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Simultaneous Surgery for Synchronous Colorectal Liver Metastases

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Abstract

Colon cancer is one of the leading malignant diseases in the Western world, leading to significant morbidity and has significant predilection for liver metastases. Synchronous metastases account for approximately 15–25% of the newly discovered liver lesions. The only curative treatment for colon cancer liver metastases (CLM) remains surgery. Several strategies have been developed for the treatment of synchronous CLM, including simultaneous resection, two-stage liver surgery, and liver-first approach. The timing of surgery is not universally determined. Even more reports support the simultaneous resection strategy with results showing similar morbidity, length of hospital stay, and perioperative mortality comparable to staged resection. In conclusion, SCLM patients can successfully be treated with simultaneous approach or stages, both having similar perioperative and long-term outcomes. With the advance of liver surgery techniques, minor and major liver surgeries can be performed safely with low morbidity and mortality as part of either a simultaneous or a staged operative strategy.

Keywords: colon cancer, simultaneous resection, hepatectomy, liver metastases, adjuvant therapy

1. Introduction

Colon cancer remains one of the leading causes of cancer-related death in the Western world. The most common site for metastases from colon cancer is the liver [1]. According to studies, liver metastases develop in almost half of the colon cancer patients. Approximately 15–25% of

them are synchronous metastases. Surgical therapy for liver metastases remains the only potentially curative therapy for patients with colon liver metastases (CLMs) [1, 2]. The resection of synchronous CLMs, also known as SCLMs, appears to have survival rates similar to those of metachronous metastases [3]. The most appropriate moment for surgery in SCLM and primary tumor is not completely determined. The most common approach is resection of the primary tumor and consequent liver resection after 2–4 months later [4–7]. The advocates of this approach consider the probability of increased morbidity associated with the simultaneous procedure. This issue has been addressed in many studies comparing the simultaneous and staged approach. The results show similar morbidity, length of hospital stay, and perioperative mortality between the two [8–11]. Moreover, since a second laparotomy can be avoided by the simultaneous removal of the primary tumor and liver metastasis of colon may be preferred, it allows sooner completion of surgery, thereby permitting faster initiation of adjuvant therapy. However, there is no consensus on when to perform surgical resection of liver metastases and primary colon for patients with SCLM.

This chapter is aimed to present the efficacy and safety of simultaneous resections for synchronous colon cancer liver metastases.

2. Definition of resectability

As we know, the criteria defining when to perform the resection have significantly changed in recent years. Older criteria include patients with less than four unilobular metastases, resection margins over 1 cm and lack of extrahepatic disease. The main consideration for resectability is the ability to complete curative (*R0*) resection with adequate liver remnant. Modern definitions of resectability of liver metastatic disease criteria were presented by the Consensus Conference on the Multidisciplinary Treatment of Liver Metastases of colorectal cancer in 2012 [12].

The preoperative staging is aimed at the determination of surgical resectability. With the improved accuracy of combined computed tomography, positron emission tomography, liver contrast-enhanced magnetic resonance imaging and high-resolution CT, the ability to detect small-volume disease has been significantly enhanced [13]. Patients with positive celiac and/or paraaortic lymph nodes may not benefit from liver resection [14]. Although positive retropancreatic lymph nodes are suggestive of poor prognosis, the survival is proven to be better in patients with positive celiac lymph nodes and therefore these patients may benefit from liver surgery especially when they are subjected to perioperative chemotherapy [15]. Considering the individual characteristics of each case, all patients must be referred to specialized centers with multidisciplinary team to determine the proper timing of resection for primary tumor and SCLM [1].

