

<https://doi.org/10.15407/exp-oncology.2023.03.379>

O. Dronov, Y. Kozachuk*, Y. Bakunets, P. Bakunets, F. Prytkov

Bogomolets National Medical University, Kyiv, Ukraine

* Correspondence: Email: general.surg1@nmu.ua

THE CRYOGENIC TECHNOLOGIES APPLICATION IN THE COMPLEX TREATMENT OF GALLBLADDER ADENOCARCINOMA WITH INVASION INTO THE PORTAL VEIN BRANCHES: CASE REPORT

The right trisectionectomy is the main treatment modality for locally advanced gallbladder cancer with invasion of the intraparenchymal portal vein branches because it allows the achievement of negative resection margins (R0). However, only 10%—25% of such patients are eligible for surgery. The cryosurgical method has been successfully used in the complex treatment of hepatopancreatobiliary malignant neoplasms for many years. The possibility of its application close to major blood vessels is one of its advantages. In the presented case, the cryodestruction of the residual tumor with invasion into the anterior wall of the left branch of the portal vein was used as a debulking option during liver resection (R2) due to locally advanced gallbladder cancer. The cryodestruction was performed with application method with a double cryocycle and spontaneous thawing using a Cryo-Pulse device and liquid nitrogen as a cryoagent. No postoperative complications related to cryodestruction were noted. The cryogenic technologies application in the debulking surgery of gallbladder cancer can be a safe treatment modality for residual tumors with invasion into the intraparenchymal branches of the portal vein.

Keywords: gallbladder cancer, cryogenic technologies, portal vein invasion.

Gallbladder cancer (GC) is one of the most common malignant epithelial neoplasms of the biliary tract and takes the 6th place among the gastrointestinal malignancies in the world [1, 2]. Despite the significant improvement in the management of such patients, the 5-year survival rate remains at the level of 10%—25% [2, 3]. A surgi-

cal treatment, i.e. right trisectionectomy, is the main treatment modality for locally advanced GC with the invasion of the intraparenchymal portal vein branches, which allows negative resection margins (R0) achieving [2]. However, only 10%—25% of such patients are eligible for surgery [2, 3].

Citation: Dronov O, Kozachuk Y, Bakunets Y, Bakunets P, Prytkov F. The cryogenic technologies application in the complex treatment of gallbladder adenocarcinoma with invasion into the portal vein branches: case report. *Exp Oncol.* 2023; 45(3): 379-385. <https://doi.org/10.15407/exp-oncology.2023.03.379>

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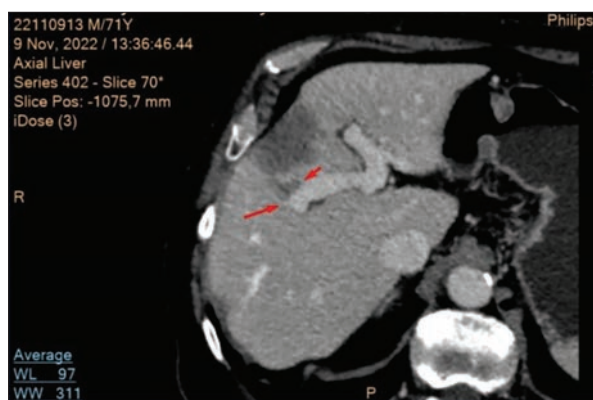


Fig. 1. MSCT image (axial section): gallbladder tumor with invasion of liver parenchyma Sg 4—5 along the gallbladder periphery (reduced density, no clear margins) with invasion of the wall of the portal vein

The cryosurgical method was successfully used in the complex treatment of hepatopancreatobiliary malignant neoplasms for many years [4]. The possibility of the cryosurgical method application close to the major blood vessels is one of its advantages [5]. However, the effectiveness of cryoablation of tumors, including residual ones, with vascular invasion, remains controversial. Unfortunately, the application of cryogenic technologies for hepatic tumors with a vascular invasion treatment is rarely highlighted in the scientific literature. As usual, such clinical cases are considered unresectable.

