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Comparative analysis of the results of laparoscopic and classical hepatic resections for multiple tumors in patients with hepatocellular carcinoma

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Abstract

Laparoscopic removal of the affected part of the organ and classic laparotomic resection with open access for surgical manipulations are widespread. The choice of resection method is still controversial because researchers are currently talking about the importance of minimally invasive surgical techniques. The purpose of this study was primarily to compare the intraoperative, early, and late postoperative status of patients who underwent laparoscopic or laparotomic hepatic resection for multiple foci of hepatocellular carcinoma. In general, the operations using the laparoscopy method are much safer, because perioperative complications (including intense stress reactions with the appearance of hypertension, suppression of the immune response, tachycardia, and hypercoagulability) occur much less frequently than in the case of open-access intervention. Less invasiveness of laparoscopic operations contributes to a better recovery of patients after resection. On the other hand, laparotomy provides wider and faster access to the liver. This meta-analysis compares the effectiveness of minimally invasive laparoscopic resections over classic laparotomic operations in patients diagnosed with hepatocellular carcinoma with multiple tumors.

Introduction

According to the World Cancer Research Fund International, primary malignant neoplasms of the liver (including hepatocellular carcinoma) are the sixth most common tumors worldwide. More than

900,000 new cases were reported in 2020 alone. The main approach for treating liver tumors is resection of the affected organ, which can be performed both laparoscopically and laparotomically.

The term “Laparoscopically” denotes a surgical procedure executed via laparoscopy, a minimally invasive methodology involving the insertion of surgical instruments and a laparoscope (a thin, flexible tube equipped with a light source and camera) through small incisions made in the abdomen. By utilising this methodology, the abdominal cavity can be effectively observed, enabling a range of surgical procedures to be executed while minimising damage to adjacent tissues.

The term “laparotomically” denotes a surgical procedure executed via laparotomy, a conventional open surgical technique. A single large incision is made in the abdominal wall during laparotomy to gain direct access to the abdominal cavity. In contrast to laparoscopy, this technique affords the surgeon an expanded field of view and improved access to organs and tissues. However, it is important to note that the larger incision typically necessitates a more protracted recovery period, may entail increased postoperative pain, and increases the risk of complications.

It is better to use the laparoscopic method for patients who have neoplasms in the anterolateral hepatic segments, which include segments 2, 3, 4b, 5, and 6. In case of bilateral liver damage or massive resection of three or more adjacent segments, laparoscopic surgery becomes quite technically complex.[1]

In 2014, the Second International Consensus Conference on Laparoscopic Hepatic Resection was held in Japan, and the researchers concluded that small laparoscopic resections had become a standard practice among surgeons around the world.[2] However, large resections for multiple tumor lesions are still innovative methods. The Louisville conference, held in 2008, was more about introducing laparoscopic minimally invasive technologies into standard surgical practice.[3] The main disadvantage of both meetings was the fact that there were no prior randomized evidence-based comparisons of an open-access laparoscopy, which could provide an adequate basis for recommendations. So, the evidentiality of both intervention methods was rated as “low”. The next one was the Southampton

Consensus Conference in 2018, but it also did not provide any meaningful randomized evidence for both techniques of hepatectomy for hepatic neoplasms.[4]

Studies in favor of laparoscopic resections over open hepatectomy were published with the participation of Ciria *et al*., who studied minimally invasive surgical methods for hepatocellular carcinoma.[5] However, the main drawback of these studies became the fact that they were based on retrospective data (which had a substantial impact on the results of comparisons). Similar studies were conducted by Komorowski *et al*. in their literature review and meta-analysis comparing hepatic resection.[6] The authors noted that there was a minimal number of randomized studies on this topic at that moment, but those that already existed were of poor quality and had a high risk of selection bias in clinical cases. However, even with such conclusions, the researchers had emphasised that laparoscopic surgery was more acceptable when choosing the method of hepatic resection if it was performed in experienced hepatobiliary surgery centers. The inaccuracies in the opinion of most authors regarding the use of minimally invasive techniques of hepatic resection for large-scale lesions of hepatosegments in hepatocellular carcinoma became the reason for this study, namely the investigation of the course of operations and possible complications after the intervention, which can have a substantial impact on the formation of the final conclusion. In addition, an important point that should be considered in a broad assessment of these two resection techniques was that performing laparoscopic resections was significantly more costly, which was explained by the need for modern surgical equipment. These issues were highlighted in the papers by Schmelzle *et al*.[7] and Cipriani *et al*.[8]

