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*REVIEW*

# Simultaneous colorectal and parenchymal-sparing liver resection for advanced colorectal carcinoma with synchronous liver metastases: Between conventional and mini-invasive approaches

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## Abstract

The optimal timing of surgery in case of synchronous presentation of colorectal cancer and liver metastases is still under debate. Staged approach, with initial colorectal resection followed by liver resection (LR), or even the reverse, liver-first approach in specific situations, is traditionally preferred. Simultaneous resections, however, represent an appealing strategy, because may have perioperative risks comparable to staged resections in appropriately selected patients, while avoiding a second surgical procedure. In patients with larger or multiple synchronous presentation of colorectal cancer and liver metastases, simultaneous major hepatectomies may determine worse perioperative outcomes, so that parenchymal-sparing LR should represent the most appropriate option whenever feasible. Mini-invasive colorectal surgery has experienced rapid spread in the last decades, while laparoscopic LR has progressed much slower, and is usually reserved for limited tumours in favourable locations. Moreover, mini-invasive parenchymal-sparing LR is more complex, especially for larger or multiple tumours in difficult locations. It remains to be established if simultaneous

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resections are presently feasible with mini-invasive approaches or if we need further technological advances and surgical expertise, at least for more complex procedures. This review aims to critically analyze the current status and future perspectives of simultaneous resections, and the present role of the available mini-invasive techniques.

**Key Words:** Synchronous colorectal liver metastases; Colorectal surgery; Liver surgery; Simultaneous resection; Parenchymal-sparing liver resection; Mini-invasive surgery; Intraoperative ultrasonography



**Core Tip:** The optimal timing of surgery in case of synchronous colorectal cancer and liver metastases is debated. Staged approaches are traditionally preferred, but simultaneous resections are increasingly performed in appropriately selected patients. Since major liver resections (LR) may determine worse perioperative outcomes, parenchymal-sparing LR should be considered whenever feasible. While mini-invasive colorectal surgery is widely diffused, mini-invasive LRs are usually reserved for limited tumours in favourable locations, and parenchymal-sparing LR is more complex. It remains to be established if simultaneous resections are presently feasible with mini-invasive approaches or further technological advances and surgical expertise are needed, at least for more complex procedures.

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## INTRODUCTION

Colorectal cancer (CRC) is a very common cause of cancer-related death in developed countries, with synchronous liver metastases (SCRLM) in about 15 to 25% of patients at the time of diagnosis[1,2]. Radical liver resection (LR) of colorectal liver metastases (CRLM) may achieve 5-year overall survival (OS) rates of 37% to 58%[3-6]. However, the expanding availability of therapeutic tools, that include medical, radiological and surgical treatments, alone or in combination, has made the management of metastatic CRC increasingly complex[7,8]. Patients with CRC and synchronous metastases require specific consideration, because may have less favourable cancer biology and oncological outcomes than those with metachronous CRLM, therefore requiring appropriate multimodal treatments[1,9]. The optimal timing of surgery in these patients is still under debate. Traditionally most surgeons prefer a staged approach with initial colorectal resection (CRR) followed by LR, eventually after interval chemotherapy (CHT)[4]. Traditional staged strategies are believed to avoid increased morbidity and mortality[3,10], and may warrant better selection for LR, excluding patients who experience disease progression while awaiting hepatectomy, especially when occurred during interval CHT[9,10]. However, simultaneous procedures may be safely performed in selected patients, with perioperative results comparable to staged resections. This approach avoids a second surgical procedure and the risk of interval progression of liver disease, and permits an earlier initiation of adjuvant CHT[11-18]. At present most authors consider that simultaneous CRR and minor hepatectomy are usually safe and should be preferred in selected patients with limited liver disease[4,9,11-18], while patients requiring simultaneous colorectal and major liver resection should be accurately evaluated, since increased morbidity and mortality rates have been reported[3]. Some authors, however, suggest that simultaneous colorectal and major liver resection may have similar perioperative risks compared to major LR alone[19,20], so that even simultaneous resection of rectal tumours and major hepatectomies are considered reasonable in appropriate patients[20,21].