In this article, we present a case report of a successful surgical treatment of GC using cryosurgery for residual tumors with the intraparenchymal portal vein branch invasion performed at the Department of General Surgery 1 of the Bogomolets National Medical University.

Case presentation

Patient P., 61 years old, was admitted to the Department of General Surgery 1 of the Bogomolets National Medical University in November 2022. The patient complained of abdominal pain and distension, nausea, constipation, loss of ap-

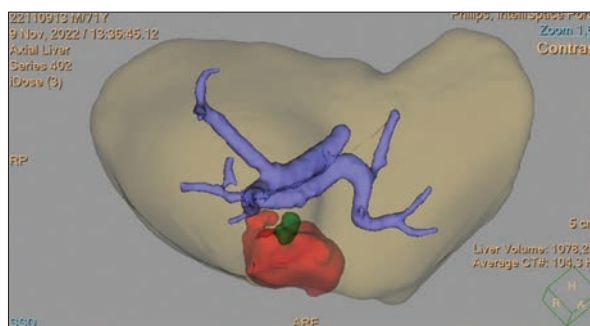


Fig. 2. MSCT 3D modeling of the liver: 3D image of the localization of the gallbladder tumor and spread of the tumor process to the surrounding parenchyma of the liver

petite, severe fatigue, and weight loss of more than 10 kg over the last 6 months.

The patient was examined following the national and international standards of diagnosis and treatment of cancer patients accepted in Ukraine.

Multislice computed tomography (MSCT) with intravenous and oral enhancement (Philips Brilliance 64 CT): CT-signs, neoplastic process gallbladder with invasion of liver parenchyma (Fig. 1). Disabled gallbladder, gallbladder and choledochal calculi.

The MSCT-volumetry of the liver with 3D modeling (Fig. 2) demonstrates that the functional volume of the liver is 998.0 cc, and the volume of the lateral section with Sg1 is 26.8%.

Tumor markers (November 2022): CA 19-9 — 49543.0 U/ml and CEA — 231.38 ng/ml.

MRI with intravenous enhancement (Philips Achieva 1.5 T): signs of an infiltrative lesion of the gallbladder, with the invasion of the adjacent liver parenchyma; a probable involvement in the process of the hepatic angle of the colon; an adhesive process in the abdominal cavity, with stenosis of the small intestine loops at the level of the hypogastrium with signs of partial small intestinal obstruction.

X-ray examination of the chest: no focal pathology was detected. The laboratory blood tests (complete blood count, liver and kidney

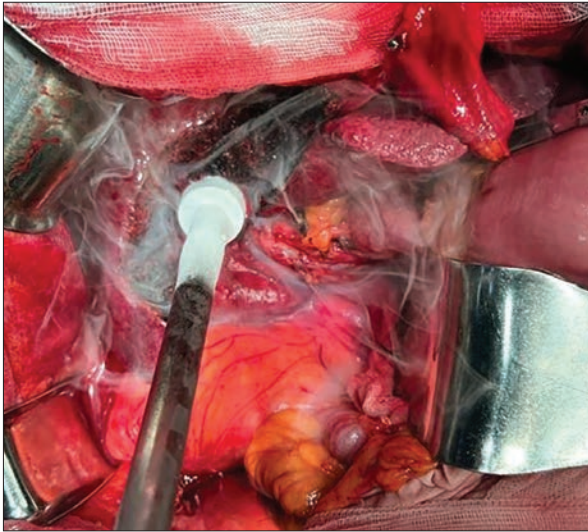


Fig. 3. Cryodestruction of the residual tumor with invasion into anterior wall of the portal vein left branch: freezing process (the first cryocycle, exposure 3 min)



Fig. 4. Cryodestruction of the residual tumor with invasion into the anterior wall of the portal vein left branch: the process of spontaneous thawing (the first cryocycle)

tests, and coagulogram) were within normal ranges.

According to the preoperative examination, the diagnosis was gallbladder cancer, stage IV, T4NxMx, clinical group 2; gallstone disease: chronic calculous cholecystitis, choledocholithiasis; adhesive peritoneal disease; acute subcompensated small intestinal obstruction.

