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Application of cryogenic technologies in complicated cases of surgical treatment of colorectal cancer liver metastases. Case report

O. I. Dronov, Y. S. Kozachuk, Y. P. Bakunets, P. P. Bakunets, F. O. Prytkov, D. Y. Yurkin

Bogomolets National Medical University, Kyiv

✉ Yelyzaveta Kozachuk: lizakozachuk@gmail.com

O. I. Dronov, http://orcid.org/0000-0001-9639-6721
Y. S. Kozachuk, http://orcid.org/0000-0002-2453-2496
Y. P. Bakunets, http://orcid.org/0000-0002-8716-335X
P. P. Bakunets, http://orcid.org/0000-0003-2792-0993
F. O. Prytkov, http://orcid.org/0000-0002-4177-1771
D. Y. Yurkin, http://orcid.org/0009-0003-5071-7069

Surgical resection is a standard treatment strategy for both primary and secondary malignant liver neoplasms. Liver transplantation is considered the most effective treatment method for colorectal cancer liver metastasis. Palliative debulking liver resection is one of the optimal alternative procedures for patients ineligible for a liver transplant, as it improves overall survival. Resectability rates depend on the functional efficiency of the remaining portion of the liver, which can be improved by increasing the future liver remnant. The application of cryogenic technologies for the ablation of a residual tumour invading the intraparenchymal segments of the major hepatic vessel may have advantages in cases where it is impossible to expand the scope of the surgical intervention due to the insufficiency of the future liver remnant and/or the presence of severe concomitant pathology.

Objective — to present a case report of cryogenic technology application in complicated cases of surgical treatment of patients with colorectal cancer liver metastases.

Case report. The case report presents an experience of cryoablation of the metastasis tissue with invasion into the intraparenchymal portal branch of Sg III, which was revealed during the I stage of the split *in situ*/ligation of the portal vein (ALPPS) liver resection. Cryoablation was performed by the application method with a single cryocycle and spontaneous thawing. Device — Cryo-Pulse (Ukraine). Cryoagent — liquid nitrogen (T -180...-196 °C). Exposure time was 3 min. The specific complications associated with cryoablation were not observed.

Conclusions. The application of cryogenic technologies for combined debulking surgical treatment of malignant focal liver lesions may be a safe treatment option in cases of residual tumour invasion into portal vein branches. The study is still ongoing.

Keywords
colorectal cancer, liver metastases, split in situ, liver resection, ALPPS, cryoablation, vascular invasion.

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Surgical resection is a standard treatment strategy for both primary and secondary malignant liver neoplasms, which ensures a 5-year survival rate of about 70 % for patients with hepatocellular carcinoma (HCC) and up to 60 % for those with colorectal liver metastasis (m-CRC). Unfortunately, recurrence after liver resection in m-CRC, HCC, or cholangiocarcinoma is common and is diagnosed in almost 75 % of cases [1, 3]. Moreover, almost 80 % of such patients are ineligible for surgery due to severe comorbidity status or liver function insufficiency caused by local tumour spreading and/or the accompanying liver pathology (for example, cirrhosis, hepatitis, toxic damage after chemotherapy) [1, 3].

Liver transplantation is considered the most effective treatment method for multiple liver m-CRC. However, strict patient-selection criteria, difficulties associated with donor material collection, and

prolonged waiting list times limit its availability. Palliative debulking liver resection is an optimal alternative procedure for patients ineligible for a liver transplant, as it may enhance long-term outcomes [1, 2].

Recently, the indications and patient selection criteria for liver resection in multiple liver m-CRC have expanded significantly, especially the criteria related to the number of foci and resection margin status — the removal of all malignant foci with adequate future liver remnant (FLR) preservation and achieving the tumour-free resection margin. Thus, R0 resection gradually evolved to R1 resection, if necessary, then R1 resection for patients who responded well to chemotherapy, and finally R1 with vascular resection. In addition, according to the LiverMetSurvey Registry, the 5-year survival of such patients, even with R2 resection, can reach 22 % [1, 3, 7].