Major hepatectomies have been traditionally preferred to achieve curative resection of CRLM, especially in the case of large or multiple lesions; however extensive hepatectomies may determine significant perioperative complications, mostly related to posthepatectomy liver failure (PHLF)[22,23]. Several therapeutic strategies have been undertaken to minimize the risk of PHLF after LR. These include preoperative systemic and/or locoregional CHT, that may significantly reduce the neoplastic burden in the liver, thus limiting the extension of the hepatectomy[24], and specific technical innovations that increase the volume of the future remnant liver (FRL) when major LR are planned, mainly preoperative portal vein embolization (PVE) and two-stage procedures (TSH), comprising the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) strategy[25,26]. An alternative approach, termed "conservative" or "parenchymal-sparing" liver surgery (PSLR), involves the resection of liver neoplasms with the minimum sufficient resection margin (RM), to preserve as much normal liver parenchyma as possible along with the major intrahepatic vessels[27,28]. This approach is based on careful preoperative planning and expert use of intraoperative ultrasonography (IOUS). PSLR has the advantage of limiting the risk of perioperative PHLF even in patients with extensive liver disease[23], and increases the chance of repeat LR in the case of recurrence (salvageability)[27,28]. Repeat LR of CRLM has a well-demonstrated potential for cure in selected patients with recurrent disease[29,30]. In the last decade liver surgery for CRLM has progressively shifted toward more conservative procedures that result in decreased morbidity and mortality rates than major LR, with comparable oncological results[6,31-33].

Mini-invasive surgery, including laparoscopic and robotic procedures, has known a progressive diffusion in oncological colorectal surgery[34-36], even though some controversies still exist for rectal cancer surgery[36-40]. Diffusion of mini-invasive techniques of liver surgery has progressed much slower, since the acquisition of adequate experience in mini-invasive LR is difficult, requires specific complex training with a prolonged learning curve, and may be accompanied by a significant increase of costs per procedure[41-43]. Although the vast majority of laparoscopic liver resections (LLR) are minor resections and mainly involve anterior and inferior liver segments (segments S2, S3, S4b, S5 and S6)[43,44], more complex procedures, including major hepatectomies, are increasingly performed in most experienced centers[41-43,45,46]. In case of difficult procedures, some surgeons adopt hand-assisted or hybrid approaches[42,43]. Mini-invasive procedures have been recently proposed also for TSH, including the ALPPS strategy[47,48]. Mini-invasive LR has usually better perioperative results than conventional open LR, with comparable oncological outcomes[41,49-54], even though patients undergoing mini-invasive LR are in most cases highly selected, with limited liver disease in favourable locations[50,54-57].

Based on the growing consensus toward simultaneous procedures in selected patients bearing resectable CRC with SCRLM, the mini-invasive techniques have been utilized also for simultaneous colorectal and liver resections[58,59], including simultaneous major LR[60,61]. Mini-invasive simultaneous procedures usually determine better perioperative results than conventional open resections, with comparable oncological outcomes[62,63]. However, patients considered for mini-invasive simultaneous procedures are highly selected either for the site or the extension of the primary and metastatic disease, so that the perioperative and oncological outcomes cannot be generalized[64,65]. While PSLR with adequate resection margin should be considered the standard of care, there is concern that LLR may sometimes involve larger procedures resecting more nontumorous liver parenchyma, since smaller parenchymal-sparing procedures for multiple or non-favourably located tumours may be more complex with mini-invasive approaches[42-46,66,67]. Technological advances, as well as the growth of surgical experience and skills, are favouring the development of mini-invasive parenchymal-sparing approaches[45,66,68-72]. Nonetheless, simultaneous colorectal and conservative liver resections may require long operative times in complex resections[21,73,74]. Therefore, it remains to be established if the available surgical strategies for the treatment of advanced CRC with liver metastases are presently feasible with mini-invasive approach during the same procedure or if we need further technological advances and surgical expertise, at least in more complex surgical situations.

This review aims to critically examine the available data to determine whether simultaneous colorectal and conservative liver resections represent a safe and effective surgical strategy for advanced CRC with SCRLM, and which is the present role of the available mini-invasive techniques when more complex colorectal procedures along with conservative liver resections are required.

## SEARCH STRATEGY AND SELECTION CRITERIA

We identified data for this review through a non-systematic literature search conducted using the Medline, Embase, and Web of Science databases, updated to December 2019. Papers in core clinical journals were included, describing studies on surgical strategies for synchronous CRLM, neoadjuvant CHT (NACHT) of resectable CRLM, conservative/parenchymal-sparing LR, anatomic *vs* nonanatomic LR, prognostic role of the resection margin, clinical and prognostic relevance of genetic mutations of CRLM, surgical strategies for multiple bilobar CRLM, mini-invasive colorectal surgery, mini-invasive liver surgery, mini-invasive *vs* open LR, mini-invasive *vs* open simultaneous colorectal and liver resection, mini-invasive *vs* open parenchymal-sparing LR. The reference lists of selected papers and prior reviews were checked manually to identify further significant papers not retrieved by the initial search.