The risk of surgical intervention was IV (by ASA). At the end of November 2022, a surgical treatment was performed.

During the intraoperative revision of the abdominal cavity, a small amount of transparent ascitic fluid (up to 100 ml) was found. The stomach was moderately dilated. The small intestine (jejunum and ileum) loops were significantly dilated up to 6–7 cm, with strictures (multiple), at a distance of about 150 cm from the ileocecal angle. Severe infiltration of the mesentery (suspicion for the metastatic lesion) was found. The liver shrank, wrinkled, and was affected by a cirrhotic (macronodular) process with a pale-brown discoloration of the surface. After liver mobilization, we examined the gallbladder, which was hard, shrunken, and white, affected

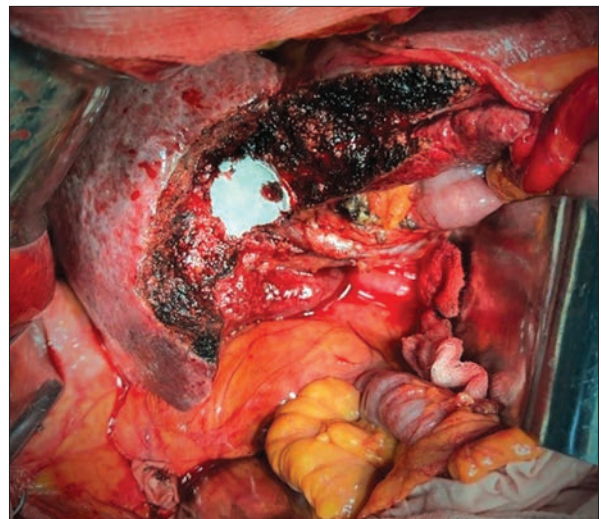


Fig. 5. Cryodestruction of the residual tumor with invasion into the anterior wall of the portal vein left branch: after the second cryocycle (exposure for 5 min), the "ice-ball" zone

by cancer spread with the invasion of the liver parenchyma in the SgIV, SgV. No invasion of the common bile duct or colon was revealed.

Considering the data of the intraoperative revision (the presence of cirrhotic changes in the liver parenchyma and signs of intestinal obst-

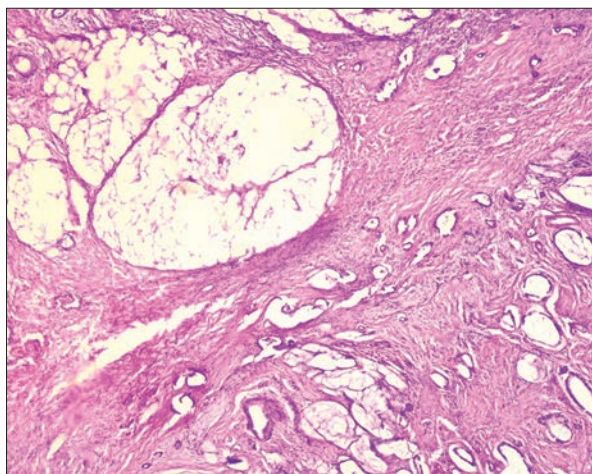


Fig. 6. Moderately differentiated gallbladder adenocarcinoma with spreading to paravesical tissues and liver capsule. Hematoxylin-eosin; original magnification $\times 100$

ruction) and the preoperative examination data (insufficiency of the residual volume of the liver parenchyma: the volume of the lateral section with Sg1 was 26.8%), we made a decision to perform an atypical resection of the SgIVa, SgV liver with gallbladder; resection of a segment of the small intestine; entero-enterostomy.

During liver resection, we revealed spreading of a lesion to the anterior wall of the left branch of the portal vein (intraparenchymal part), due to which the tumor was partially left in this area (R2). Cryodestruction of the residual tumor was applied as a debulking option. Cryodestruction was performed using application method with a double cryocycle and spontaneous thawing. Device: Cryo-Pulse. Cryoagent: liquid nitrogen (-180°C -196°C). Exposure time: the first cycle – 3 min., the second cycle – 5 min. The applicator diameter: 2.5 cm (Figs. 3–5). Two drains to the site of liver resection were installed.

