

## Review Article

# Factors influencing the selection of liver resection for adult patients with colorectal cancer liver metastases

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## ABSTRACT

The selection of liver resection surgery for adult patients with colorectal cancer liver metastases is a complex process influenced by various patient, tumor, and surgical factors. A systematic review was conducted with the PICO model research question, "are hepatectomy surgeries more effective than non-surgical treatment or alternative surgical treatments in improving survival and quality of life in adult patients?". A comprehensive scientific literature search was conducted using recognized medical and scientific databases. A narrative-question-answer synthesis was used to provide a comprehensive overview of the factors influencing the choice of hepatic resection surgery in adult patients with liver metastatic liver cancer. Concluding, the choice of liver surgery in adults with liver cancer metastasis depends on a wide range of factors such as the patient's age, characteristics of the tumor, peri and postoperative complications, and the number of metastases. Considering this is essential to the decision-making process and should be individualized for each patient.

**Keywords:** Colorectal neoplasms, Neoplasm metastasis, Liver neoplasms/surgery, Liver resection/methods, Decision making, Patient preference, Surgical procedures, Operative

## INTRODUCTION

Colorectal cancer liver metastases are the spread of cancerous cells from the colon or rectum to the liver, which occurs in nearly half of colorectal cancer cases and is often life-threatening.<sup>1</sup>

Hepatic resection, or surgery to remove affected part of the liver, is preferred treatment for colorectal liver metastasis.<sup>1</sup> Repeat liver resections for metastatic colorectal cancer involve removing fewer lesions and less extensive surgery, and substantial proportion of patients achieve long-term survival.<sup>2</sup> In cases where synchronous metastasis occurs, simultaneous liver resection seems

safe in patients with small metastases and limited number of them.<sup>1</sup> Repeat liver resection for relapsing liver metastases is safe and effective surgical procedure that results in similar outcomes to initial liver resection.<sup>3</sup> However, timing of liver resection and identifying patients with the most significant survival benefit remain unclear.<sup>1</sup> Patients undergoing laparoscopic liver resection surgery for colorectal liver metastases expressed unmet informational needs related to new technique, time after discharge, surgery outcomes.<sup>4</sup> Overall, hepatic resection is important treatment option for patients with colorectal liver metastases. However, carefully considering patient's circumstances is necessary to determine optimal timing and approach to surgical intervention.

The presence of liver metastases significantly impacts the overall prognosis. Patients without liver metastases had a median survival of 86 months compared to 10 months for synchronous metastases and 43 months for metachronous metastases.<sup>5</sup> Prevalence and impact of liver metastases in colorectal cancer highlight the importance of early detection and development of effective treatments.

Liver metastases are a common complication of colorectal cancer, affecting 23.6% of patients.<sup>5</sup> Patients with liver cirrhosis have a higher incidence density of liver metastasis, with a 10-year cumulative risk of 27.1% compared to 23.6% for non-liver cirrhosis patients.<sup>6</sup> For early-stage colorectal cancer patients receiving surgery alone without adjuvant anti-cancer treatments, those with liver cirrhosis have a higher 10-year cumulative risk of liver metastasis than those without.<sup>6</sup> In the Egyptian population, patients with liver metastasis had higher biomarkers such as CEA and CA19.9 and a higher frequency of vascular invasion and nodal involvement.<sup>7</sup>

Multiple nodules significantly worsen patient prognosis, but the life expectancy of patients with four or more nodules makes their resection mandatory. The primary tumor stage, lymph node metastasis, a high preoperative CEA level, a short interval between treatment of the primary and metastatic tumors, and invasion at hepatectomy are all associated with a poor prognosis. Although resection of liver metastases from colorectal cancer improves survival, liver metastases within one year of colorectal resection may need an observation interval before liver resection.<sup>9-11</sup>

It is crucial to investigate factors influencing selection of liver resection for treating colorectal cancer liver metastases in adult patients because indications for surgical resection remain controversial, several clinical risk factors have been reported to influence survival.

## LITERATURE RESEARCH

A narrative review was conducted using the PICO model for the research question, "Are liver resection surgeries more effective than non-surgical treatment or alternative surgical treatments in improving survival and quality of life in adult patients with liver metastases from colorectal cancer?"

The PICO model allows us to define the Patient population (P), Intervention (I), Comparison group (C), and Outcome measures (O) clearly and systematically. In this case, our PICO model is as follows: P (Patient population): Adult patients with liver metastases from colorectal cancer. I (Intervention): Liver resection surgery. C (Comparison group): Non-surgical treatment or alternative surgical treatment and O (Outcome measures): Improved survival and quality of life.