3. Perioperative results

The specialization of general surgeons in hepatobiliary surgery training, development of hepatobiliary techniques, and up-to-date anesthetic and intensive care management has made

hepatic resection safer [16]. Nowadays, the major liver resections are showing minimal morbidity and mortality [11, 17]. According to a meta-analysis, patients undergoing staged resection had more postoperative complications, which are attributed to the need of two or more laparotomies. More incisions result in a greater risk of wound complications [2]. Staged resections are preferred to synchronous colonic resection and hepatic resections in some centers. A perceived increase in perioperative risk with simultaneous resection has traditionally provided the rationale for performing the resection in stages. On theory, the staged resection must have the advantage of better perioperative outcomes. The supporting evidence states that staged resection has significantly lower morbidity and mortality, and thus leads to better long-term results [5, 18–20]. On the other hand, more and more reports emerge in support of simultaneous resection without significant change of mortality and morbidity rates [21, 22]. Chua et al. [11] analyzed retrospectively 96 patients with synchronous colorectal cancer and liver metastases. These patients have been subjected to synchronous or staged resection. The analysis of postoperative results demonstrates that the two groups did not differ significantly in terms of postoperative complications and both lacked operative mortality.

Simultaneous and staged resections for SCLM have comparable morbidity and mortality and close long-term oncologic outcomes. In a study on this topic, the overall morbidity and mortality were 19.6 and 3.0%, respectively. Perioperative outcomes show no difference in patients treated with a staged or simultaneous approach.

Morbidity and mortality rate is similar between patients with major or minor liver resection and does not depend on the operative strategy. In a study by Martin et al. on patients with SCRLM, the reported morbidity and mortality were similar in the groups of staged and simultaneous approach [23]. Another study by Brouquet et al. had similar findings but it should be noted that the results were not stratified for major or minor liver resection [46]. According to the study by Reddy et al. [25], the major liver resection is associated with an increase of morbidity and mortality, although minor liver resection has similar perioperative results with the staged approach.

In conclusion, the safety of staged and simultaneous approach for minor and major hepatectomy is equal. The two strategies have similar operative time and no difference in blood loss. Analysis shows that patients with the staged resection have longer recovery period in the hospital and these with simultaneous resection have lower morbidity rate. A meta-analysis by Chen et al. on 14 studies compares concomitant resection to staged resection in patients with resectable synchronous hepatic metastases. The study includes 2204 patients who were divided into two groups—with simultaneous resection and with staged resection. In analysis, attention to quality of life (QoL) was turned. There are indicators for QoL such as operative time, intraoperative blood loss, and hospital stay. Postoperative morbidity rate is lower in groups of patients with simultaneous resection of the primary tumor and the synchronous liver metastases. And with other study on this topic is improved that simultaneous resection can play a role in better outcome [27]. After searching and analyzing the literature, there is review that deserved attention. It shows that results for patients with simultaneous and delayed resections are similar, and this meta-analysis is in agreement with studies [28]. Fukami et al. reported a series of 158 patients, 63 patients with synchronous colorectal liver metastases.

Of those with synchronous colorectal liver metastases, 41 patients (65%) underwent synchronous resection, and 22 (35%) underwent delayed resection. They noticed shorter total postoperative hospital stay in the synchronous resection group [29].

Synchronous		Staged	
Benefit	Risk	Benefit	Risk
Reduced complications due to single operation	Increased infectious liver complications due to bacterial contamination from intestinal resection		Increased morbidity associated with multiple procedures
Reduced length of hospital stay	Risk of complications from unresected primary	Reduced complications from unresected primary	Risk of hepatotoxicity from chemotherapy given between colorectal and hepatic resections
	Increased anastomotic complications due to impaired liver function		
	Extent of hepatic resection limited due to concomitant intestinal resection	Larger hepatic resections may be performed without increased morbidity	
No delay in initiating systemic treatment	Chemotherapy-associated hepatotoxicity may limit extent of liver resection		Risk of complications following colorectal resection may delay chemotherapy prior to liver resection
Opportunity to observe tumor response to neoadjuvant chemotherapy	No opportunity to assess tumor response if resection precedes systemic therapy		

Table 1. Potential risks and benefits of synchronous versus staged resection [34].

