CLINICAL TRIAL

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STUDY PROTOCOL FOR A DUAL-CENTER RANDOMIZED CONTROLLED TRIAL COMPARING LAPAROSCOPIC AND OPEN 'MINOR' LIVER RESECTIONS IN UKRAINIAN COLORECTAL CANCER PATIENTS WITH LIVER METASTASES

Background. World statistics demonstrates that about 15% of liver resections are performed laparoscopically. Nevertheless, in Ukrainian specialized centers, this figure is about 5% or even less. The **aim** of the forthcoming trial is to determine whether laparoscopic liver resections (LLR) performed in the state Ukrainian specialized centers have better surgical and long-term oncological outcomes compared to an open approach (OLR) with the parallel examination of the surgically induced systemic stress response. **Methods.** This trial is a national (Ukrainian) multicenter randomized controlled trial, with patients and ward personnel blinded to the treatment approach. Patients will be randomized in a 1:1 ratio to LLR or OLR with REDCap® software. The primary end-point is to compare the time to discharge in the cohorts under study. The goal is to reduce the length of hospital stay in the LLR group at least by 28%. To obtain a power of 80% and an alpha level of 0.05 for a two-sided *p*-value, a minimum of 126 patients (63 in each group) are to be included. **Discussion.** Conducting a randomized trial in Ukraine comparing laparoscopic and open minor liver surgery techniques can leverage the country's diverse patient demographics and healthcare infrastructure. This study will be able to provide crucial insights into the effectiveness, safety, and feasibility of both surgical approaches in a population that may have different disease presentations and healthcare access compared to Western countries. **Trial registration and status**. The trial was registered in Researchregistry.com (UIN10336) on May 26, 2024, and currently has recruited 38 patients.

Keywords: laparoscopic liver resection, randomized controlled trial, functional state of hepatocytes.

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in men and the second in women, and, according to the World Health Organization database GLOBOCAN, it accounts for nearly 1.4 million new cases annually worldwide [1]. By the data of the National Cancer Registry of Ukraine, CRC accounts for almost 16,700 patients annually [2]. About 20% of CRC patients have metastases either exclusively or predominantly in the liver at the time of primary tumor presentation [3]. Moreover, metachronous liver metastases are diagnosed during the follow-up in more than 50% of cases [4].

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In the case of colorectal liver metastases (CLM), hepatic resection represents the only curative option, with rates of overall survival (OS) for 5 and 10 years of 50% and 35%, respectively [5]. The traditional (open) liver surgery is still a standard surgical approach for liver resections due to CLM [6]. Nevertheless, the open surgical incision is highly traumatic and associates with a prolonged postoperative hospital stay (4—12 postoperative days), and the wound infection rate increases by to 13% [7, 8]. This applies especially to patients with concomitant liver pathology (fibrosis, cirrhosis, etc.), when the liver is enlarged, and its mobilization requires extended incisions [9]. The most common incisions used in an open hepatectomy for right-sided liver cancers include the inverted L-shape and Mercedes- or middle incision [10]. Therefore, open incisions have various risks of complications that affect the patient's quality of life [11].

Over the last two decades, there has been a progressive move toward the increased use of minimally invasive techniques, and three international consensus statements have been published [12—14]. The world statistics demonstrates that about 15% of liver resections are performed laparoscopically [15] while in the setting of the Ukrainian state specialized centers, this figure is about 5% or even less [16]. Therefore, conducting a study aimed at demonstrating the superiority of laparoscopic over traditional surgery in patients with CLM who are suitable to both surgical methods will shorten the length of hospital stay, reduce morbidity, and change the existing practice at the national level in Ukraine.

The Enhanced Recovery After Surgery (ERAS) protocols have been shown to decrease postoperative complications and duration of stay after several types of surgery due to a reduction in response to surgical stress. The recommendations of the ERAS Society in liver surgery require the laparoscopic approach as an important factor for its implementation and compliance [17].

The surgical stress is a main indicator of the systemic response to the surgical trauma [18]. As known, it leads to the release of the main pro-inflammatory cytokines. In particular, the expression of IL-6 results in the hepatic release of C-reactive protein (CRP) causing a systemic inflammatory response [19, 20]. If cytokine homeostasis is not maintained, there may be an increased risk of postoperative morbidity or mortality and a decline in oncological outcomes. According to the experimental data, hepatic cytochrome P450 (CYP) isoform CYP1A2 is one of the important enzymes for many drugs metabolism. Some studies demonstrate that liver hypoxia can influence the CYP1A2 expression [21, 22]. The current surgical technique for liver resection requires control of blood in- and out-flow with the intermittent Pringle maneuver. Thus, the pathophysiological organ-specific and systemic stress responses after the surgical trauma can be evaluated by measuring the hepatocytes functional state and systemic markers of inflammatory response in randomized cohorts.