An extensive scientific literature search was conducted using various recognized medical and scientific

databases, PubMed. A bibliographic search extension was also performed using the research Rabbit search engine. This search engine provides an additional tool for identifying studies, reviews, and scientific publications that may not be present in the databases mentioned above, increasing the likelihood of finding relevant and up-to-date studies on the research topic.

## Search strategy

The search strategy will consist of controlled MeSH vocabulary and free language using the following keywords: PubMed search protocol: (liver resection colorectal cancer metastases) OR (factors selection liver resection colorectal cancer metastases) OR (liver resection decision making colorectal cancer metastases) OR (surgical indication liver resection colorectal cancer liver metastases) OR (medical criteria liver resection colorectal cancer metastases)

Two independent reviewers will screen the articles identified in the initial search based on the title and abstract to determine their relevance to the research question. Any discrepancies between the two reviewers will be resolved by discussion, and a third reviewer will be involved if necessary.

Full-text articles will be retrieved for all potentially relevant studies, and a final selection of articles will be made based on the inclusion and exclusion criteria. Data will be extracted from the selected articles and synthesized to address the research questions.

## Inclusion criteria

Studies investigating liver resection techniques include laparoscopic liver resection (LLR) and open liver resection (OLR). Studies comparing outcomes of different liver resection methods. Research involves hepatocellular carcinoma (HCC) patients, colorectal cancer liver metastases (CRLM), and other liver-related conditions. Studies assessing the impact of preoperative chemotherapy on liver histology and surgical outcomes. Research analyzing perioperative and short-term outcomes of liver resection. Studies were conducted in various locations (Korea, Norway, China, Taiwan, Italy, Sweden, Poland, Spain, Tunisia, Japan, Canada, the Netherlands, and the United Kingdom). Research involving a wide age range of patients, from young adults to elderly populations. Studies investigating the role of intraoperative ultrasound (IOUS) in liver resection.

## Exclusion criteria

Studies have not focused on liver resection or liver-related conditions, research involving non-human subjects or in vitro studies, studies without a clear comparison between different liver resection techniques or lacking a focus on surgical outcomes, research must provide more patient demographic information or specific

details regarding the surgical procedure, case studies or anecdotal reports without a larger sample size, studies with major methodological flaws or significant biases and research published before 2000, as more recent studies provide up-to-date information on liver resection techniques and outcomes were excluded.

After collecting and reviewing the relevant literature from the previous research protocol, the next step will be to analyze and synthesize the data. A narrative-question-answer synthesis will provide a comprehensive overview of the factors influencing the choice of liver resection surgery in adult patients with liver metastases from colorectal cancer.

Specifically, the data will be organized and presented according to the following themes identified after the research protocol was conducted. For each theme, a search protocol was designed, including specific keywords relevant to each question. The search protocol for each theme is outlined below the corresponding question.

### ***Data synthesis and analysis***

This analysis will address the research questions, providing a comprehensive and in-depth understanding of the factors influencing the choice of liver resection surgery in adult patients with liver metastases from colorectal cancer. We will discuss the results under the identified themes: patient-related factors, tumor-related factors, surgical-related factors, oncologic outcomes, postoperative outcomes, clinical and pathological factors, preoperative chemotherapy and radiation therapy, perioperative and postoperative complications, and long-term outcomes.

### ***Study limitations***

Despite its comprehensive approach, this review bears some limitations. Heterogeneity amongst included studies in design, patient populations, interventions, and outcome measures could constrain data comparison and aggregation. Language bias could be present as the search might be primarily restricted to English studies, potentially missing valuable data from non-English research. The time frame, confined to January 1, 2010, to April 30, 2023, may also exclude relevant studies outside this period. Moreover, missing or incomplete data from some studies may complicate a thorough assessment of the intervention's effectiveness, generating uncertainties in the findings.

The review's generalizability could be limited if the included studies primarily focus on specific subgroups, thereby not being universally applicable. Lastly, variations in outcome definitions and measurements across studies could hinder comparability. Nonetheless, despite these limitations, the review will provide valuable insights into the effectiveness of liver resection surgeries

for patients with liver metastases from colorectal cancer. This will contribute to evidence-based decision-making in clinical practice.

