




REVIEW

Simultaneous Resection of Primary Colorectal Cancer and Synchronous Liver Metastases: Contemporary Practice, Evidence and Knowledge Gaps

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ABSTRACT

The timing of surgical resection of synchronous liver metastases from colorectal cancer has been debated for decades. Several strategies have been proposed, but high-level evidence remains scarce. Simultaneous resection of the primary tumour and liver metastases has been described in numerous retrospective audits and meta-analyses. The potential benefits of simultaneous resections are the eradication of the tumour

burden in one procedure, overall shorter procedure time, reduced hospital stay with the likely benefits on quality of life and an expected reduction in the use of health care services compared to staged procedures. However, concerns about accumulating complications and oncological outcomes remain and the optimal selection criteria for whom simultaneous resections are beneficial remains undetermined. Based on the current level of evidence, simultaneous resection should be restricted to patients with a limited liver tumour burden. More high-level evidence studies are needed to

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evaluate the quality of life, complication burden, oncological outcomes, as well as overall health care implications for simultaneous resections.

Keywords: Colorectal cancer; Colorectal resection; Liver resection; Simultaneous resection; Surgical oncology; Surgical outcomes; Synchronous liver metastasis

Key Summary Points

High-level evidence in simultaneous resection of colorectal cancer and colorectal liver metastasis remains scarce.

Simultaneous resections may be considered in patients with good performance status and limited liver tumour burden.

Simultaneous resections should be avoided when requiring major liver resection and major colorectal resection.

Treatment strategies should be made by a multidisciplinary team.

Simultaneous resections should be performed as part of a clinical trial.

DIGITAL FEATURES

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INTRODUCTION

The optimal timing of surgical resection of synchronous liver metastases from colorectal cancer is not well defined. Traditionally, resection of the primary tumour and the liver metastases is done at separate admissions, with

a period of recovery allowed between the two procedures. This could be done either as resection of the liver metastases before the colorectal tumour or in the reversed order. Simultaneous resection of both the colorectal cancer and the liver metastases has gained popularity due to several appealing factors. The tumour burden can be eradicated in one procedure, which intuitively could have a positive impact on quality of life. One versus two procedures is likely to reduce the overall burden on health care institutions and lower hospital costs with a reduced admission rate. However, an increase in overall and procedure-specific post-operative morbidity after simultaneous resection have been reported [1, 2]. Conversely, the traditional approach with staged resections may also be argued. An interval between the resection of the primary tumour and the resection of the liver metastases allows a test of time to evaluate the individual tumour biology of the metastatic disease. The consequence of a staged procedure might be progression of the liver metastases to such an extent that they are no longer considered resectable. While tumour progression in the perioperative “window” between the two procedures may be unfavourable, it may spare the patient of a potentially futile liver resection that would otherwise have had a limited effect on cancer biology and the long-term survival.

There is currently a lack of high-level evidence to accurately determine the role of simultaneous resection of colorectal cancer with liver metastases. Previous reports are generally biased by the fact that patients selected to simultaneous versus non-simultaneous surgery differ in many aspects concerning both the primary tumour and the manifestation of the liver metastases. Furthermore, recent investigations reveal considerable differences in the perioperative management of synchronous colorectal liver metastases, with no clear surgical outcome or survival advantage towards any approach, being liver-first, colorectal-first or simultaneous resection [3, 4]. This invited opinion article aims to address the current level of evidence concerning simultaneous resection of primary colorectal cancer and synchronous liver metastases. We propose selection criteria, based on available data, for whom a

simultaneous procedure is likely to be beneficial. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CURRENT EVIDENCE

Throughout the last two decades, numerous retrospective studies have compared simultaneous versus staged resection for synchronous colorectal liver metastases. The findings have been reported in several reviews and meta-analyses (Table 1) [3, 5–10]. However, the results are somewhat difficult to interpret due to inherent selection bias [11]. Generally, the outcomes from these studies show equal short- and long-term results between simultaneous and staged approaches, besides shorter hospital stay for patients with simultaneous resection. Patients with bilobar liver metastases and in need for major hepatectomy have traditionally been scheduled for staged surgery. Also, most of the register-based studies do not account for patients with an initial intent for a staged strategy, but in whom a proportion of patients never reached hepatectomy due to disease progression. Indeed, some studies report that between 16 and 35% of patients with an either liver-first or primary tumour-first strategy do not reach the second operation, likely due to disease progression or complications from the first procedure [12–14]. Hence, in the above-mentioned systematic reviews and meta-analysis, there is an inherent selection bias in favour of patients completing a staged approach, as they likely harbour a favourable tumour biology in order to reach the second procedure. Also, for patients receiving a simultaneous resection, there is a selection bias in favour of a limited liver tumour burden.