The aim of the trial will be to determine whether laparoscopic liver resections have better surgical and long-term oncological outcomes compared to the open approach within the state Ukrainian specialized centers with the parallel examination of the surgically induced systemic stress response.

The objectives of the trial are as follows:

To compare the surgical (surgery duration, length of hospital stay, morbidity, mortality, readmission percentage, hospital costs, etc.) and oncological (disease-free and overall survival) efficacy in cohorts of laparoscopic vs. open liver surgery.

To evaluate the functional state of hepatocytes in the adjacent and remote parenchyma in the groups of open and laparoscopic liver surgery.

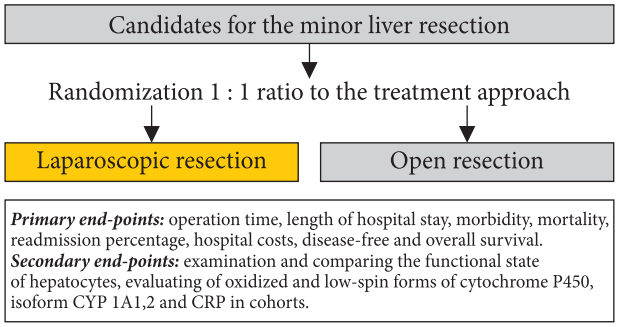
To compare the systemic marker of inflammatory response with acute-phase reactant protein (CRP) in cohorts of open vs. laparoscopic liver surgery.

The trial protocol is written in accordance with the SPIRIT guidelines [23].

Study design

This trial is a national (Ukrainian) multicenter randomized controlled trial, with patients and ward personnel blinded to the treatment approach (Figure). At least two state centers that have considerable experience in performing both open and laparoscopic liver surgery in Ukraine are envisaged to enroll the patients with CLM.

Molecular analysis. It is planned to assess the functional state of hepatocytes in the adjacent and distant anatomical zones in relation to the stroma of the metastatic focus using EPR spectroscopy and zymography. The degree of hypoxia will be assessed by determining the activity of the oxidized and



Schematic representation of the study design

low-spin forms of cytochrome P-450 isoform CYP 1A2 after liver tissue transection completion. The predictive value of the postoperative Day 1 and 3 CRP levels will be evaluated to determine the presence of a correlation with the surgical stress in the studied cohorts.

Inclusion criteria. CRC patients with LM, candidates for a minor liver resection, age 18—82 years, ASA physical status I—III, and ECOG 0—1 who will understand the essence of the study and sign an informed consent to participate in it will be included.

Exclusion criteria. Patients unable/unwilling to sign an informed consent, patients with ASA physical status ≥ IV, patients with previous liver ablations, and patients with an unrespectable extrahepatic disease will be excluded.

Co-primary end-points are to compare the surgical outcomes of interest such as the surgery duration, time to discharge, surgical and medical complications recorded 90 days after surgery according to the Clavien — Dindo classification system [24], readmission rates, and hospital costs. The oncological outcomes will comprise the overall and disease-free survival rates.

Co-secondary end-points are chosen to demonstrate the laparoscopic and open approaches' effects on the level of the systemic inflammatory response (surgical stress) to the surgical trauma. These include the examination and comparison of the functional state of hepatocytes (by evaluating the oxidized and low-spin forms of cytochrome P450 and isoform CYP 1A1,2). Also, the systemic expression of CRP on the 1st and 3rd POD is to be measured.