A new challenge for the surgeon is the laparoscopic simultaneous resection of synchronous colorectal metastases and the primary tumor. The studies have discussed the technical feasibility and short-come outcomes of the procedure. Tranchart et al. reported a preliminary series questioning the feasibility of combined laparoscopic resection of colorectal cancer (CRC) and synchronous colorectal liver metastases (SCRLM). The aim of this study was to compare the short- and long-term outcomes for matched patients undergoing combined resections. A total number of 89 patients were matched in the analysis. There was no difference in global operative time, blood loss, and transfusion rates between the two groups. A conversion was required in 7% of the laparoscopic procedures. Morbidity rates were similar in the two groups ($p = 1.0$). Their conclusion is that in patients without severe comorbidities presenting with one,

small (≤ 3 cm), CRLM resectable by a wedge resection or a left lateral sectionectomy, combined laparoscopic resection of CRC and SCRLM allows similar short- and long-term outcomes compared with the open approach [30]. Another international large study was published by Feretti et al., comparing the duration of the intervention, blood loss, transfusion rate, conversion rate, resection margin, specific and overall morbidity, perioperative mortality, length of hospital stay, and survival. Univariate and multivariate analyses were performed examining postoperative morbidity in all cohorts of patients. The combined data show that in experienced centers, simultaneous laparoscopic approach is technically feasible, safe, and associated with good oncological outcomes [31]. Miyamoto et al. reported earlier 13 patients who underwent simultaneous laparoscopic colectomy and hepatic resection. The primary sites were right colon in four, left colon in six, and rectum in three. The liver procedures included 14 partial resections or three left lateral hepatectomies. The results of the study conclude that the combined approach is feasible and safe in selected patients with primary CRC and synchronous liver metastases [32]. Other authors such as Muangkaew et al., Miyamoto et al., and Inoue et al. confirm that the feasibility of simultaneous laparoscopic colectomy and hepatectomy for primary colorectal cancer with synchronous liver metastases appears feasible with low morbidity and favorable outcomes [27, 33, 51] (**Table 1**).

4. Long-term oncological results

One of the studies is aimed at the long-term oncologic outcomes in patients with sCLM submitted to resection of both the primary CRC and CRLM. Results show that 57% of patients experienced a recurrence. Other conclusion is that operative strategy for sCLM had no connection with long-term outcomes. In a much smaller, single institution cohort, Brouquet et al. had similarly reported comparable overall survival among patients treated with the classic, simultaneous, or liver-first approach [46]. Rather than operative strategy, tumor-specific factors were associated with long-term oncologic success. These data serve to underline the importance of biology and not technique in the prognosis of patients with SCLM [23].

While the presence of synchronous metastases has been demonstrated to be a negative prognostic factor, it is not a contraindication to hepatectomy if a hepatic resection with curative intent can be achieved. The reported 5-year survival rates after liver resection for patients with SCLM range from 20 to 40%. Although some authors reported poorer prognosis for simultaneous resections compared with staged resections [5, 18], more recent studies demonstrated that the strategy to simultaneously resect the primary tumor and the synchronous metastases yielded no difference in survival compared to staged liver resection [8–10, 21, 35, 36]. Nonetheless, some authors argued that a waiting period of 2–6 months is necessary between the resection of primary tumor and liver resection, to make for subclinical metastases to become evident, in order to enable a better clearance of the tumor [19]. According to the “cascade” theory, in which cancer cells must first form metastases in the liver and then cells from these metastases migrate to the lungs, subsequently disseminated in an arterial pattern, dissemination of cancer cells toward the lungs may occur during the period between the resection of the primary tumor and the resection of the synchronous liver metastases [37].

At Zhongshan Hospital, Shanghai performed an analysis in 154 patients with consecutive synchronous colorectal liver metastasis who underwent simultaneous resection. The study for 10 years shows that this approach to simultaneous resection is safe and has significantly better outcomes in short and long term [38].