In addition, the location of the neoplasm in the posterolateral segments could become a complicating factor when performing laparoscopic resection for multiple lesions, which greatly complicated the process of removal of the part of the organ invaded by the pathological process. Rubinkiewicz *et al*. described in detail the complexities of such unfavorably located lesions and concluded that laparoscopic resection was useful in such situations but required a surgeon to have a high level of operational skills.[9]

Guerrini *et al*. started a broad meta-analysis in 2020 that compared laparoscopic and open hepatic resection for intrahepatic cholangiocarcinoma.[10] The authors have concluded that laparoscopic resection in the case of that oncopathology had fully provided positive surgical results because the patients in that group had fewer prerequisites for intraoperative blood transfusion, the Pringle manoeuvre, were under medical supervision for less time, and had a lower disease incidence in the postoperative period in general. Nevertheless, with the laparotomy resection, there was a higher tendency for lymph node dissection; thus, the researchers' conclusions may be biased due to the differences between clinical pictures included in the analysis.

The purpose of this study was primarily to compare the intraoperative, early, and late postoperative status of patients who underwent laparoscopic or laparotomic hepatic resection for multiple foci of hepatocellular carcinoma.

Materials and Methods

Studies relating to the implementation of laparoscopic and laparotomic hepatic resection in patients with hepatocellular carcinoma were selected for direct analysis. A systematic review of relevant studies was conducted in evidence-based medicine databases such as PubMed, EMBASE, Web of Science, and the Cochrane Library. The search for relevant studies was conducted using keywords covering the topic of this meta-analysis, which are most often used in similar medical papers. Only the studies published between 2012 and 2022 were selected for the review, and the type of publication as well as the language of writing were not substantial. Articles by the same author were excluded from the meta-analysis (only more relevant and recent works had been selected), as well as papers that duplicated existing data in order to prevent repetition. Experimental studies or those describing animal experiments were excluded from this meta-analysis.

The clinical cases of 26 patients who underwent laparoscopic major resection and 78 patients who underwent open major resection were retrospectively evaluated. In all the above patients, the indication for surgery was hepatocellular carcinoma, and the number of tumor nodes in the liver was

3 or more. The location of tumors necessitated extensive resection. The option of laparoscopic resection was not considered for those patients in whom the tumor was located near the main portal pedicle, inferior vena cava, or infiltrated into these anatomical sites. Considering the terminology of The Brisbane 2000, the authors referred to a major hepatic resection as one that includes the removal of more than three segments, and posterior and anterior right sectionectomy.[11] According to the Child-Pugh scale, patients were divided into categories A and B, which substantially increases the prognosis for a positive resection result in the subsequent postoperative period.[12] This classification is based on the assessment of total bilirubin, serum albumin, the examination of an external cascade of plasma coagulation, and the presence or absence of ascites and hepatic encephalopathy.

Information from medical reports, which included postoperative data, demographic collection, and follow-up to identify the long-term complications of surgical interventions, was taken into account. All patients were divided into two general groups according to the classification of the operation performed: patients who underwent laparoscopic hepatic resection and those who underwent laparotomy hepatic resection. All data were calculated and processed using Statistical Analysis Software – STAT 15.3. Data were presented according to the $p\text{-value}<0.05$.