## **RESULTS**

### ***Patient-related factors***

Patient characteristics such as advanced age and comorbidities are known to be associated with increased perioperative risks after liver resection.<sup>12</sup> However, this study suggests that the impact of age and comorbidities on long-term overall survival (OS) following hepatectomy for primary and secondary malignancies may be time dependent. Age and comorbidities did not have an impact on OS within 39 and 55 months after resection, respectively, but a significant decline in OS was shown after that time. For patients with HCC, the effect of age increased earlier (17 months) than in those with colorectal metastases (70 months).<sup>12</sup> Additionally, preexisting comorbidities, major estimated blood loss, and postoperative complications have been found to decrease the OS in contrast to younger patients markedly.<sup>13</sup> However, the study also suggests that increased age should not be a contraindication for liver resection. Hepatic resection for primary and secondary malignancies should not be categorically denied due to age and comorbidities.<sup>12</sup> Another study found that hepatic resection for elderly patients over 80 can be safely performed, given careful patient selection.<sup>14</sup>

### ***Tumor-related factors***

The size of liver metastases greatly affects their detection and subsequent surgical treatment. In patients with metastases from colorectal cancer, studies have shown that the size of dominant metastases is associated with survival after hepatic surgery, with the large group (metastases  $\geq 6$  cm) having a much poorer survival rate than the small group (metastases  $< 3$  cm) and the medium group (metastases  $\geq 3$  cm and  $< 6$  cm).<sup>15</sup> However, in a separate study of patients with colorectal liver metastases treated with liver resection, total tumor volume, size, and the number of metastases were not independent risk factors for worse overall survival, and increased values of these factors should not be a contraindication for surgical treatment.<sup>16</sup> In patients with breast cancer liver metastasis, those with solitary metastases had a better prognosis after partial liver resection, with an overall 5-year survival rate of 37% and a median overall survival time of 55 months.<sup>17</sup> Therefore, tumor-related factors such as size, location, and number of liver metastases should be considered when deciding to perform liver resection surgery, as they can impact the patient's overall survival.

### ***Surgical-related factors***

The use of intraoperative ultrasound (IOUS) affects the surgical decision-making process for the resection of

primary and secondary hepatic cancers, as it is the most sensitive indicator of the number of lesions present in the liver and helps determine both the feasibility and extent of resection required.<sup>18</sup> The use of IOS also plays a significant role in patients undergoing liver resection for colorectal liver metastases (CRLM), leading to changes in surgical strategy in 27.2% of patients and resulting in a lower rate of early intrahepatic recurrence.<sup>19</sup> The extent of liver resection and operative time are risk factors that influence postoperative morbidity in cirrhotic liver resection surgeries.<sup>20</sup> However, there is no significant difference in liver regeneration and recovery rates between laparoscopic and OLR procedures.<sup>21</sup>

### Oncologic outcomes

There is evidence that LLR for HCC and CRLM, as well as open hepatectomy (OH) for CRLM and hepatectomy for gastric cancer liver metastases (GCLM), can result in comparable or favorable long-term oncologic outcomes in terms of overall survival and disease-free survival.<sup>22-25</sup> In some studies, factors such as tumor characteristics, tumor growth pattern, tumor grade, and use of neoadjuvant chemotherapy were found to be associated with worse survival outcomes.<sup>23,25</sup> However, these findings may vary depending on the specific patient population and must be considered in a multidisciplinary treatment setting.<sup>25</sup>

### Postoperative outcomes

Short-term and long-term postoperative outcomes associated with liver resection surgery vary depending on the type of surgery performed. Laparoscopic liver resection has been found to have lower overall morbidity, lower intraoperative and postoperative transfusion rates, and a shorter hospital stay compared to open liver resection in patients with recurrent hepatocellular carcinoma.<sup>26</sup> In addition, in patients with colorectal liver metastases, both laparoscopic liver resection and open liver resection have comparable operation time, duration of intensive care stay, and resection margins. However, laparoscopic liver resection has favorable outcomes for transfusion rates, length of hospital stays, and postoperative complications.<sup>27</sup> Patients who have undergone liver surgery for metastatic colorectal cancer have excellent global quality of life, high levels of function, and few symptoms.<sup>28</sup> More studies are needed to fully understand liver resection surgery's short- and long-term postoperative outcomes.