Thus, the final volume of surgical treatment was debulking combined surgery: atypical resection of SgIVa, SgV of the liver (R2-resection) with the gallbladder; cryodestruction of the residual tumor with invasion into the

anterior wall of the portal vein left branch; resection of the small intestine segment; entero-enterostomy.

No intraoperative complications were noted. The operation lasted 5 h and 30 min. Intraoperative blood loss was 450 ml.

The results of the pathological histology test of the removed surgical material: no metastases in the mesenteric lymph nodes or paranodular tissue were found; in a monoblock of the gallbladder and parenchyma SgIVa, SgV of the liver — moderately differentiated adenocarcinoma of the gallbladder with wall ingrowth, tumor growth into the paravesical tissue and the adjacent liver parenchyma (tumor lesion $40 \times 3.5 \times 5.0$ mm), small foci of carcinoma along the margin of the liver resection; in a section of the small intestine with a tumor (15×9 mm) — a similar carcinoma in the mesentery and the wall of the intestine to the level of the mucous membrane (Fig. 6).

Considering the data of the preoperative examination, intraoperative revision, and postoperative pathohistological findings, the final diagnosis was made: gallbladder cancer, stage IVa, pT4N0M1 (ileum), G2, clinical group 2; cirrhosis of the liver, class A (by Child — Pugh); gallstone disease: chronic calculous cholecystitis, choledocholithiasis, and acute subcompensated small intestinal obstruction.

In the 30-day postoperative period, no specific complications were detected. The drains were gradually removed until the 8th postoperative day. The postoperative wound healed up with primary tension. In total, the patient stayed in the hospital for 14 days.

Discussion

Until now, liver tumor invasion into the gallbladder and bile ducts were contraindications to cryoablation [5]. However, recent studies present the effectiveness of cryogenic technologies application in the treatment of patients with gallbladder diseases associated with a high risk of cholecys-

tectomy and endobiliary drainage [6]. In addition, one of the advantages of the cryosurgical method is the possibility of its application close to the major blood vessels [5]. This is due to the ability of vessel walls to regenerate after cryoinfluence. In particular, the cryodestruction of the vessel wall is accompanied by the destruction of endothelial and smooth muscle cells, while vascular patency is preserved due to the intact elastic fibers. Subsequently, the adhesion of platelets to "bare" elastic fibers and the restoration of the integrity of the inner vessel wall by endothelial cells migrating from intact areas are observed. This process takes place in the first week after the cryodamage. In the next 2 weeks, leiomyocytes are restored by subendothelial migration and subsequent proliferation. A complete restoration of the vascular wall structure is observed after about 1 month [7, 8]. However, there is an opinion that the effectiveness of the local application of extra-low temperatures may decrease in cases of foci localization directly adjacent to large blood vessels. This may be explained by the inhomogeneity of the cold front spreading from the cryoapplicator surface to the depth of the tumor foci, due to the specific features of local blood perfusion. At physiological temperatures, a local blood perfusion counteracts the cooling effect by local heating of the tissue and removal of the cooled blood. This process was called the "thermal sink" effect [8, 9]. Also, there is a risk of a clinically significant blood vessel thrombosis in the area of local cryoimpact. However, Sainani, et al. [7] showed that thrombosis of the portal branches and branches of the hepatic vein is common in small branches after cryoablation of liver tumors, which were resolved spontaneously without consequences in most cases.

In addition to the endothelial and leiomyocytes damage, the destruction of the vascular wall's nerves (axons with neurofilaments) occurs in the cryolesion area [10]. This effect promoted a new approach development in interventional

radiology and cardiology — a cryogenic sympathetic denervation of renal arteries as a method for severe arterial hypertension management [11].