## THERAPEUTIC STRATEGIES FOR SYNCHRONOUS COLORECTAL LIVER METASTASES

Therapeutic strategies in patients with resectable CRC and upfront resectable SCRLM have been widely debated in the last decades and shared solutions are beyond to come (Table 1). The traditional "staged" or "classic" approach with initial resection of the primary CRC followed by LR is probably still preferred by most surgeons, because the risks of the colorectal and the liver procedures are not cumulated[3,10], but also because CHT can be usefully administered before the LR[9,10]. In patients with more advanced liver disease and uncomplicated primary cancer, the therapeutic strategy may be reversed to avoid the risk of liver tumour progression to unresectability. This option is termed "reverse" or "liver-first" approach[10,75,76], and is usually considered in patients with borderline resectable liver disease and uncomplicated primary tumour, or when a locally advanced rectal cancer eligible to neoadjuvant chemoradiotherapy (CHRT) is present[9,10,75,77,78]. A complete response of the rectal tumour to CHRT after initial liver surgery has been occasionally described, thus delaying or even avoiding the planned rectal resection[78]. However, simultaneous colorectal and liver resection represents the most attractive strategy, with growing consensus and a progressive expansion of resectability criteria[6,28]. Simultaneous resections improve the patient experience, by reducing the number of surgical procedures and also the duration of perioperative CHT in selected cases[4,17], and may substantially decrease the cumulative costs of hospitalization[79]. Nonetheless, the real impact on the perioperative results and the overall oncological outcome are still under debate[1,3].

Numerous experimental studies suggest that surgical manipulation of metastatic CRC can activate inflammation, immune depression, release of multiple factors and shedding of tumour cells[80]. These events can exert local tumour-promoting effects that predispose to local recurrences, but also activation of dormant tumour cells in distant organs, thus predisposing to the development of distant metastases[80]. Furthermore, LR soon activates multiple molecular changes to restore the optimal liver volume, with upregulation of multiple growth factors and cytokines, and subsequent activation and proliferation of the intrahepatic cells. These specific pro-regenerative effects result in a complex microenvironment that can promote the proliferation of residual tumour cells in the remnant hepatic parenchyma and even the spread of cancer at distant sites[80-82]. In patients with multiple CRLM, extended LR may achieve potentially curative surgery. PVE with or without TSH has been proposed in selected patients to cause hyperplasia of the FRL and augment resectability. As for liver regeneration, however, also PVE has been demonstrated to promote tumour progression, either by intrahepatic haemodynamic changes or through an upregulation of growth factors and cytokines, that may adversely affect the subsequent management of the neoplastic disease[81-83]. Taken together, this clinical and experimental evidence supports the theoretical advantages of simultaneous resection of the colorectal and the liver tumours, to avoid the disadvantages of multiple surgical procedures, and of conservative liver surgery, to contain the adverse effects of liver regeneration on tumour development and dissemination.

### *Preoperative evaluation*

The accurate preoperative staging is of paramount importance to plan the surgical strategy and can be achieved with cross-sectional imaging by CT, MRI[1,2,8,9,84] and 18FDG-PET-CT in selected patients, mainly to detect extrahepatic disease[1,5,9,84].

**Table 1 Controversial issues involving surgical strategies for colorectal cancer with synchronous resectable liver metastases**