Surgical techniques in cohorts include anatomy-oriented parenchyma-sparing liver resection (LR). All the surgical procedures will be performed by surgeons who are trained in HPB surgery and experienced in open liver surgery (≥50 resections). Laparoscopic interventions will be performed by surgeons who also completed laparoscopic and open HPB training programs and experienced more than 25 laparoscopic liver resections (LLRs). The complete removal of at least one Couinaud's segment containing the tumor burden together with the related portal vein and the corresponding hepatic territory will be defined as an anatomical LR, whereas resections of the metastatic lesion with a margin of at least 1 mm, whenever possible, without regarding the segmental anatomy of the liver will be recognized as a non-anatomical LR. All parenchyma-sparing surgical LRs will include crash-clamping or a cavitron ultrasonic surgical aspirator with a resection margin size of at least 1 mm. When possible, tactics of "vascular detachment" will be used. The ischemia technique will include the classical Pringle maneuver (20 min ischemia, 5 min reperfusion). All parenchyma-sparing LRs will be accompanied by intraoperative ultrasound navigation [25]. The ports will be placed as preferred by the surgeon and oriented on the present guidelines or expert recommendations [26—29]. Resection of ≤ 2 liver segments will be classified as minor in accordance with the "New World" terminology [30].

Principal timeline, data collection, and follow-up. The preoperative assessment will consist of the collection of baseline data information: age, gender, body-mass index, ASA score, ECOG, diagnosis, and dates of randomization and operation. All data will be entered into the REDCap database program, available only to the project owners, ensuring that anonymity is maintained and data security is respected. Ethical principles for medical research will follow the Declaration of Helsinki [31]. Mass spectrometry, electron paramagnetic resonance, histological and histochemical examinations of the liver tissue samples, and biochemical analysis of blood will be performed in the local laboratories. The time of participation of each enrolled patient in the study is 5 years, and the follow-up observation will be carried out after 1, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, and 60 months.

Sample size calculation. The sample size calculation will be based on the selected primary endpoint (length of hospital stay) with the online service Clincalc.com. In 2016—2023, the median of the hospital stay in the clinic of the National Cancer Institute was 7 ± 4 days [32]. A goal of this study is to reduce this duration in the LLR group by at least 28%. To obtain a power of 80% and an

alpha level of 0.05 for a two-sided *p*-value, we envisage enrolling a minimum of 126 patients (63 in each group).

Randomization and blinding. Patients will be randomized in a 1:1 ratio to LLR or OLR with REDCap® software [33]. The randomization will be performed by the principal researcher of the project. All the staff in hospitals and patients will be blinded to the intervention type.

Statistical analysis. The descriptive data will be presented with the means, SDs, medians, interquartile ranges, numbers, and percentages. The categorical variables will be compared using the χ^2 or Fisher exact test when applicable. The survival will be analyzed using the Kaplan — Meier method, the log-rank test, and Cox proportional hazards regression to compare the outcomes between groups. The differences between median values will be compared using the Mann — Whitney *U*-test. For the comparison between two groups with categorical variables, the two-sided Fisher's exact test will be used. *P*-values less than 0.05 will be considered statistically significant. To identify predictors of survival, univariable and multivariable analyses will be done using the log-rank test and the Cox proportional hazards model. The statistical analyses will be performed using Prism 10.0.

Safety. All adverse events according to CTCAE will be reported to the principal investigator within 24 h.

Discussion

In 1977, the first multicenter study was published, which included the analysis of 621 liver resections, the average rate of postoperative mortality was 13%, and intraoperative blood loss was the main cause of mortality in such patients [34]. Over the past 40 years, technological improvement and high-tech surgical support development have led to a significant decrease in the level of blood loss. In the 1990s, perioperative mortality averaged 5%, which led to a geometric progression of the number of liver resections in the world [35]. World statistics demonstrates that the therapeutic potential of liver surgery exceeds any state-of-the-art chemotherapy and, in some cases, becomes the only possible treatment option [36].

However, the last three decades of the global experience of liver surgery revealed the problem that can jeopardize the positive oncological outcomes of liver resections in CRC patients with liver metastasis [37, 38]. Namely, open liver resections are highly traumatic and associated with a longer hospital stay or increasing wound infection rates [39, 40]. Surgical trauma is considered a significant factor capable of potentiating the processes of surgical stress [41]. Since the introduction of laparoscopy for liver resection in the 1990s, the performance of LLR has been steadily increasing [42]. Generally, LLRs account for approximately 15% of all liver resections performed worldwide but this percentage may vary depending on the institution, surgeon expertise, patient characteristics, and specific indications [43]. Currently, the use of LLR is becoming increasingly common as the laparoscopic techniques and technology continue to advance allowing for more complex liver resections to be performed laparoscopically.