Tranchart et al. presented a propensity score-matching analysis of 142 patients who underwent combined laparoscopic resection of CRC and SCRLM, which were compared to a database of 241 patients treated by open during the same period. The 3-year-old overall survival in the laparoscopy and open groups was similar [30]. Another study by Ferreti et al. reported large international multicenter series of laparoscopic simultaneous resection of CRC and SCRLM. The results showed that overall 1-, 3-, and 5-year survival were 98.8, 82.1, and 71.9%, respectively [28]. Fukami et al. [29] compared two groups of simultaneous resection and delayed resection of SCRLM and found similar survival rate between the two groups ($p = 0.054$). Another study published by Wang et al. reports that there are no significant differences in postoperative complication rate and long-term survival between curative simultaneous and staged resection [39].

There is effective adjuvant therapies for colorectal cancer and simultaneous resection provides sooner completion of surgical therapy and earlier initiation of adjuvant therapy in patients with high risk of additional microscopic disease, which is of advantage to the patients [1].

5. Strategies in the treatment of synchronous colon cancer liver metastases

The most discussed topic for surgeons is the management of sCLM and how to balance between operative timing and strategy. The situation is complicated because of efficacious systemic chemotherapy regimens, targeted biological agents, and adjunctive strategies (e.g., ablative therapies) [1]. Regardless of the information, surgeons need to answer three important questions, summed up by Castellanos et al. in their review [2]:

1. Should the primary and metastatic lesions be resected at the same time?
2. If surgical resection is staged, should the primary or metastatic lesion be resected first?
3. What is the role of perioperative chemotherapy with surgical resection?

Simultaneous resections for primary tumor and liver metastases have technical and oncological specifics. According to standard guidelines, treatment plan is decided by regular tumor board plus hepatobiliary surgeon. Simultaneous resection is the choice for right colon primary cancers and smaller and fewer metastases. In patients with synchronous metastases, operation is done only when safe and good resection margins can be achieved. Simultaneous resection could be done independently of location of the primary cancer and the extent of liver metastasis without fatal postoperation complications [1]. Four prognostic factors were identified in a study by Capussoti et al., which have no effect on survival in the staged resections: more than three liver metastases, T4-primary colorectal tumor, liver metastases infiltrating surrounding structures, and male sex. The optimal timing of surgery should be based on patient's charac-

teristics such as the extent of disease, comorbidities, body habitus, and surgical experience [40]. Simultaneous resections for patients with peritoneal carcinomatosis are not advised [41].

While there is an abundance of evidence demonstrating the benefit of hepatectomy for CLM, there is only limited evidence available to empirically guide the timing of resection for sCLMs. The conventional paradigm has been to first resect the primary tumor, and then perform a hepatectomy. This approach is suggested to avoid complications associated with a major combined surgery. Another argument in favor of this approach is related to the tumor biology —the time windows between surgeries allow the aggressive disease to manifest and thus spare the patient the risk of major liver surgery. This has been supported by observations that staged resection does not result in increased risk of unresectability due to growth of CLM, but rather to appearance of new liver and/or extrahepatic disease. The time window between the staged resections provides the option for systemic treatment, which may decrease the risk of new metastatic lesions and thus improve overall survival. On the other hand, staged resection for SCRLM may result in increased hospitalization, additional cost, as well as increased pain, stress for patients subjected to staged approach instead of one single procedure [1, 2]. Considering the increasing number of studies showing decreased morbidity associated with simultaneous approach for SCRLM, it could be used in selected patients. The evidence for similar short-term and long-term outcomes after simultaneous or delayed resection is growing, even for major liver resection [1]. On the other hand, other groups of authors suggest that perioperative mortality is significantly higher for simultaneous resection, especially after major liver resections [1]. A multicenter retrospective analysis of 1004 patients with SCRLM treated between 1982 and 2011 demonstrates no difference in postoperative complications or a 90-day postoperative mortality between staged and simultaneous approaches for SCRLM [1]. The authors defined the major liver resection as resection of more than three segments. This procedure was more frequently performed in a staged strategy (39%) versus simultaneous approach. A meta-analysis by Slessor et al. compares the outcomes of simultaneous and staged resections for SCRLM of 3159 patients from studies from 1991 to 2010. They found no significant difference in operative blood loss, duration of operation, postoperative complications, overall survival, and disease-free survival. The total number of 1778 (56.3%) patients underwent delayed resection and had significantly larger liver metastases with increased bilobar distribution, and most of those patients underwent major liver resection [42]. Yin et al. presented a meta-analysis of studies including 2880 patients. The findings were similar although significantly lower incidence of postoperative complications was noted in the simultaneous resection group. This meta-analysis recommended the following criteria for the selection of patients for simultaneous approach: metastases in less than four liver segments, age <70 years, and exclusion of severe comorbidities [34].