A recent population-based cohort study confirmed an increased tendency towards simultaneous resection and a wide variation in surgical approach according to hospital trust of diagnosis in the UK [4]. Survival analysis on propensity score-matched groups showed no difference in 4-year survival between the primary tumour-first and simultaneous cohort.

Interestingly, the presence of a hepatobiliary surgical team on site appeared to have an impact on decision-making, as patients diagnosed at hospital trusts with such service were more likely to undergo a simultaneous or liver-first approach.

Recently, a randomized controlled trial addressed the question of whether synchronous colorectal liver metastases should be resected simultaneously with the primary cancer or delayed [15]. There are several interesting findings and lessons to be learned from this trial. First, there was no difference in major complications comparing synchronous to delayed resection. Second, although 10 centres were involved in the study, the overall recruitment time was a decade. Even this was not enough to reach the calculated sample size (estimated 222 patients), in spite of rather broad inclusion criteria, accepting major hepatectomy, patients with bilobar liver metastases and patients with rectal cancer. According to the authors, this was mainly explained by the fact that (i) colorectal cancer with initially resectable synchronous liver metastases remains a rare situation, (ii) centres involved in the study often had patients referred with poor overall status and initially non-resectable synchronous liver metastases and (iii) the majority of patients were referred after the primary tumour had been resected. The first point is debatable, as data for colorectal liver metastases reflect a highly divergent attitude among surgeons towards what is considered ‘resectable’ disease [16]. Furthermore, novel techniques have been developed in order to increase resectability [17]. The latter two points reflect challenges in logistical and hospital organizational structure rather than the lack of patients eligible for the procedures. Not all colorectal units have hepatobiliary surgeons available and vice versa, which should be taken into account when planning for simultaneous resection. Hence, this also reflects the third point, that referral between pure colorectal units and hepatobiliary units is required if patients are not discussed at the same multidisciplinary team (MDT) meeting. Even at institutions with both services available, most MDTs are run separately, thus representing a barrier in planning simultaneous resection if

Table 1 Recent reviews and meta-analyses of different treatment strategies for colorectal cancer with liver metastases

Author, year	Number of patients/studies included	Groups compared	Primary outcome	Results	Comments
Hillingsø et al. 2009 [8]	Not available/ 16 studies	Simultaneous vs delayed	Length of stay, morbidity, mortality, OS	Lower morbidity for simultaneous resection, lower mortality for delayed resection, similar OS	Systematic review without meta-analysis. Simultaneous resection performed for patients with fewer, unilobar metastases and right-sided colon cancer. Surgery for left-sided colon cancer and major hepatectomy were mainly staged procedures
Slesser et al. 2013 [9]	3159 patients/ 24 studies	Simultaneous vs delayed	Length of stay, 30-day mortality and morbidity, OS and DFS	No difference in blood loss or duration of surgery. No differences in morbidity, OS or DFS. Reduction of 5.6 days in hospital stay for simultaneous resection	More major hepatectomy and patients with bilobar distribution of metastases for patients undergoing delayed resection
Kelly et al. 2013 [3]	3605 patients/ 18 studies	Liver first, simultaneous and colon first	5-year OS, 30-day mortality, morbidity	No differences in primary outcome among the three groups	No clear statistical surgical outcome or survival advantage towards any approach
Yin et al. 2013 [10]	2880 patients/ 17 studies	Simultaneous vs delayed	Morbidity, mortality, OS and DFS	No difference in primary outcome	
Feng et al., 2014 [6]	22 studies/ 4494 patients	Simultaneous vs delayed	Mortality, morbidity, OS, DFS	Similar morbidity, mortality, OS and DFS	
Baltatzis et al. 2016 [5]	1203 patients/ 3 studies	Liver first, simultaneous and colon first	Morbidity, mortality, 5-year OS	Low treatment mortality, similar survival among the groups compared	

Table 1 continued

Author, year	Number of patients/studies included	Groups compared	Primary outcome	Results	Comments
Gavriilidis et al. 2018 [7]	30 studies/ 5300 patients	Simultaneous vs delayed	OS, safety and efficacy	Similar long-term OS, no difference in parameters relating to safety and efficacy	An average of 6 days shorter length of stay for simultaneous resection. More patients with bilobar disease and major hepatectomy in the delayed surgery group

OS overall survival, DFS disease-free survival

the surgeons are biased towards one strategy over another. Of note, payer systems vary across health care providers, and the financial incentives for any approach (primary first, liver first or simultaneous) have an impact on decisions in some countries where billing for service is implied.