| Controversial issue | Advantages | Disadvantages |
|---|---|---|
| Surgical strategies for synchronous CRLM: | | |
| • Traditional "staged" or "classic" approach | Risks of CRR and LR are not cumulated; CHT can be usefully administered before the LR | May determine progression of CRLM, sometimes up to unresectability; manipulation of metastatic CRC may have adverse effects on distant metastases and oncological outcome |
| • "Reverse" or "liver-first" approach | Avoids progression of borderline resectable CRLM; permits appropriate NACHRT for locally advanced rectal cancer, sometimes up to complete response | Comparative results with the traditional approach are still uncertain |
| • Simultaneous colorectal and liver resection | Reduces the number of surgical procedures; may reduce the duration of perioperative CHT; may decrease the cumulative costs of hospitalization | Requires accurate selection of candidates; may increase perioperative morbidity and mortality; oncological outcomes are still uncertain |
| NACHT of resectable CRLM | May reduce the extent of LR; may increase the R0 resection rates; eradicates micrometastases; may select patients with favourable oncological prognosis after LR | May determine progression of CRLM, sometimes up to unresectability; may determine parenchymal damage and increase perioperative morbidity; its overall beneficial impact on oncological outcomes has not been confirmed |
| Nonanatomic/parenchymal-sparing *vs* anatomic LR | May reduce the extent of LR; may increase resectability; may achieve better perioperative results; may favour reresection in case of hepatic recurrence, with consequent improvement of oncological results | May reduce the extent of the RM; its overall impact on oncological outcomes is still controversial |
| The prognostic role of the RM: | | |
| • ≥ 10 mm | May reduce the overall risk of recurrence; may achieve better oncological outcomes | May reduce resectability |
| • 1 to 10 mm | May reduce the extent of LR; may increase resectability | May favour tumour recurrence; may determine worse oncological outcomes |
| • < 1 mm (R1 resection) | May increase resectability | Determines worse oncological outcomes; perioperative CHT is mandatory |
| • "R1 vascular" RM (detachment of CRLM from vessels) | May reduce the extent of LR; may increase resectability | May favour tumour recurrence; may determine worse oncological outcomes |
| Evaluation of genetic mutations of CRLM | Predict response to CHT; may predict response to perioperative CHT; may predict oncological results of LR; may predict positive RM in candidates for LR; may suggest more extensive/anatomical LR; may predict response to local (RFTA) and loco-regional (chemo and radioembolization) treatments | Its overall role in establishing individualized therapeutic strategies is still uncertain; its overall impact on oncological outcomes is still uncertain |
| Treatment of multiple bilobar CRLM: | | |
| • NACHT of multiple resectable CRLM | May favour curative LR; may reduce the extent of LR; may increase the R0 resection rates; eradicates micrometastases; may select patients with favourable oncological prognosis after LR | May determine progression of CRLM, sometimes up to unresectability; may determine parenchymal damage and increase perioperative morbidity; its overall beneficial impact on oncological outcomes is uncertain |
| • PSLR *vs* major LR, including PVE, TSH and ALPPS | Reduces the extent of LR; may increase resectability; reduces the risk of PHLF; may achieve better perioperative results; may favour reresection in case of hepatic recurrence | May reduce the extent of the RM; its overall impact on oncological outcomes is still controversial |
| • Intraoperative local ablation techniques | May reduce the extent of LR; may increase resectability; may favour curative LR | Higher risk of local recurrence, especially for larger tumours; its overall beneficial impact on oncological outcomes is still uncertain |
| The impact of PSLR on simultaneous resections | May reduce the extent of LR; may increase resectability of CRLM; may improve the propensity for simultaneous resection; may achieve better perioperative results | May reduce the extent of the RM of LR; its overall impact on oncological outcomes is still controversial |

CRLM: Colorectal liver metastases; CRR: Colorectal resection; LR: Liver resection; CHT: Chemotherapy; CRC: Colorectal cancer; NACHRT: Neoadjuvant chemoradiotherapy; RM: Resection margin; RFTA: Radiofrequency thermal ablation; NACHT: Neoadjuvant CHT; PSLR: Parenchymal-sparing liver resection; PVE: Portal vein embolization; TSH: Two-stage hepatectomy; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; PHLF: Posthepatectomy liver failure.

Preoperative liver imaging should define the number and the location of CRLM, the tumour-vessels relationship, the pattern of the hepatic vasculature and the FRL volumes[23,84-86].

Definition of patient performance status, coexisting morbidities and liver steatosis is mandatory to determine suitability for complex procedures, especially if major liver surgery is considered[8]. Although up to 70% of the normal liver parenchyma can be excised, prior CHT may remarkably compromise liver parenchyma. Various degrees of non-alcoholic fatty liver disease, from bland steatosis to steatohepatitis, and of sinusoidal injury, from sinusoidal dilation to hepatic sinusoidal obstruction syndrome and regenerative nodular hyperplasia, have been associated with modern CHT protocols[87]. Parenchymal damage is regimen specific: oxaliplatin-based regimens have been associated with significant sinusoidal injury, and irinotecan-based regimens with various degrees of non-alcoholic fatty liver disease[87,88]; these parenchymal alterations may prejudice the liver function and the consequent ability to tolerate extended resections[89], while the impact of targeted molecular therapies is still controversial[90]. In a meta-analysis based on 28 studies, Robinson *et al*[88] found that NACHT before resection of CRLM determines an increased risk of regimen-specific liver damage, which may impact on the functional hepatic reserve of candidates for major hepatectomy[88]. To prevent or at least limit these adverse outcomes, extended preoperative CHT should be avoided, and an appropriate interval between CHT completion and liver surgery should be planned[1,8,9,87].