Conducting a randomized trial in Ukraine comparing laparoscopic and open minor liver surgery techniques can leverage the country's diverse patient demographics and healthcare infrastructure. This study will be beneficial for the crucial insights into the effectiveness, safety, and feasibility of both surgical approaches in a population with different disease presentations providing the healthcare access in Ukraine comparable to that in Western countries.

Availability of data and materials

All data generated or analyzed during this study will be included in the published results. The source data will be kept on RedCap for 10 years. The datasets analyzed during the current study will be available from the corresponding author upon request.

Author contributions

A. Bu and S. Ze. — conception and design, manuscript writing; V.Be. — collection and assembly of data; A.Be. — administrative support.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This study was designed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the National Cancer Institute (protocol No. 244/3, 03/OCT/2023). The study was registered in Researchregistry.com.

All patients meeting the inclusion criteria will be invited to participate. Recruitment is provided by the principal investigator and authorized researcher. If a patient is willing to participate, study information will be provided. Following oral and written consent, patients are assigned a subject number in the electronic data capture software REDCap, which will be used for data collection throughout the study.

Dissemination

The final report will be submitted for publication in a high-quality peer-reviewed international journal and presented at relevant international scientific meetings.

Trial status

Two centers in Ukraine (the National Cancer Institute and the University Clinic of the Bogomolets National Medical University) have gained ethical approval. The trial was registered in Researchregistry.com (UIN10336) on May 26, 2024 and currently recruited 38 patients.

Consent for publication

All authors have given consent for publication. The trial protocol does not contain any individual patient data.

Limitations

Currently, we expect possible problems with funding for our center given the war situation in the country, which may affect the supply of surgical instruments. We are actively seeking grants to implement this study. In addition, in the process of recruiting patients in 2024, we began performing totally laparoscopic simultaneous resections of primary colon tumors with synchronous metastases. We plan to evaluate that cohort separately.

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ПРОТОКОЛ ДВОЦЕНТРОВОГО РАНДОМІЗОВАНОГО КОНТРОЛЬОВАНОГО КЛІНІЧНОГО ДОСЛІДЖЕННЯ З ПОРІВНЯННЯ ЛАПАРОСКОПІЧНОЇ ТА ВІДКРИТОЇ «МІНОРНОЇ» РЕЗЕКЦІЇ У ХВОРИХ УКРАЇНИ НА КОЛОРЕКТАЛЬНИЙ РАК З МЕТАСТАЗАМИ ДО ПЕЧІНКИ

Стан питання. Згідно світовій статистиці приблизно 15% резекцій печінки виконується лапароскопічно. Однак у спеціалізованих центрах України цей показник становить 5% і навіть менше. **Мета** дослідження, що планується, — з'ясувати, чи будуть безпосередні хірургічні та віддалені онкологічні результати лапароскопічних резекцій печінки (ЛРП) кращими за такі в разі відкритої резекції печінки (ВРП) в умовах спеціалізованих державних центрів України. Паралельно буде досліджено системну стресову відповідь на хірургічне втручання. **Методи**. Плановане дослідження являє собою національне двоцентрове рандомізоване контрольоване подвійно сліпе клінічне дослідження в Україні. Рандомізація хворих у співвідношенні 1:1 до груп ЛРП або ВРП буде проводитись за допомогою програмного забезпечення REDCap®. Первинною кінцевою точкою буде порівняння тривалості знаходження в стаціонарі. При цьому завдання полягатиме в зниженні часу перебування в стаціонарі для групи ЛРП принаймні на 28%. Для досягнення статистичної потужності у 80% та альфа-рівня в 0,05 для двобічного *p* критерію, потрібно щонайменше 126 хворих (по 63 в кожній групі). **Обговорення**. Проведення рандомізованого дослідження в Україні з порівняння результатів лапароскопічного та мінорного відкритого хірургічного втручання на печінці дозволить оптимізувати отримані результати з врахуванням відмінностей в демографічних показниках хворих та інфраструктурі закладів охорони здоров'я. Усе це дозволить скласти критичне уявлення щодо ефективності, безпечності та можливостей обох хірургічних методик в Україні, де існують певні відмінності в організації лікування онкологічних хворих у порівнянні із західними країнами. **Реєстрація та статус дослідження**. Дослідження зареєстровано 26 травня 2024 р. на Researchregistry.com (UIN10336). На цей час до дослідження залучено 38 хворих.

Ключові слова: лапароскопічна резекція печінки, рандомізоване контрольоване дослідження, функціональний статус гепатоцитів.