The main central component assessed was postoperative complications. All common and single complications described in the trials were included for evaluation. Blood loss, the need for transfusion therapy, the total duration of operation, the diameter of tumors, the overall survival, and the functional ability of patients after resection were considered for secondary comparison. Complications directly related to hepatic resection included all pathological conditions that appeared within 30 days after the surgical intervention. Death occurring within 90 days of surgery was classified as postoperative mortality.

When choosing the type of resection, first of all, the functional ability of the organ, localization and damage of the hepatic vessels, and the degree of damage of the parenchyma by cancer cells were taken into account. After hepatic resection, both groups underwent liver function tests and blood tests. In the postoperative period, patients were evaluated by laboratory blood tests every 2 months for a

year, which directly included monitoring of the alpha-fetoprotein level, ultrasound examination, computed tomography, and examination of liver functional capacity.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. A study was approved by the National Ethics Commission of the Ministry of Health of Poland on December 21, 2022, No. 2515-1. All patients consented to the processing of their data in writing, maintaining confidentiality.

Results

All clinical cases were carefully selected from the previously published papers to compare the immediate results of two types of hepatic resection with multiple segmental lesions. The selected patients were divided into two groups to facilitate the evaluation of the results: patients who underwent laparoscopic resection and those who underwent laparotomy resection. The first category included 26 patients, and the number of patients in the second group was three times more – 78 patients. In addition, to improve the formation of conclusions, the patients were divided depending on the clinical data (Table 1).[13]

There were no striking differences between gender, age, Child-Pugh characteristics, and concomitant diseases between the two groups.[12] The Child-Pugh score, also known as the Child-Turcotte-Pugh score, is a clinical scoring system used to assess the severity of liver disease and predict the prognosis of patients with cirrhosis. This scoring system helps healthcare providers classify the severity of liver dysfunction and guides treatment decisions for patients with liver cirrhosis. According to the Child-Pugh scale, patients were divided into categories A and B, which substantially increases the prognosis for a positive resection result in the subsequent postoperative period. This classification is based on the assessment of total bilirubin, serum albumin, the examination of an external cascade of plasma coagulation, and the presence or absence of ascites and hepatic encephalopathy. The assessment of all data is used to predict intraoperative mortality and the likelihood of future postoperative liver

complications. The patients were divided according to the identical principle into two groups to evaluate the operational results (Table 2).[13]

Eighteen patients in the first group (69.2%) and 54 in the second group (69.2%) underwent a right hemihepatectomy. No deaths were registered during the operations. Two of the patients (who underwent laparoscopic hepatic resection) underwent a conversion to a laparotomy due to bleeding during the operation, which was difficult to control in the laparoscopic approach due to the limited field of view of the surgeon. In addition, 55 patients from the group who underwent open hepatic resection (representing 70.5% of the total) and 15 patients from the category that underwent laparoscopic resection (which amounts to 57.7% of this group of patients) underwent the Pringle maneuver. In the first group, there was substantially less blood loss during the operation, almost half as much as in the second group. This aspect of the operation can be explained by better visualization of the liver structures in the case of laparoscopic resection and, accordingly, less vascular damage. This fact can explain the need for more transfusions after an open hepatic resection. However, in terms of the percentage, approximately the same part of patients in both groups needed intraoperative transfusion (in the group with laparoscopic resection 7 patients, which is 26.9%, and in the group with laparotomic resection 23 patients, which is 29.5% of the total). The time spent by the surgeons to perform the operations was also almost the same in both groups, amounting to approximately 259.8 minutes. It is important to note that the second group had a higher percentage of surgical complications, including ten cases of intra-abdominal fluid accumulation, one case of bleeding, five cases of pulmonary infection, and six cases of wound infection; while in the first group, these complications were either absent or were observed in a minimal number of patients. The mechanism of development of postoperative ascites has not yet been finally identified. Nevertheless, it can be assumed that it is partially associated with an increased pressure in the portal vein system after extensive resection. The lower incidence of ascites in patients after laparoscopic surgery was likely associated with a less intense immune response of the body due to the less invasive nature of the

surgery, and with a lower complication rate. The pathological anatomical examination of the free resection margin also did not reveal any differences between the two groups.