### *Neoadjuvant chemotherapy for resectable CRLM*

Evaluation of the available CHT protocols to enhance resectability of initially unresectable SCRLM is out of scope for this review. In patients with resectable CRLM, the role of NACHT is still controversial. After considerable enthusiasm toward systemic NACHT, mainly based on the fact that response to preoperative CHT may select patients with favourable oncological prognosis after LR[10], its overall beneficial role has been substantially questioned by multiple recent studies. The EORTC Intergroup randomized controlled trial (RCT) 4098386 compared perioperative oxaliplatin-based CHT plus LR to LR alone, in patients with limited resectable CRLM (≤ 4) at baseline assessment[91]; the overall results revealed an improved progression-free survival at 3 years after perioperative CHT, but significantly more frequent reversible postoperative complications. Nonetheless, this study received much criticism[16,18], and in the long-term follow-up report of the trial, the OS rates were not different between groups[92]. A systematic review evaluating the impact of systemic NACHT on resectable CRLM indicated that preoperative CHT may determine objective response with improved disease-free survival (DFS)[93], but also this review was deemed to have substantial limitations to influence the conclusions[18]. Another systematic review concluded that combination regimens increased cancer response and resectability rates in case of unresectable CRLM, while studies on NACHT failed to definitely prove a survival benefit for resectable tumours, with enhanced risks of perioperative complications[90]. In the new EPOC RCT[94], the addition of cetuximab to perioperative systemic FOLFOX CHT of *KRAS* exon 2 wild-type resectable or suboptimally resectable CRLMs resulted in unexpected shorter progression-free survival rates than systemic CHT alone; these disappointing results were related to disease progression consistent with failure of systemic micrometastatic disease control[95] and have been confirmed in the updated analysis of this study[96], where patients in the cetuximab group experienced significantly worse OS rates. Recent retrospective series do not support the use of NACHT in upfront resectable CRLM. A study based on the LiverMetSurvey International Registry could not find any survival advantage for NACHT plus LR in resectable CRLM compared to surgery alone[97]. In a multicentre series of 300 patients with upfront resectable CRLM collected between 2008 and 2015 in 2 French institutions, which favoured perioperative FOLFOX CHT, and 2 Japanese institutions, which systematically preferred upfront LR plus adjuvant CHT[98], perioperative FOLFOX CHT did not improve DFS compared to adjuvant CHT alone after LR. The potential adverse effects of NACHT on morbidity, mortality and oncological outcome of candidates for LR[90], and in determining a shift in the growth pattern of CRLM, from a pattern with a good prognosis to another with a worse prognosis[99-101], represent further controversial issues. Nevertheless, preoperative CHT is still the preferred option in case of resectable CRLMs in some Western countries[8]. In patients with CRC and resectable SCRLM, preoperative CHT is usually advocated in Western countries, while upfront simultaneous resections are usually considered, if they can be safely performed, in Asian countries, although there is no significant evidence to support either therapeutic strategy[5,9,98].