This analysis confirmed that treatment strategy can change because of the clinical condition of the patient, surgeon, or on the recommendation of a multidisciplinary committee [2].

New retrospective analysis about mortality and morbidity after hepatectomy, colorectal resection, and synchronous resection for colorectal cancer in 43,408 patients shows reliable results that morbidity after synchronous hepatic and colorectal resections is variable and risk

is similar. Comparison of outcomes leads to conclusion that there is potential benefit for synchronous resections with minor hepatectomy [44].

The timing of the procedure has also been questioned by Feng et al. in a meta-analysis. Their conclusion is balanced and gives no clear advantage to the simultaneous approach in comparison to the delayed approach. According to the authors, the number of liver metastases was the major confounding factor for postoperative morbidity, especially in staged resections. Without baseline imbalances, simultaneous resection took no statistical significant advantage in safety and efficacy [43].

Over the past years with establishing of laparoscopic technology, there are studies about laparoscopic approach in the simultaneous resection of colorectal primary tumor and liver metastases. Results of studies show that there are 142 patients with laparoscopic liver resection for synchronous colorectal liver metastases. In conclusion, from these data, this approach is safe and offers good outcomes from an oncological view of point [44].

6. The role of perioperative chemotherapy

Despite the improvements in surgical approaches of liver resection, recurrence of disease has been reported in up to two-thirds of patients, with half of these occurring in the remnant liver. In patients with SCRLM who appear resectable on diagnosis, the National Comprehensive Cancer Network guidelines recommend simultaneous resection followed by adjuvant therapy (FOLFOX or CapeOx (capecitabine, oxaliplatin)) or neoadjuvant therapy for 2–3 months before surgery. The recommendations for neoadjuvant chemotherapy are toward FOLFIRI, FOLFOX, or CapeOx with or without bevacizumab. The KRAS status of the tumor defines whether panitumumab or cetuximab will be combined with FOLFOX or FOLFIRI [1, 2].

7. Conclusion

The role of surgery for synchronous colorectal liver metastases is well established. The remaining issue addresses the timing of the procedure. The choice between staged or simultaneous resection of SCRLM is a matter of careful selection of patients, based on tumor characteristics—extent of disease, degree of liver involvement, and patient's factors—performance status, age, and comorbidities. The sequence of actions considering systemic therapy and surgery is also open to discussion. Some authors reported poorer short-term results for synchronous resections compared with staged resections [5]. Conversely, more recent studies have shown that simultaneous colorectal and liver surgery are feasible and safe [8, 9]. Resection of synchronous colorectal cancer liver metastases is a safe and effective procedure compared to minor hepatic resection alone.

In conclusion, SCRLM patients may benefit from both approaches, which are supported by the short-term and long-term outcomes reported in various studies. Both minor and major liver surgeries are feasible with comparable morbidity and mortality for staged and simulta-

neous surgery. Despite the promising results, major liver surgery should be approached with caution as a simultaneous procedure with primary tumor resection. Laparoscopic simultaneous resections also present a feasible option with similar short-term and long-term outcomes. The key to the selection of strategy might be found in the tumor biology because survival in patients with SCRLM is more or less independent of the surgical strategy.

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