Improving the volume of FLR is crucial for enhancing resectability. Advances in interventional therapy and surgical techniques have made it possible to increase the future remnant of the liver through multimodal tactics. These new methods include portal vein embolization, two-stage hepatectomy with or without transection of the hepatic parenchyma, and ligation of the portal vein (ALPPS) [1, 5, 7].

In complicated liver resection cases, surgeons face a dilemma: what should be done when a tumour invades intraparenchymal vascular structures and it is impossible to expand the scope of the surgical intervention due to the insufficiency of the future liver remnant and/or the presence of severe concomitant pathology?

We suggest that the application of cryogenic technologies for the ablation of a residual tumour invading the intraparenchymal segments may resolve this issue.

The cryosurgical method has long been successfully implemented in the complex treatment of malignant hepatopancreatobiliary neoplasms. One of the benefits of cryosurgery is the possibility of its application in close proximity to the major blood vessels [18]. The problem of cryogenic technology application in the ablation of tumours invading intraparenchymal vascular structures is rarely highlighted in the literature since such clinical cases are usually considered unresectable. Thus, there is an ongoing debate regarding the effectiveness of cryoablation for tumours with vascular invasion, including residual ones.

Objective — to present a case report of cryogenic technology application in complicated cases of surgical treatment of patients with colorectal cancer liver metastases.

Case presentation

The patient M., aged 70 years, was admitted to the Surgical Division of Kyiv Municipal Clinical Hospital, which is the clinical base of the Department of General Surgery No. 1 of Bogomolets National Medical University, in December 2022.

Diagnosis at admission: recto-sigmoid colon cancer, stage IVa, pT3pN2pM1a (hepar), state after combined treatment in May 2022 (Hartmann's operation + adjuvant PCT + Bevacizumab), clinical group 2.

Hospitalization was aimed at performing debulking surgery for liver m-CRC, due to the stabilization of the oncoprocess after specific chemotherapy.

The ECOG (Eastern Cooperative Oncology Group) Performance Status of the patient was Grade 2. The ASA (American Society of Anesthesiologists) Physical Status was ASA IV.

Multislice computed tomography (MSCT) liver volumetry with 3D modeling was performed for evaluation of the future liver remnant volume (FLRV) and to obtain precise information on the anatomical location of vessels and tumour foci within the liver parenchyma.

The treatment strategy was determined by a multidisciplinary council based on the patient's preoperative examination results and following the standard protocols for the management of cancer patients at the time of the study.

The future liver remnant volume was 32.2 % (517.5 cm^3). Thus, the decision was made to perform a split *in situ*/ALPPS resection (Fig. 1).

Split *in situ*/ALPPS liver resection was performed in 2 stages:

I stage: ligation of the branch of the portal vein with complete transection of the hepatic parenchyma;

II stage: removal of the affected part of the liver (final resection).

At the end of December 2022, the I stage of liver resection with metastasectomy of II, III, and IVa, b segments was performed (Fig. 2).

During the I stage of the split *in situ*/ALPPS, a metastatic tumour with an invasion of the intraparenchymal portal branch of Sg III was revealed (Fig. 3).

During the surgery, it was decided to perform metastatic lesion resection (R2) with cryoablation of metastatic tissue on the portal branch of Sg III (Fig. 4).

Informed permission for cryoablation was obtained from the patient's relatives.

Cryoablation was performed by the application method (equipment: Cryo-Pulse (Ukraine) apparatus, cryoagent: liquid nitrogen, $t = -180... -196$ °C, exposure: 3 min). A single cryocycle with spontaneous thawing was used.

The I stage of the split *in situ*/ALPPS duration was 220 min, and blood loss was 480 ml.

In the postoperative period, complications related to cryoablation and the I stage of liver surgery were not observed.

Since the patient was under occupation by the russian troops as a result of russian aggression against Ukraine, a control MSCT volumetry of the liver was performed after de-occupation, 35 days after the I stage.

According to the control imaging, the FLRV increased to 45.9 % and was 730.3 cm^3 compared to the initial 517.3 cm^3 (Fig. 5).

Consequently, FLRV increased by 42.1 %, and the growth per day was 6.08 cm^3 and 0.39 %, respectively.

Considering the positive effect of the I stage, the II stage of split *in situ*/ALPPS resection — right hemihepatectomy — was completed (Fig. 6).