### *Simultaneous vs staged colorectal and liver resection*

Perioperative and long-term outcomes of simultaneous *vs* staged procedures for SCRLM have been compared in many recent systematic reviews and meta-analyses[11-13]. Simultaneous procedures were usually compared to staged approaches where the SCRLM were resected at a later stage. Although these series show a somewhat shorter hospital stay and lower morbidity rates for simultaneous resections, postoperative mortality rates seem to be lower with the staged procedures in some series, while long-term survivals are similar between the strategies[11-13]. However, the studies included in these systematic reviews and meta-analyses had a general bias, since staged approaches were usually favoured in patients with left-sided CRC and more advanced liver disease. Yin *et al*[14] performed a systematic review and meta-analysis including 2880 patients and found that patients in the simultaneous group had lower perioperative complications, whereas perioperative mortality within 60 d, OS and recurrence-free survival (RFS) rates were similar. In a wider meta-analysis evaluating 3159 patients[15], the authors suggested that patients undergoing delayed LR may achieve better outcomes, since they had similar intraoperative parameters, perioperative complications and survival rates compared to patients with simultaneous resection, despite having a more extensive liver disease. However, a subsequent meta-analysis including 4494 patient[16] questioned the reliability of some previous meta-analyses as a consequence of important biases, mainly the fact that significantly more patients with mild conditions received simultaneous resections, and found comparable perioperative and long-term oncological results between simultaneous and staged resections after correction of baseline imbalance regarding primary tumour and metastases characteristics. Similar results were found in another recent meta-analysis evaluating 5300 patients[17]. However, the numerous studies comparing simultaneous and classical staged resections with CRR followed by hepatectomy should be interpreted with caution, because simultaneous resections are more likely considered for patients with better clinical conditions, right-sided CRC and more limited liver disease[11,14-18]. On the other hand, the staged groups more frequently include patients who respond to perioperative CHT[15-17], while patients who do not complete the planned LR due to disease progression during the interval CHT are excluded from evaluation: consequently, the oncological results of patients selected for staged procedures may be overestimated comprising only those with more favourable tumour biology or responsive to perioperative (neoadjuvant and/or interval) CHT. Further studies should prevent this selection bias by using "intention-to-treat" analyses, including also patients with progressive metastatic disease after CRR who missed the subsequent LR[16]. A small prospective RCT that involved 10 French tertiary referral centers specialized in colorectal and hepatobiliary surgery, has recently compared simultaneous *vs* delayed colorectal-first resection in patients with CRC and resectable SCRLMs[102]; the study was discontinued because of recruitment problems, so that only 85 patients were finally evaluable, 39 in the simultaneous and 46 in the delayed resection groups, respectively. Major perioperative complication rates were similar between groups; in the delayed resection group, 8 patients did not reach the LR stage, due to disease progression in 6 cases; 2-year OS and DFS rates tended to be improved in simultaneous resection group ($P$ = 0.05), a tendency which persisted for OS at multivariate analysis after a median follow-up of 47 mo ($P$ = 0.07). The authors recognized the numerous limitations of their study and cautiously suggested that simultaneous resection of the primary CRC and of the resectable SCRLMs is an acceptable strategy, even though delayed treatments still has an important role in these complex patients.

Some recent studies have compared all the available surgical strategies, simultaneous *vs* staged primary-first *vs* staged liver-first resections. In a small series of patients with rectal cancer and SCRLM, van der Pool *et al*[103] suggested an individualized approach, where both simultaneous and liver-first approaches were effective alternatives to traditional staged primary-first procedures. In another study evaluating 156 consecutive patients, Brouquet *et al*[75] found comparable 3- and 5-year OS rates for the three different strategies. Likewise, a multi-institutional study[76] with over 1000 patients found similar oncological outcomes for the three groups; male sex, a rectal primary and combined LR plus ablation were independent factors of worse long-term prognosis; thus the authors suggested that tumour biology rather than the surgical procedure is the main determinant of prognosis. More recent robust systematic reviews and meta-analyses confirmed previous results, with comparable perioperative and oncological results for the three surgical strategies[104-106]. In a population-based study referring to 1830 patients with CRC and SCRLM who underwent colorectal and liver resection with bowel-first, simultaneous or liver-first approach, and were included in the English National Bowel Cancer Audit dataset,

Vallance *et al*[107] found a progressive increase in the use of either simultaneous or liver-first approach over the study period, along with wide variations among different hospital trusts. A simultaneous approach was more frequently adopted where a local hepatobiliary unit was present. There was no difference in 4-year survival rates between the propensity score-matched groups according to surgical strategy. A very recent network meta-analysis based on 32 retrospective studies has compared the three surgical strategies and again found no significant differences in major morbidity and 5-year survival rates[108].