The number of postoperative biliary fistulas in patients after laparoscopic resection was lower: only one case was described in patients after laparoscopy and 5 cases – after the classical surgery. Most likely, this can be explained by better visualization of the transacted surface of the liver during laparoscopic surgery. There were no substantial differences in the process of restoration of the defecation act in both groups; however, there was a substantial difference between the postoperative stay of patients in the hospital for observation. This figure averaged 15.5 days in the second group, and approximately 11 days in the first group.

After the hepatic resection, the patients were followed up for 33.3±15.6 months for the group with laparoscopic resection and 31.4±15.7 months for the group with laparotomy resection. After one year of follow-up, it was difficult to identify a substantial difference between patients in the different groups. Regarding the median 4-year survival rate, it was 64.7% in patients after open surgery and 10.7% higher (75.4%) in patients after laparoscopic resection. This difference can be explained by less traumatization when performing minimally invasive surgical techniques, as well as by the fact that open (laparotomic) hepatic resection is more often indicated in patients with a more complex clinical picture of hepatocellular carcinoma, or in patients with a very large number of tumors, which can be localized in difficult places to create laparoscopic access. In addition, in comparison with the first group, the patients with laparotomy resection were more likely to experience relapses of the disease.

In 11 patients from the open resection group, postoperative progressive liver failure was observed, which required mainly radical treatment in the form of liver transplantation; while in patients from the first group, these pathological processes were not observed. In addition, two patients from the second group had acute myocardial infarction. These two causes mainly influenced the mortality rate in patients who underwent open hepatic resection for hepatocellular carcinoma with multiple lesions.

The comparative study reflects the substantial advantages of laparoscopic methods of surgical interventions compared with open operations. This can be explained by smaller incisions to access the liver, less pain after surgery, substantially less time required for full recovery, a lower immune and metabolic response from the body, and a lower percentage of complications observed in the postoperative period. But the disadvantage is still the fact that the performance of the laparoscopic resection requires a specialized surgical team with high qualifications and skills, as well as limited access to the organ during laparoscopic operations in emergency situations.

Nevertheless, there are a number of relative contraindications for laparoscopic resection, including the localization of neoplasm close to the central vessels of the liver due to the likelihood of their damage, the number of tumors, poor tolerance of the pneumoperitoneum, and the functional ability of the liver to postoperative restoration. If all these parameters are considered separately, they are not contraindications for performing laparoscopy, but they can substantially complicate the course of surgery, which can affect the subsequent recovery period of the patient after the removal of the affected part of the organ.

When comparing the costs of the two liver resection techniques, an analysis revealed that the intraoperative expenses associated with laparoscopy are significantly greater than those of open resection; but this is directly related to the need for high-tech laparoscopic equipment and a slightly longer duration of the operation if it concerns the liver invasion with a large number of oncological neoplasms. There is a high probability that the cost of laparoscopic instruments will gradually decrease in the near future, which can be associated with an increase in demand and the use of minimally invasive techniques in surgery.

Discussion

Over time, small hepatic resections have become a standard practice in modern surgery. Recently, when performing extensive resections (for example, multiple liver lesions), surgeons prefer

laparoscopic methods because this technique is not inferior in safety and has a high postoperative possibility for function compared to standard open surgery techniques.

A systematic review and meta-analysis were conducted at Guangzhou Medical University led by Z.Y. Wang, to compare laparoscopic and open resection for hepatocellular carcinoma lesions of the organ.[14] After the study, the researchers received standard results, reflecting substantially less blood loss, a lower level of postoperative complications, and substantially less time required for hospital observation when performing a laparoscopic resection. Nevertheless, laparoscopic resection of large parts of the liver had a substantially longer surgical time, which increased the risks of intraoperative complications.