The II stage of the split *in situ*/ALPPS lasted for 170 min., and blood loss amounted to 350 ml.

In the 30-day postoperative period, no specific complications occurred. The postoperative wound healed with primary tension. Currently, the patient is receiving specific adjuvant cytostatic therapy.

Discussion

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a two-stage surgical procedure that aims to induce rapid hypertrophy of the future liver remnant. In 2012, the ALPPS International Registry (Web Data Entry System) was established to share knowledge, conduct audits, facilitate research, and identify applications of ALPPS through a collaborative effort. As of September 2019, a total of 1219 ALPPS were performed in 156 centres in 44 countries, with the majority of cases (65.4 %) in Europe [4]. The team of the Department of General Surgery No. 1 of Bogomolets National Medical University was one of the first to gain access to this registry and supplemented the global database with the results of its own experience in implementing ALPPS.

Despite many years of studying ALPPS safety by the global community of hepatobiliary surgeons, the

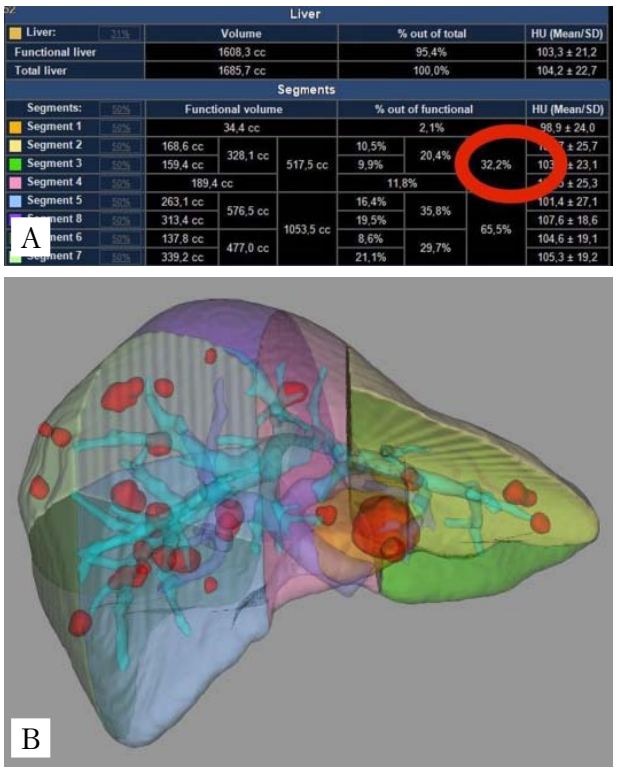

Figure 1. **MSCT volumetry (A) and 3D modelling of the liver (B) in a patient**

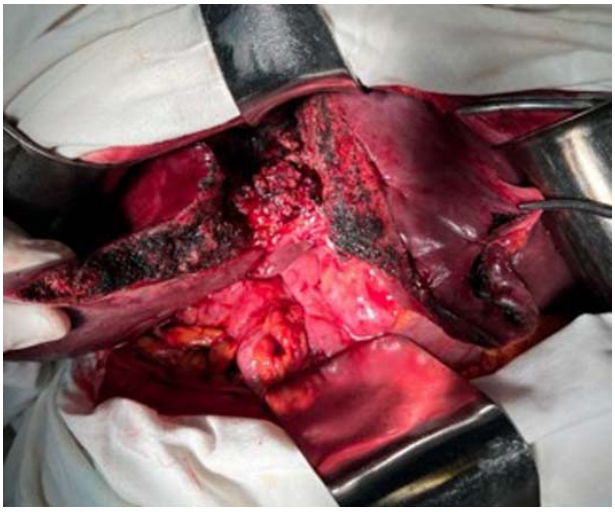

Figure 2. **The I stage of split in situ liver resection. State after metastasectomy: Sg II, Sg III, Sg IVa,b**