## PARENCHYMAL-SPARING LIVER RESECTION

Resectability of liver neoplasms has considerably improved over the last decades. At present CRLMs are mostly considered resectable if complete cancer excision can be achieved with curative intent, *i.e.* when macroscopically free RMs are resulting, without unresectable extrahepatic disease, and the estimated FRL is sufficient to avoid liver failure[109]. Most surgeons still usually consider major LR, including conventional major hepatectomies and two-stage procedures, to achieve curative resection, particularly in case of large and/or multiple tumours. However, extensive LRs have been related to significant perioperative complications, mainly due to various degrees of PHLF[22,23]. The progressive expansion of IOUS as an essential tool in liver surgery has favoured the diffusion of more conservative hepatectomies to reduce the risk of PHLF[23], but also to spare major intrahepatic vessels and increase salvageability in case of recurrence[27,28] (Table 1). Conservative procedures are based on at least three factors: (1) The intrahepatic diffusion patterns of CRLMs are different from that of the hepatocellular carcinoma so that anatomic resections (AR) per se have limited or no effect on the clinical outcome; (2) The concept of "negative resection margin" without considering margin width has progressively replaced the "1-cm rule"[110]; and (3) There is increasing evidence that also multiple and/or bilobar CRLM are eligible to potentially curative hepatic surgery in the context of multimodal treatment strategies.

### *Anatomic vs nonanatomic liver resection*

Liver tumours should be resected with enough margins to achieve potentially curative treatment and to prevent recurrence. The propensity of hepatocellular carcinoma for vascular invasion and metastatic spread through the portal venous system requires AR whenever possible as it eradicates the portal tributaries near the tumour. AR may reduce the risk of local recurrence and achieve better survival rates than nonanatomic resection (NAR)[111,123]. The expert use of IOUS has favoured the development of surgical techniques that limit the extension of hepatectomies while respecting the segmental or subsegmental distribution of intrahepatic vessels, either for primary or metastatic liver tumours[28,112-114]. Metastatic tumours can spread within and outside the liver through lymphatic vessels, portal and hepatic veins, bile ducts and perineural spaces[115,116]. Migration of tumour cells from CRLM through intrahepatic lymphatic vessels adversely affects survival[115,117], while the prognostic role of portal or hepatic vein invasion is still uncertain[115,116]. Accordingly, AR comprising portal vessels close to the cancer and the corresponding hepatic tissue should not be theoretically justified for CRLM, and NAR with adequate RM is actually regarded as a proper surgical option[23,86,118-122]. In a meta-analysis including 1662 patients with CRLM, NAR reduced the blood transfusion requirements and operation times compared to AR, while perioperative morbidity, mortality, surgical margins, OS and DFS rates were similar[118]. Another systematic review including 2505 patients compared PSLR to AR for CRLM[119] and found a similar incidence of R0 resection, postoperative length-of-stay and OS. A more recent meta-analysis based on 18 studies including 7081 CRLM patients compared the clinical outcome of PSLR ($n$ = 3974) and non-PSLR ($n$ = 3107)[123]; the perioperative outcomes were better in PSLR than in non-PSLR group, since non-PSLR was significantly associated with longer operative time, increased estimated blood loss, higher intraoperative transfusion rate, and more postoperative complications; OS and RFS rates were similar between groups. However, since the authors included segmental resections among PSLRs, we consider that the results of their comparison should be referred to limited *vs* major LR. The clear evidence that non-anatomical limited LR for CRLM were equivalent to major anatomic LR in patients with limited hepatic disease came from Japanese series since the early 2000s[23]. Kokudo *et al*[120] compared major AR to limited NAR in patients with unilobar single or double tumours and reported similar survival rates, concluding that major AR was unnecessary in 80.4% of the patients resectable by limited NAR. They thus

suggested to consider limited NAR as the mainstay surgical procedure for CRLM to minimize surgical stress and operative risks. In a series of 300 patients with a solitary CRLM ≤ 30 mm, Mise *et al*[121] compared PSLR to more extended hepatectomies, including right hepatectomy, left hepatectomy, or left lateral sectionectomy and found that OS, RFS, and liver-only RFS were similar between the groups, but PSLR significantly increased the opportunity of salvage repeat LR and 5-year OS in case of relapse. These results have been confirmed in a multicentric cohort of 1720 patients receiving either PSLR or right hepatectomy for a single CRLM ≤ 30 mm located in the right hemi-liver[122], where PSLR had significantly lower rates of major complications and 90-d mortality; although 5-year OS, RFS and liver recurrence rates were similar between groups, in patients with liver-only recurrence, repeat LR was more frequently performed after PSLR, with significantly higher 5-year OS rates. Taken together, these data suggest that a combination of a first parenchymal-sparing NAR followed by repeat hepatectomy in case of recurrence offers superior oncological benefits compared to major LR in most patients with limited liver disease[120-122]. Similar results have been described also in case of two or more CRLM. A recent case-matched study by Lordan *et al*[124] comparing 238 patients with PSLR to 238 patients with major LR, found fewer blood transfusions, lower incidence of severe complications, lower 90-d mortality and shorter hospital stay in PSLR patients, while OS and DFS rates were similar. The authors concluded that conservative LR should be proposed whenever technically feasible because it is safer than major LR, without compromising oncological results. Also in case of deeply placed CRLM, where major LR are traditionally preferred, PSLR resulted in similar perioperative and oncological results compared to major LR, increasing the number of patients eligible for direct LR without the need of PVE[125].