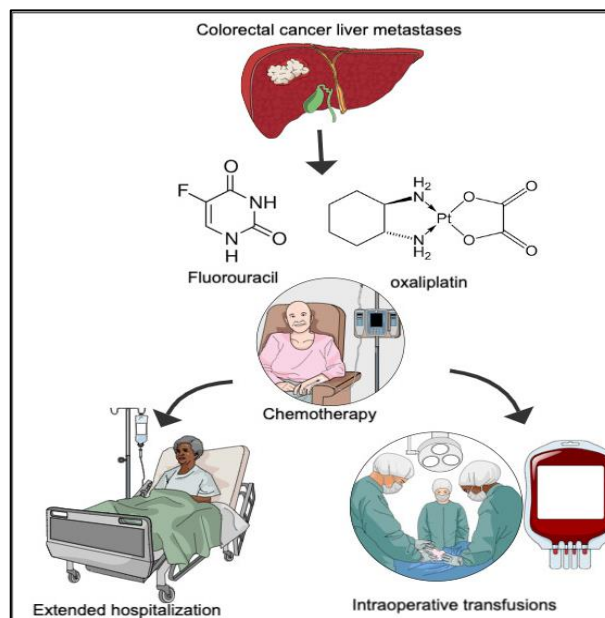
### Clinical and pathological factors

The optimal surgical procedure for hepatic resection in determining prognostic factors for adult patients with liver metastases from colorectal cancer is still controversial. However, safe hepatectomy with adequate tumor-free margins leads to a better prognosis. Factors that do not correlate with patient survival include sex, age, temporal relationship, primary tumor site, tumor

stage, pathological depth, pathological vascular invasion, pathological lymphatic invasion, pathological lymph node metastases of the primary tumor, the maximum diameter of liver lesions, intrahepatic distribution patterns, type of hepatectomy, and the number of hepatectomies. The number of liver tumors and the tumor-free margins are significantly associated with a good prognosis. In addition, anatomical liver resection of liver metastases from colorectal cancer improves survival, but patients with more than three metastatic tumors, recurrence within a year of colorectal and liver resections, and bilobar disease have a significantly poorer prognosis.<sup>29</sup>

### Impact of preoperative chemotherapy and radiation therapy

Preoperative chemotherapy can alter liver parenchyma but does not increase postoperative complications and should be considered before deciding on a major liver resection. Responses to chemotherapy are as important as achieving complete resection in cases of multiple hepatic metastases, and preoperative chemotherapy may be preferentially considered for such patients. Preoperative chemotherapy consisting of fluorouracil and oxaliplatin can induce vascular lesions in the noncancerous liver, which can increase the need for intraoperative transfusions and predispose patients to reoperation and more extended hospitalization. Moreover, preoperative chemotherapy can induce hepatotoxicity in the noncancerous liver, which may increase the risk of surgical morbidity and mortality.<sup>30-34</sup>



**Figure 1: Pre-op chemotherapy with fluoroacil and oxaplatin is an important step in colorectal cancer liver metastases treatment. Even though it can produce intrahepatic lesions leading to mayor blood loss during surgery, resulting in extended hospitalization time and intra-op transfusions.**

### **Perioperative and postoperative complications**

Perioperative and postoperative complications following liver resection surgery for colorectal liver metastases (CLM) can have a negative impact on long-term survival.<sup>35,36</sup> Complications may include minor or major adverse events, such as bleeding, infections, bile leaks, and liver failure, and may result in a higher risk of shorter recurrence-free and overall survival rates.<sup>35,36</sup> Blood transfusions, steatohepatitis, lymph node metastasis, concomitant extrahepatic disease, and serum carcinoembryonic antigen level of at least 100 ng/dl are potential independent risk predictors for postoperative complications following liver resection surgery for CLM, which may result in decreased survival rates.<sup>37,35</sup> Preventive and management strategies for postoperative complications may be crucial in reducing these adverse events, as they may affect long-term outcomes.<sup>35</sup>

### **Long-term outcomes of liver resection surgery**

Surgical resection is a valuable and effective treatment for liver metastases from colorectal cancer, with overall 3-, 5-, 10-, and 20-year survival rates of 51%, 36%, 26%, and 25%, respectively.<sup>9</sup> Patients with four or more nodules had almost the same survival rate as those with 2 or 3 nodules, indicating that resection is still necessary for patients with multiple nodules.<sup>11</sup> In a retrospective study, liver resection was found to result in prolonged survival compared to chemotherapy alone for patients with liver metastases and limited extrahepatic disease.<sup>10</sup> However, the indications for surgical resection and the number of metastases that impair prognosis remain controversial. In addition, the stage of the primary tumor, lymph node metastasis, multiple nodules, a high preoperative CEA level, and a short interval between the primary and metastatic tumors were significantly associated with a poor prognosis.<sup>9,11</sup>

## **DISCUSSION**

Liver resection surgery, a viable option for managing both primary and secondary hepatic malignancies, is influenced by various patient-related, tumor-related, and surgical-related factors. Moreover, the oncologic and postoperative outcomes significantly impact the quality of life and survival rates of patients.