Over the past decade, numerous studies have presented a novel benefit of the malignant tumor cryoablation, namely the stimulation of anti-tumor immune response. According to the authors' data, tumor destruction by extra-low temperature in situ is associated with the exposure of tumor antigens and neoantigens release. This leads to their more active detection and recognition by immune cells and, as a result, to the enhancement of specific antitumor immunity. Thus, the effect of cryogenic destruction of a malignant tumor may be considered in vivo vaccination [12–14]. Moreover, the cryoablation induces an antitumor immune response both local and systemic, which may promote the immune damage of distant tumor foci, that is, an abscopal effect [15–17].

Pancreatic cancer (PC) is the most common tumor of the hepatopancreatobiliary area that is accompanied by a vascular invasion. Over the past 20 years, we have successfully applied cryotechnologies in the treatment of locally advanced PC with major vessel invasion. The main indications were: the presence of a residual tumor on the vessel; the downstaging after neoadjuvant chemotherapy; the detected scarred changes of the vessel wall at the site of its contact/tumor invasion after the gastroduodenopancreatic complex removal; the procedure difficulties in the vascular resection due to tumor invasion in the area of superior mesenteric vein branches confluence; a significant vessels damage along their length and an increased risk of purulent complications in the area of vascular grafting. The cryodestruction was also performed in case of residual tumor total invasion into the vessel's wall with protective grafting of the cryodamage zone to prevent the development of possible erosive bleeding. In the assessment of the short-term results, it was found that the postoperative

morbidity, relaparotomy, and mortality after cryoablation of the vessel did not differ from the routine vessel resection [4]. The obtained results prompted us to further study the role of cryogenic technology application in the treatment of other hepatobiliary malignant tumors with an invasion into vessels, which is presented in this case report.

In conclusion, the cryogenic technologies application in the debulking surgery of gallbladder cancer can be a safe treatment modality for re-

sidual tumors with invasion into the intraparenchymal branches of the portal vein.

Competing Interests

We declare the absence of a conflict of interests.

Consent for Publication

The patient's informed consent for publication of the case report was obtained.

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Submitted: April 10, 2023

О.І. Дронов, Є.С. Козачук, Ю.П. Бакунець, П.П. Бакунець, Ф.О. Притков
Національний медичний університет імені О.О. Богомольця, Київ, Україна

ЗАСТОСУВАННЯ КРІОГЕННИХ ТЕХНОЛОГІЙ У КОМПЛЕКСНОМУ ЛІКУВАННІ АДЕНОКАРЦИНОМИ ЖОВЧНОГО МІХУРА З ІНВАЗІЄЮ В ГІЛКИ ВОРІТНОЇ ВЕНИ: КЛІНІЧНИЙ ВИПАДОК

Правобічна трисегментектомія є однією з основних лікувальних опцій при місцево-розповсюдженому раку жовчного міхура з інвазією гілок портальної вени, оскільки вона дозволяє досягнути негативних країв резекції (R0). Але лише в 10—25% хворих даної категорії є можливість виконати оперативне втручання. Кріохірургічний метод давно й успішно застосовується в комплексному лікуванні злоякісних новоутворень гепатопанкреатобіліарної зони. Однією з його переваг є можливість застосування в безпосередній близькості від великих кровоносних судин. У наведеному клінічному випадку нами виконано кріодеструкцію резидуальної пухлини з інвазією передньої стінки лівої гілки ворітної вени під час резекції печінки (R2-резекція) з приводу місцево-розповсюдженого раку жовчного міхура. Кріодеструкцію виконували аплікаційним методом, подвійним кріоциклом із спонтанним таненням. Кріоапарат – Кріо-Пульс. Кріоагент — рідкий азот (–180 °C ... –196 °C). Післяопераційних ускладнень, пов'язаних з кріодеструкцією, не зафіксовано. Застосування кріогенних технологій в циторедуктивному комбінованому хірургічному лікуванні раку жовчного міхура може бути безпечною лікувальною опцією в разі інвазії резидуальної пухлини в інтрапаренхіматозні гілки ворітної вени.

Ключові слова: рак жовчного міхура, кріогенні технології, інвазія ворітної вени.