения клинической фармакологии и химиотерапии ФГБУ «Национальный медицинский исследовательский центр онкологии им. Н.Н. Блохина» Министерства здравоохранения Российской Федерации. ORCID: <https://orcid.org/0000-0003-2624-9341>

Сергеева Ольга Николаевна, к.м.н., старший научный сотрудник лаборатории интервенционной радиологии ФГБУ «Национальный медицинский исследовательский центр онкологии им. Н.Н. Блохина» Министерства здравоохранения Российской Федерации. ORCID: <https://orcid.org/0000-0003-1932-5983>

Виршке Эдуард Рейнгольдович, д.м.н., заведующий лабораторией интервенционной радиологии ФГБУ «Национальный медицинский исследовательский центр онкологии им. Н.Н. Блохина» Министерства здравоохранения Российской Федерации. ORCID: <https://orcid.org/0000-0002-4006-3642>

Макаров Евгений Сергеевич, к.м.н., научный сотрудник отделения радиохирургии ФГБУ «Национальный медицинский исследовательский центр онкологии им. Н.Н. Блохина» Министерства здравоохранения Российской Федерации.

Антонова Елена Юрьевна, клинический ординатор кафедры онкологии института клинической медицины ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет) на базе НИИ клинической онкологии им. Н.Н. Трапезникова ФГБУ «Национальный медицинский исследовательский центр онкологии им. Н.Н. Блохина» Министерства здравоохранения Российской Федерации отделения химиотерапии № 1 торако-абдоминального отдела.

Киршин Александр Александрович, заведующий онкологическим отделением хирургических методов лечения № 1 БУЗ УР «Республиканский клинический онкологический диспансер им. С.Г. Примушко» Министерства здравоохранения Удмуртской Республики

Подлужный Данила Викторович, к.м.н., заведующий онкологическим отделением хирургических методов лечения № 7 (опухолей гепатопанкреато-билиарной зоны) ФГБУ «Национальный медицинский исследовательский центр онкологии им. Н.Н. Блохина» Министерства здравоохранения Российской Федерации. ORCID: <https://orcid.org/0000-0001-7375-3378>

Information about authors:

Aleksandr N. Polyakov, MD, PhD, the senior researcher of the oncology department of surgical treatment methods № 7 (tumors of the hepatopancreatobiliary zone) N.N.Blokhin National Medical Research Centre of Oncology. ORCID: <https://orcid.org/0000-0001-5348-5011>

Yuriy I. Patyutko, MD, PhD, DSc, professor, chief researcher of the oncology department of surgical treatment methods № 7 (tumors of the hepatopancreatobiliary zone), N.N.Blokhin National Medical Research Centre of Oncology. ORCID: <https://orcid.org/0000-0001-9254-1346>

Anna Y. Syskova, postgraduate, department of oncology and radiation therapy, faculty of therapy, N.I. Pirogov Russian National Research Medical University (RNRMU). Passes trained the Oncology Department of surgical methods of treatment No. 7 (tumors of the hepatopancreatobiliary zone). ORCID: <https://orcid.org/0000-0001-7163-2089>

Ksenia A. Romanova, MD, PhD, researcher of the diagnostic radiology department, Research Institute of clinical and experimental radiology, N.N.Blokhin National Medical Research Centre of Oncology. ORCID: <http://orcid.org/0000-0002-8938-3313>

Igor S. Bazin, MD, PhD, DSc, senior researcher of the department of clinical pharmacology and chemotherapy, N.N.Blokhin National Medical Research Centre of Oncology. ORCID: <https://orcid.org/0000-0003-2624-9341>

Olga N. Sergeeva, MD, PhD, senior researcher of the interventional radiology laboratory, N.N.Blokhin National Medical Research Centre of Oncology. ORCID: <https://orcid.org/0000-0003-1932-5983>

Eduard R. Virshke, MD, PhD, DSc, head of the interventional radiology laboratory, N.N.Blokhin National Medical Research Centre of Oncology

Evgeniy S. Makarov, MD, PhD, researcher of the oncology department of radiosurgery, N.N.Blokhin National Medical Research Centre of Oncology. ORCID: <https://orcid.org/0000-0002-4006-3642>

Elena Y. Antonova, clinical resident of the department of oncology, institute of clinical medicine, I.M. Sechenov First Moscow State Medical University (Sechenov University), at the Institute of clinical Oncology. N.N. Trapeznikova, N.N.Blokhin National Medical Research Centre of Oncology of the Ministry of Health Ministry of the Russian Federation.

Kirshin A. Aleksandr, head of the oncological department of surgical treatment methods № 1, S.G. Primushko Republican clinical Oncology dispensary

Danila V. Podluzhnyi, MD, PhD, head of the oncology department of surgical treatment methods № 7 (tumors of the hepatopancreatobiliary zone), N.N.Blokhin National Medical Research Centre of Oncology of the Ministry of Health Ministry of the Russian Federation. ORCID: <https://orcid.org/0000-0001-7375-3378>