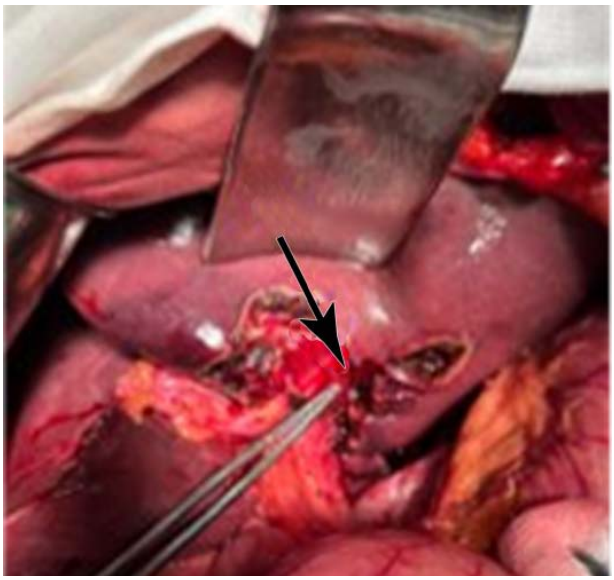

Figure 3. **Metastatic colorectal cancer that has spread to the intraparenchymal portal branch of Sg III (indicated by the arrow)**

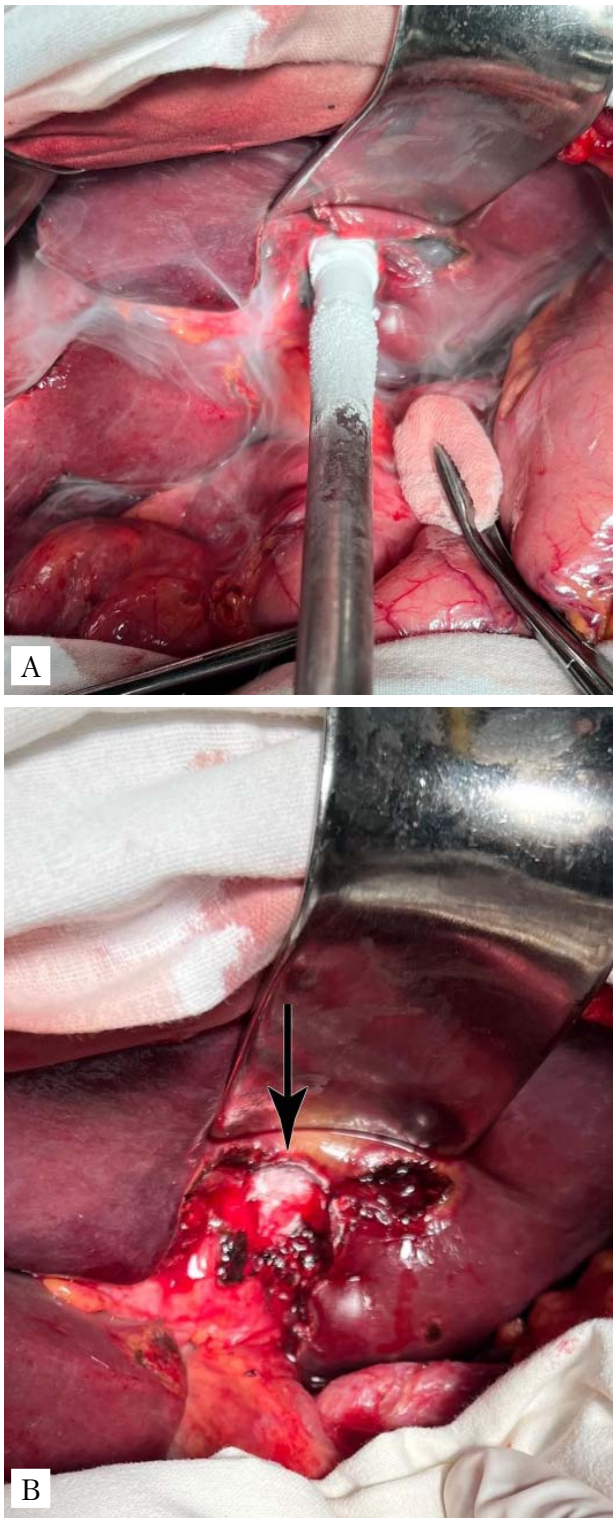

Figure 4. **Cryoablation of residual metastatic tissue that has spread to the intraparenchymal portal branch of Sg III: A — freezing process; exposure — 3 min; B — the «ice-ball» zone — the process of spontaneous thawing (indicated by the arrow)**