The problem of choosing laparoscopic or laparotomic resection if the patient has concomitant cirrhosis is quite interesting. Studies on the choice of resection in this situation were performed by Japanese researchers Yamamoto *et al*. and Kabir *et al*. at Oxford University.[15,16] In a meta-analysis, the researchers compared early and long-term postoperative outcomes after laparoscopic and open hepatic resections. The randomized controlled and propensity score matching studies were evaluated, providing the necessary information to form the final conclusions. The following data has been selected as the main indicators to determine outcomes: data on the overall survival of patients, the time required for surgical intervention, the volume of intraoperative blood loss, and accordingly, the need for blood transfusions, the need to perform the Pringle maneuver, postoperative complications, and the total time required for hospital observation for the patients. After evaluating all the information received and its competent systematization, the authors concluded that the laparoscopic resection method in the case of hepatocellular carcinoma complicated by cirrhosis is a safe option that can improve the indicators of overall postoperative survival and patient recovery, due to the reduction of invasiveness and injury to body tissues.

In addition, in 2021, a large-scale study was conducted with the participation of Troisi *et al*., which examined in detail the clinical cases of cirrhosis of class B according to the Child-Pugh scale and the effectiveness of laparoscopic hepatic resection in such patients.[17] The authors concluded that if

patients did not have high pressure in the system of the portal vein before surgery, such patients tolerated laparoscopic resection without complications; and had no significant complications in the early and separated results, which could classify the operation as traumatic and ineffective.

It is not uncommon in surgical practice to perform repeated liver resections for relapsed hepatocellular carcinoma, which is a rather dangerous pathological condition for the patient. When performing repeated hepatic resection by laparoscopic method, there is a high risk of abdominal organ trauma due to adhesion and the change in anatomical correspondence of organs and tissues. Therefore, during repeated hepatic resection, surgeons usually prefer the open laparotomy method, which reduces the risk of complications and damage to other organs of the patient. However, the studies by Inoue *et al*. showed that the laparoscopic method of re-resection of the liver also demonstrates positive postoperative dynamics, which makes it non-threatening to perform routinely in similar conditions.[18]

There is also a technique for performing robotic hepatic resection, which in recent years has gained increasing adoption in various surgical branches, including the spectrum of hepatobiliary surgical interventions. In August 2021, the US Food and Drug Administration made a statement that robot-assisted surgical procedures are safe for use in all branches of interventional medicine.[19] In his study, F. Di Benedetto detailed all the advantages of using the methods of robotic laparoscopic resection because this approach increases the surgeon's ability to control the operating area by leveling possible complications that may be associated with excessive traumatization.[20] The only major disadvantage is the need for a high-tech robotic transection device, which is currently only available in highly specialized centers for minimally invasive surgery. Despite the growing demand and the development of the latest technologies in the field of medicine, robotic surgery has not yet been sufficiently explored for large-scale implementation into standard practice.

Machairas *et al*. conducted a comparison of robotic technique and laparotomic resection and concluded that robotic surgical interventions for liver cancer were much less accompanied by concomitant postoperative complications than in the case of open liver resection.[21] However, only

ten non-randomized retrospective studies were included in their analysis, which cannot provide an adequate evidence base in favor of one of the techniques of liver resection performance. An important problem also standing in the way of introducing laparoscopic techniques into standard approaches for the treatment of hepatocellular carcinoma with multiple lesions is that there is currently a deficit in laparoscopic training programs for young surgeons. There is also a lack of a single educational program that can be used in this field of minimally invasive surgery.

In 2019, the paper was published by Halls *et al*., who compared the effectiveness of training young surgeons according to modern educational materials on laparoscopic resection and analyzed the safety and adequacy of performing hepatectomy by young surgeons and self-taught surgeons.[22] Their study showed that junior surgeons had a substantially higher learning rate with informative and structured training programs, and subsequently, they also performed both simple and complex laparoscopic hepatic resections safely and efficiently without the supervision of more experienced surgeons.