Starting with patient-related factors, it is observed that characteristics like age and comorbidities are traditionally associated with increased perioperative risks.<sup>12,13</sup> Although they may not impact the overall survival immediately post-hepatectomy, their significant effects emerge over time.<sup>12</sup> It is thus imperative to note that despite these challenges, advanced age should not be a categorical contraindication to liver resection.<sup>14</sup> Comprehensive patient evaluation and careful selection are of utmost importance. However, the influence of tumor burden remains unclear in the decision-making process and necessitates further investigation.

Regarding tumor-related factors, the size, location, and number of liver metastases hold a significant influence on surgical decisions.<sup>15-17</sup> Size is notably associated with patient survival post hepatic surgery, and solitary metastases appear to offer better prognosis.<sup>15,17</sup> Yet, same study indicates that the number, total volume, and size of metastases are not independently detrimental to overall survival.<sup>16</sup> This implies that increased values of these factors shouldn't deter decision for surgical intervention.

In terms of surgical-related factors, intra-op ultrasound (IOUS) holds pivotal role. It provides valuable insights into the number of lesions present and the feasibility of resection, ultimately affecting the extent of resection required.<sup>18,19</sup> Furthermore, extent of liver resection and operative time are crucial determinants of postoperative morbidity in cirrhotic liver resection surgeries.<sup>20</sup> Despite no observable differences in liver regeneration and recovery rates between laparoscopic and open liver resection (OLR) procedures, understanding these factors is fundamental to optimizing surgical outcomes.<sup>21</sup>

As for oncologic outcomes, studies have shown comparable or favorable overall survival and disease-free survival rates following liver resection surgery.<sup>22-25</sup> Factors such as tumor characteristics, growth pattern, grade, and use of neoadjuvant chemotherapy, however, can negatively impact these survival outcomes.<sup>23,25</sup> Therefore, the incorporation of a multidisciplinary approach, considering individual patient factors and specific cancer types, is crucial for successful patient management.

Concerning postoperative outcomes, both short and long-term results are notably variable. Laparoscopic liver resection (LLR) tends to result in lower morbidity, lower transfusion rates, and shorter hospital stays compared to OLR.<sup>26,27</sup> Patients undergoing liver surgery for metastatic colorectal cancer report a high quality of life and functionality.<sup>28</sup> More research, however, is needed to gain comprehensive insight into liver resection surgery's short- and long-term postoperative outcomes.

Finally, regarding liver resection surgery in adult patients with liver metastases from colorectal cancer, several clinical and pathological factors can guide the decision-making process. The most critical factors include the number of liver tumors and tumor-free margins.<sup>29</sup> Preoperative chemotherapy can offer potential benefits but may also induce hepatotoxicity.<sup>31-34</sup> Perioperative and postoperative complications, including bleeding, infections, bile leaks, and liver failure, can affect long-term survival.<sup>35,36</sup> Thus, risk management strategies should be considered for reducing these adverse events. In comparison with other treatment options, such as chemotherapy/radiation therapy, liver resection can result in prolonged survival.<sup>9,10</sup> However, exact indications for resection and the factors impairing prognosis remain controversial and require further exploration.

Decision for liver resection surgery in patients with liver metastases from various cancers requires holistic approach, taking into consideration multitude of factors, including patient's overall health status, tumor characteristics and potential outcomes of surgery. Further research is required to optimize patient selection, enhance surgical techniques, and improve postop management.

## CONCLUSION

The selection of liver resection for adult patients with colorectal cancer liver metastases is a complex process influenced by various patient-related, tumor-related, and surgical factors. Advanced age and comorbidities can impact the overall survival of patients but should not be considered an absolute contraindication for liver resection. Tumor burden, size, location, and number of metastases play a critical role in the decision-making process, while the use of intraoperative ultrasound and the extent of liver resection are key surgical factors.

Long-term oncologic outcomes, such as disease-free survival and overall survival, are comparable or favorable for different types of liver resection surgeries. Postoperative outcomes, including complication rates and quality of life, are essential aspects to consider, with LLR showing favorable results compared to open liver resection. Clinical and pathological factors, preoperative chemotherapy, and radiation therapy should also be considered when choosing liver resection surgery for adult patients with colorectal cancer liver metastases.

Periop and postop complications associated with liver resection surgery can impact long-term survival, and efforts should be made to minimize these adverse events. Long-term outcomes of liver resection surgery are generally positive and may provide better survival rates compared to other treatment options, such as chemotherapy/radiation therapy alone, in selected cases.

It is crucial to continue investigating the factors that influence the selection of liver resection for adult patients with colorectal cancer liver metastases to optimize treatment strategies, minimize complications, and improve patient outcomes. Furthermore, a multidisciplinary approach to patient care, considering the unique characteristics of each patient and their tumor, is essential in guiding clinical decision-making and maximizing likelihood of positive long-term outcomes.

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