Liver						
Liver:	Volume			% out of total		HU (Mean/SD)
Functional liver	1592,7 cc			95,3%		108,2 ± 27,6
Total liver	1671,2 cc			100,0%		107,7 ± 33,3
Segments						
Segments:	Functional volume			% out of functional		HU (Mean/SD)
Segment 1	21,1 cc			1,3%		104,6 ± 25,8
Segment 2	174,3 cc	407,1 cc	730,3 cc	10,9%	25,6%	103,0 ± 27,0
Segment 3	232,7 cc			14,6%		102,0 ± 34,0
Segment 4	323,2 cc			20,3%	45,9%	102,9 ± 40,7
Segment 5	264,2 cc	604,9 cc	841,3 cc	16,6%	38,0%	112,5 ± 27,7
Segment 8	340,7 cc			21,4%		110,5 ± 36,7
Segment 6	38,4 cc	236,4 cc		2,4%	14,8%	116,7 ± 22,9
Segment 7	198,0 cc			12,4%		113,9 ± 22,7

Figure 5. **Liver MSCT volumetry data 35 days after the I stage split in situ/ALPPS**

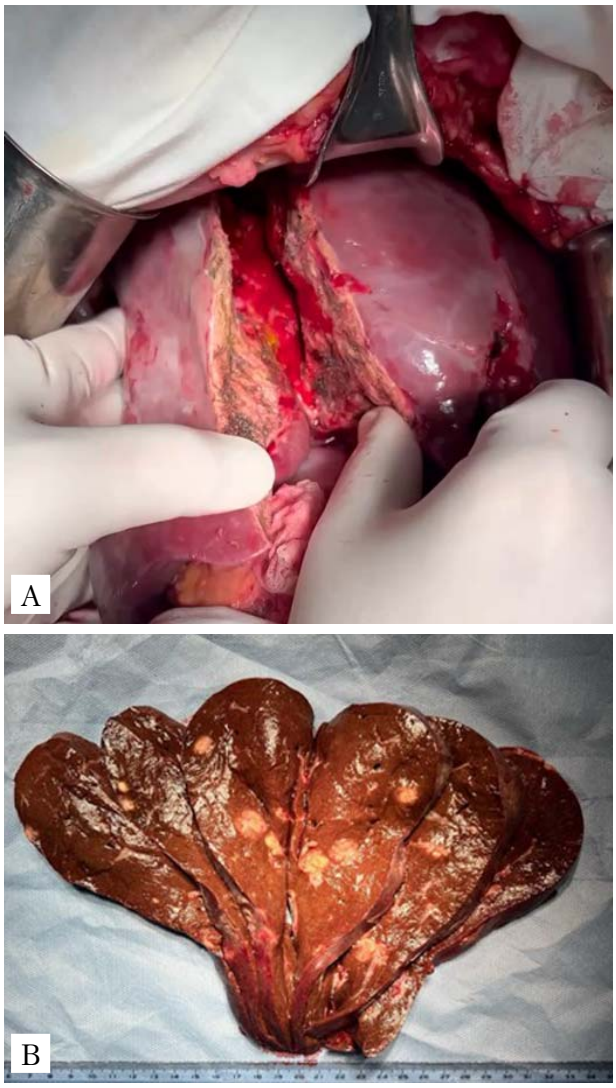

Figure 6. **The II stage split in situ liver resection: A — liver transection line, hypertrophied left lobe of the liver; B — the right lobe of the liver with multiple metastases of colorectal cancer**

short-term results are controversial, as the morbidity and mortality rates are extremely variable [10].

K.N. Wanis et al. (2021) analysed the results of the ALPPS performance in specialized centres worldwide. The authors revealed that the mortality rate at 90 days postoperatively ranged from 4.2 % (95 % CI: 0.8, 9.9) to 29.1 % (95 % CI: 13.9, 50.9), and the rate of intervention-related complications — from 17.0 (95 % CI: 7.5, 26.5) to 49.8 (95 % CI: 38.1, 61.8) and depended on the medical institution. Also, it was noted that the level of mortality and complication index decreased with time and the acquisition of experience by the medical staff [10].