The overall complication rate in this solitary RCT on the subject, mirrors the inclusion criteria, in that almost 1 out of 2 patients in both groups had a complication grade III or IV according to the Clavien-Dindo classification [15]. Again, a reduction of hospital stay was proven for patients with simultaneous surgery. Survival analysis was not conducted according to intention-to-treat principles. As the trial was underpowered to answer the primary outcome measure, the question still stands: for whom is simultaneous resection beneficial?

PRINCIPLES OF PATIENT SELECTION

As there is evidence of a negative impact from post-operative complications on long-term outcomes after liver surgery for colorectal liver metastases, the magnitude of surgical resection should be better stratified to guide patient management decisions [18, 19]. Feasibility

reports on major hepatectomy with concomitant colectomy exist, but this procedure is likely to be reserved for highly selected patients and experienced surgeons [20]. In 2015, a consensus statement was published, recommending that simultaneous resection be discouraged when the hepatectomy would be major (involving three or more adjacent liver segments) or when complex rectal surgery was to be performed, due to significantly higher post-operative mortality and morbidity [21]. Recent evidence supports this recommendation. Schubert and co-authors stratified synchronous hepatic and colorectal resections, finding increased morbidity and mortality for patients undergoing high-risk colorectal resections and major hepatectomy [22]. Driedger and co-authors recently published a 17-year experience and defined major hepatectomy as hemihepatectomy and trisectionectomy, and major colectomy as left colectomy with proximal diversion, total abdominal colectomy, total abdominal proctocolectomy and abdominoperineal resection [19]. Combining a major liver with major colorectal resection was associated with a significant increase in major morbidity and 90-day mortality. Also, more than one-third of these patients were prevented from receiving adjuvant chemotherapy secondary to post-operative morbidity. These findings are in line with a recent

investigation on surgeons' barriers in performing simultaneous resection, with low support for cases involving major hepatectomy [23].

Lastly, numerous prognostic indicators are available for patients with colorectal cancer and liver metastases, such as sidedness of primary tumour, metastatic tumour burden (number and size of largest lesion), and number of involved lymph nodes of resected primary and mutational status [24–28]. However, in the simultaneous setting, a test of time is not possible, and unsurprisingly, a meta-analysis by Slesser and co-authors found no difference in overall or disease-free survival even if the delayed surgery group had a significantly higher proportion of major liver resections, patients with bilobar distribution and an overall larger metastatic tumour size [9]. Hence, until further evidence on potential oncological benefits is available, simultaneous surgery should be offered to appropriate patients at specialized centres regardless of underlying biological features of the metastatic colorectal cancer.

In line with the above-mentioned publications and consensus statements, we believe that simultaneous resection should be considered for patients with localized colorectal cancer and with limited metastatic tumour burden in the liver, both in terms of number of lesions and required resections *and* the location of the liver metastases. We recommend avoiding resection of more than two adjacent segments (i.e. hemihepatectomy) for anatomical liver resections and preferably four or fewer metastases for non-anatomical liver resections (Table 2). The combination of ablation therapy (radiofrequency/microwave ablation) and hepatic resection has been proven a valid and safe modality without increased perioperative morbidity or mortality compared to resection alone [29]. In order to avoid accumulation of complications and thereby hamper the possibility of adjuvant chemotherapy, we believe simultaneous surgery should be restricted to patients with good performance status and not in the setting of acute bowel obstruction. Furthermore, as a higher complication profile might be the case for patients undergoing rectal cancer surgery, simultaneous resection for these patients should be considered only in selected cases. For

patients with non-resectable lung metastases and/or extrahepatic disease, simultaneous resection should be avoided. This is in line with the current National Comprehensive Cancer Network (NCCN) guidelines stating that primary tumour and resectable metastatic disease can be resected in one operation or staged, depending on the complexity of the hepatectomy or colectomy, comorbid diseases, surgical exposure and surgeon expertise [30].