Evaluating all the above-mentioned studies, it is possible to make the statement that the use of minimally invasive surgery in operations on the liver can substantially reduce the operational trauma of the body and accelerate the recovery process, without substantially limiting the scope of possible surgical interventions. The introduction of robot-assisted surgery into this area remains an innovative direction, but research on this topic requires more evidence and more extensive clinical trials to speak without *caveats* about safety and favorable intraoperative and postoperative periods for patients.

Conclusions

Laparoscopic resection is a safe and efficacious method for managing hepatocellular carcinoma with multiple lesions, providing numerous benefits in comparison to open resection, as demonstrated by this meta-analysis. Less blood loss, postoperative pain, smaller incisions, decreased relapse rates, and decreased postoperative liver failure were all outcomes of laparoscopic resection. Additionally, patients demonstrated a diminished autoimmune response, which was plausibly attributable to reduced tissue damage, thereby facilitating an expedited recuperation.

Nevertheless, the absence of long-term follow-up data subsequent to extensive laparoscopic resection undermines the reliability of these conclusions. Further randomized trials comparing open resections and large laparoscopic resections for livers invaded by multiple tumors are necessary in order to establish more conclusive findings.

Laparoscopic resection ought to be regarded as the method of choice for appropriate candidates. However, open resection may be preferred in cases of specific contraindications, such as inadequate tolerance to pneumoperitoneum, invasion of central liver vessels, or extremely large tumors. Additionally, the surgeon's proficiency with sophisticated laparoscopic techniques is crucial when performing resections of this nature.

The continued expansion of minimally invasive laparoscopic techniques for liver resection, which reduce patient trauma and accelerate postoperative recovery without restricting the scope of possible interventions, can be achieved through the implementation of structured training programs and the accumulation of experience. Additional investigation is required to validate the safety and effectiveness of nascent robot-assisted methodologies.

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Table 1. Characteristics of patients and details of the medical history.

	Laparoscopic hepatic resection (26 patients)	**Laparotomic hepatic resection (78 patients)**	**p-value**
Gender (M:F)	11:15	33:45	1
Age	56.1±10.6	52.0±12.2	0.698
Child-Pugh class, number of patients (%)			
A	23 (88.5)	70 (89.7)	1
B	3 (11.5)	8 (10.3)	
Cirrhosis confirmed histologically	16 (61.5)	45 (57.7)	0.73
Concomitant diseases, number of patients (%)			
Diabetes	2 (7.6)	7 (9)	1
Hypertension	4 (15.4)	8 (10.26)	0.489
Predominant hepatic disease	11 (42.3)	29 (37.2)	0.642
Tumor size (mm)	75.0±35.1	75.5±38.8	0.378

Table 2. Results of surgical intervention.

	Laparoscopic hepatic resection (26 patients)	**Laparotomic hepatic resection (78 patients)**	**p-value***
Time of surgical intervention (min)	264.2±14.1	255.4±36.3	0.215
Intraoperative blood loss (mL)	340.8±225.2	601.4±509.4	0.007
Intraoperative transfusions (number/%)	7 (26.9)	23 (29.5)	0.803
General complications, number of patients (number/%)	4 (15.4)	29 (37.2)	0.039
Wound infection (quantity/%)	2 (7.7)	6 (7.7)	1
Leakage of bile	1 (3.8)	5 (6.4)	1
Intra-abdominal fluid accumulation (quantity/%)	1 (3.8)	10 (12.8)	0.357
Bleeding, number of patients (%)	2	3 (2.0)	0.597
Lung infection, number of patients (%)	0	5 (6.4)	0.427
Restoration of defecation, days	1.5±0.5	3.1±0.6	0.083
Postoperative hospital stays, days	11.0±2.9	15.5±5.2	0.024
pR1, number of patients (quantity/%)	1 (3.8)	7 (9)	0.671
pRM (mm)	7.5±35.1	7.1±36.4	0.895
Number of tumors	3.3±0.6	3.4±0.7	0.381

*$p<0.05$ (considered important for direct analysis, so these values are shown in bold in the Table)

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