E. Schade et al. (2015) reviewed the treatment outcomes of 320 patients from 55 centres who were included in the international ALPPS registry and found that the overall mortality within 90 days after surgery was 8.8 %. The main cause of patients' deaths was acute post-resection liver failure (75 % of cases). Moreover, in 14 % of patients, this complication was observed after the first stage of the intervention. Also, these patients and patients with more than 10 MELD scores before stage II had a significantly higher risk of mortality at the specified time: OR 3.9 (CI 1.4—10.9, p = 0.01) and OR 4.9 (CI 1.9—12.7, p = 0.006), respectively. Other factors, such as the volume of FLR after the first stage and the duration of the period between the stages, did not have a statistically significant prognostic value [8].

P. Sandström et al. (2018) presented the Scandinavian randomized multicenter LIGRO clinical trial (n = 100) that included the results of ALPPS (n = 50) and standard two-stage liver resection (TSH) (n = 50) and showed that the groups did not differ statistically significantly in the frequency of postoperative complications (Clavien–Dindo i 3a) [43 % (19/44) vs. 43 % (12/28)] [1.01 (95 % CI 0.4—2.6); p = 0.99] and 90-day mortality [8.3 % (4/48) vs. 6.1 % (3/49)] [1.39 [95 % CI 0.3—6.6]; p = 0.68].

However, after the first stage of ALPPS, the average growth in the volume of the future liver remnant was statistically significantly higher compared to TSH. In particular, on the 7th day, FLRV after ALPPS was 605 ± 140 ml vs. TSH 450 ± 140 ml (p < 0.0001); growth in FLRV (ml/day) — 35.4 ± 17.9 vs. 12.3 ± 8.6, respectively (p < 0.0001); volume growth (ml) — 237 ± 108 vs. 93 ± 67 (p < 0.0001); volume growth (%) — 68 ± 38 vs. 36 ± 18 (p < 0.0001) [9].

Presented by Y. Liu et al. (2019), a meta-analysis revealed that the ALPPS is accompanied by higher morbidity (from 13 to 71.4 %) and mortality (from 0 to 15.0 %) rates compared to the technique of portal vein embolization (9.0—60.0 % and 0.0—6.0 %, respectively) or standard two-stage liver resection (17.6—67.9 % and 2.1—6.1 %, respectively). The risk of complications in ALPPS — RR: 1.19; 95 % CI, 0.96—1.47, and mortality — RR: 2.11; 95 % CI, 1.02—4.33 after performing the II stage. The main types of postoperative complications in ALPPS were: acute intestinal obstruction, thromboembolism of the pulmonary arteries after the first stage, liver failure, bile leakage, strictures of the biliary tract, and septic complications. However, ALPPS was accompanied by an average more effective growth in FLR per day (from 2.0 ± 0.75 % to 21.0 ± 10.0 %) than portal vein embolization (from 0.42 ± 0.15 % to 1.37 ± 1.23 %) and two-stage liver resection (from 0.32 ± 0.15 % to 1.89 ± 1.12 %); RR: 4.87; 95 % CI, 3.41—6.33 [6].

Thus, comparing our and recent studies' results, it should be noted that the frequency of postoperative complications and mortality in our centre does not differ from the data in the world literature. The effectiveness of split *in situ*/ALPPS two-stage liver resections for colorectal cancer metastases at our institution corresponds to international experience.

One of the significant advantages of the cryosurgical method is the possibility of its application in close proximity to blood vessels. The problem of cryogenic technology application in the ablation of tumours invading intraparenchymal vascular structures is rarely highlighted in the literature since such clinical cases are usually considered unresectable. Thus, the issue of the effectiveness of cryoablation for tumours with vascular invasion, including residual ones, still remains controversial.