SURGICAL TECHNIQUE IN SIMULTANEOUS RESECTION

A laparoscopic or open approach for either part of the procedures should be at the surgeon's discretion. There is reason to believe that minimally invasive techniques for both the liver and the colorectal part of the procedure are associated with beneficial short-term outcomes [31, 32]. As for laparoscopic liver surgery, there is evidence to support equal oncological outcomes for laparoscopic and open colon surgery [33, 34]. The colorectal surgery should be performed by a trained colorectal surgeon and the liver surgery by a trained hepatobiliary surgeon. There is no evidence that higher volume per surgical unit has a relationship with perioperative outcome regarding the liver resection part of the procedure [35], so specific volume requirements should not be necessary. In colorectal cancer surgery, however, high volume by surgeon and high volume by hospital have been associated with better outcomes, although the optimal threshold for a minimum number of procedures is yet to be identified [36]. Lastly, the optimal surgical treatment sequence in simultaneous resection remains debatable. A liver-first approach is reasonable, given the possible need for a Pringle manoeuvre with a subsequent venous stasis that could potentially harm a bowel anastomosis. Also, a liver-first strategy necessitates a low central venous pressure during the parenchymal transection phase. Finally, any unforeseen event during the liver resection part (major bleed or bile leak) should be considered as a contraindication from continuing with the bowel resection.

Table 2 Proposed selection criteria in favour of simultaneous resection (green box) or staged resection (red box) of primary colorectal cancer with liver metastases

<ul style="list-style-type: none"> • Less than 5 liver metastases for non-anatomical liver resections • Resections of no more than 2 adjacent liver segments for anatomical liver resections • T1-T3 colorectal cancer • Good performance status (ECOG 0-2)
<ul style="list-style-type: none"> • More than 4 liver metastases or resection of more than 2 adjacent liver segments* • T4 colorectal cancer • Pretreatment of colon cancer with stent or acute bowel obstruction • Presence of non-resectable lung metastases or extrahepatic disease • ECOG ≥ 3 • Major liver with Major colorectal**

*In the case of excessive bleeding, preoperatively under-staged tumour burden, prolonged operative time, unstable patient or any other reason to fear increased complication of either the liver-part or colorectal-part of the procedure, we recommend avoiding simultaneous surgery

**Major liver: hemi-hepatectomy or trisectionectomy. Major colorectal: left colectomy with proximal diversion, total abdominal colectomy, total abdominal proctocolectomy and abdominoperineal resection as defined by Driedger and co-authors [19]

LOGISTICAL CONSIDERATIONS IN SIMULTANEOUS RESECTION

Simultaneous resection carries some logistical challenges that have to be solved: (i) both the colorectal and hepatobiliary surgeon need to attend the MDT meeting, (ii) both surgeons have to perform their part of the surgery, (iii) an anaesthesiologist familiar with low central venous pressure during the liver parenchymal transection phase will have to be involved, and (iv) both surgeons will have to do the immediate post-operative follow-up in order to catch any sign of complications. Furthermore, adequate interventional radiology resources and inpatient facilities are mandatory in order to avoid failure to rescue. In case patients require neoadjuvant chemotherapy, treatment sequence and decision on possible simultaneous resection should be based on response

evaluation. Whether or not neoadjuvant chemotherapy is beneficial is beyond the scope of this article. There is evidence that perioperative chemotherapy increases disease-free survival for patients aged < 75 years and with ≤ 4 liver metastases. [37].

KNOWLEDGE GAPS

Based on the literature reviewed above, there are still several unanswered questions concerning simultaneous resection. With respect to simultaneous resection, no randomized trials have investigated (i) the number of liver metastases that is considered safe to resect, (ii) the number of liver resections or liver segments that is considered safe to resect, (iii) the size of the future liver remnant that is considered safe, (iv) the timing of staged resection (liver or primary tumour first), (v) whether chemotherapy

should be administered before or after surgery, (vi) oncological endpoints, (vii) quality of life or (viii) health economics. The lesson learned from current evidence is that these matters have to be addressed in well-planned multicentre randomized trials focusing on some of the above-mentioned questions and thereby filling the knowledge gaps in order to recommend simultaneous surgery to the appropriate patients.

CONCLUSION

The concept of simultaneous resection of colorectal cancer with limited-disease liver metastases is appealing, with several potential benefits for both patients and health care systems. Despite this, high-level evidence is lacking, and an inherent reluctance exists due to the perceived risk of accumulating complications. We propose a pragmatic approach, consisting of the following:

- Stringent selection criteria in order to avoid major morbidity and mortality
- Adherence to surgical experience and preference regarding technique
- Accepting simultaneous resections for patients with good performance status and a limited liver tumour burden
- Avoiding simultaneous resections when requiring major hepatectomy and major colorectal resection
- Discussions and strategies through a multidisciplinary team meeting

A liver-first strategy in the setting of simultaneous resection is reasonable. High-quality trials are much needed to evaluate the role of systemic therapy, oncological outcomes, and both patient and health care system implications for these types of resections.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article, as no data sets were generated or analysed during the current study.

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