It has been confirmed that vessel walls have the ability to regenerate after cryoinfluence, with complete restoration of their structure after about 1 month [13]. However, there is an opinion that the effectiveness of the ultra-low temperature local application may decrease in cases of cryodestruction of foci directly adjacent to large blood vessels due to the inhomogeneity of the cold front spreading from the cryoapplicator deep into the tumour foci. The peculiarities of liver blood perfusion at physiological temperatures counteract the cooling effect by local heating of tissue and the removal of cooled blood. This process was called the «thermal sink» effect [14, 15]. Also, there is a risk of clinically significant thrombosis of vessels in the area of local cryoimpact. However, Sainani N.I. et al. (2016), in their study, showed that thrombosis of portal and hepatic vein small branches is a common phenomenon after cryoablation of liver tumours, and, in most cases, spontaneously resolves without consequences [12].

Over the past 20 years, we have successfully applied the method of local cryoablation for locally advanced pancreatic cancer with invasion of major

vessels. Our experience allowed us to determine the main indications for the cryogenic technology application in the combined surgical treatment of tumours with vascular invasion. Analysing the short-term results, we found that the frequency of postoperative complications, relaparotomy, and mortality after cryogenic vessel ablation did not differ from the usual resection of vessels affected by the tumour process [16]. The obtained data prompted us to further study the role of cryosurgical approaches in the treatment of other malignant hepatobiliary tumours with invasion of major vessels, which is reflected in the presented case report.

Conclusions

The application of cryogenic technologies for combined debulking surgical treatment of malignant focal liver lesions may be a safe treatment option in cases of residual tumour invasion into portal vein branches. The study is still ongoing.

Declaration of interests

The authors declare that they have no conflicts of interest.

Ethics approval and written informed consents statements

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

The study was approved by the bioethics commission at Bogomolets National Medical University

Authors contributions

O. I. Dronov — concept and design of the study, editing of the article; Y. S. Kozachuk — processing the material and writing the article; Y. P. Bakunets, P. P. Bakunets — collecting of material, editing; F. O. Prytkov, D. Y. Yurkin — collecting of material.

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Застосування кріотехнологій у складних випадках хірургічного лікування метастазів колоректального раку в печінку. Клінічний випадок

О. І. Дронов, Є. С. Козачук, Ю. П. Бакунець, П. П. Бакунець, Ф. О. Притков, Д. Є. Юркін

Національний медичний університет імені О. О. Богомольця, Київ

Хірургічна резекція — один з основних методів лікування первинних і вторинних злоякісних новоутворень печінки. Найоптимальнішим методом лікування метастатичного ураження печінки при колоректальному раку є трансплантація печінки. Одна із можливих опцій для хворих, яким не можна виконати трансплантацію печінки, — паліативна циторедуктивна резекція печінки, що може поліпшити їхню загальну виживаність. Для підвищення резектабельності необхідно вирішити проблему функціональної недостатності залишкової частини печінки, збільшивши майбутній залишок печінки. Застосування кріогенних технологій для абляції резидуальної пухлини, що інвазує інтрапаренхіматозні сегменти магістральної судини, може мати переваги за неможливості розширити об'єм оперативного втручання через недостатність майбутнього залишку печінки та/або наявність тяжкої супутньої патології.

Мета — продемонструвати клінічний випадок застосування кріогенних технологій у складних випадках хірургічного лікування пацієнтів з метастатичним ураженням печінки при колоректальному раку.

Клінічний випадок описує досвід кріоабляції метастазу колоректального раку з інвазією в інтрапаренхіматозну портальну гілку Sg III, виявленою на етапі I split *in situ*/лігування портальної вени (ALPPS) резекції печінки. Кріоабляцію виконували аплікаційним методом, подвійним кріоциклом зі спонтанним таненням. Кріоапарат — «Кріо-Пульс» (Україна). Кріоагент — рідкий азот (t = –180... –196 °C). Час експозиції — 3 хв. Ускладнень, пов'язаних з кріоабляцією, не спостерігали.

Висновки. Застосування кріогенних технологій у циторедуктивному комбінованому хірургічному лікуванні злоякісного вогнищевого ураження печінки може бути безпечною лікувальною опцією при інвазії злоякісних пухлин в інтрапаренхіматозні гілки ворітної вени. Дослідження триває.

Ключові слова: колоректальний рак, метастази в печінку, split in situ, резекція печінки, ALPPS, кріоабляція, інвазія в судини.

FOR CITATION

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