The advantages of PSLR have been confirmed also for mini-invasive LR. In a recent series of 269 patients who underwent LLR with curative intent for CRLMs, after propensity score matching 82 patients undergoing PSLR where compared to 82 who received major LR[126]; PSLR was associated with lower rates of major perioperative complications compared to major hepatectomy; RFS and liver-specific RFS rates were comparable between groups, but salvage repeat LR for hepatic recurrence was more frequently performed in the PSLR group; in case of hepatic recurrence, the OS rate was significantly higher for patients undergoing salvage repeat LR than for those who were unable to receive further curative treatment; the PSLR group also showed a trend toward higher 5-year OS rates. Thus, the authors concluded that PSLR should be the standard approach for CRLMs, even for mini-invasive procedures.

### *The liver resection margin*

The impact of the width of the RM on the oncological outcome after LR for CRLM is controversial (Table 1). The so-called "1-cm rule", which advocates that R0 margins should be 10 mm or greater to prevent local recurrence and optimize OS, has been proposed since the 1980s and is still considered basically valid whenever technically feasible[24,110,127]. The presence of residual microscopic deposits of tumour cells on the resection margin (R1) is regarded as an important source of recurrence and a critical determinant of poor prognosis[116,127]. As for primary liver tumours, intrahepatic micrometastases (IHM) may develop in CRLM, are believed to represent re-metastasis from existing tumours, and are predominant within 4 to 10 mm of the tumour margin[28,128,129]. However, their role as a prognostic factor is controversial. One study reported that IHM is associated with higher incidence of intrahepatic recurrence and poorer survival[130]. In another study, IHM was less frequently found in patients who received NACHT than in those untreated[128]. In a study detecting tumour-specific mutant DNA in hepatic parenchyma surrounding metastases, mutant DNA was found in surrounding liver parenchyma within 4 mm of the tumour border, but not at 8, 12, and 16 mm from the tumour margin, even after tumour shrinkage due to NACHT[129]. The presence of fibrotic tissue between the CRLM and the surrounding parenchyma has also been identified as a beneficial prognostic factor and may be relevant in the assessment of the RM[115]. CRLMs showing an infiltrating growth pattern, where cancer cells spread freely through the surrounding normal liver parenchyma, have been mostly associated with worse overall oncological outcome compared to metastases with an expanding growth pattern, where cancer cells push the adjacent liver tissue, although some controversy still exists[115]. Vermeulen *et al*[131] classified metastatic growth into three different histopathological growth patterns (HGP), based on the interface between metastatic cells and the surrounding normal liver parenchyma, and the related angiogenic patterns[131]: In desmoplastic HGP, the neoplastic cells are separated from the surrounding liver parenchyma by a rim of desmoplastic tissue, there is no direct contact between cancer cells and hepatocytes, and new blood vessels

in the desmoplastic rim are formed by sprouting angiogenesis; in the pushing HGP, there is no desmoplastic rim surrounding the metastatic nodule at the interface with the liver tissue, and the surrounding liver parenchyma is pushed away and compressed, without direct contact between cancer cells and hepatocytes within the liver cell plates; in the replacement HGP, cancer cells replace hepatocytes within the liver cell plates and co-opt the sinusoidal blood vessels at the tumour–liver interface, without inducing sprouting angiogenesis, so that metastatic cells form cell plates that are in continuity with the liver cell plates, and the stromal architecture of the liver is maintained[99,101,131]. Mixed growth patterns are usually found in single patients with multiple liver metastases, but also in a single metastasis[99,101]. Desmoplastic HGP has been associated with better oncological outcomes[99,101,132], even though its prognostic role was not confirmed in patients undergoing NACHT before LR[101]. The unfavourable prognostic impact of any non-desmoplastic HGP on the incidence of R1 margin and the OS rates has been recently confirmed in a bi-institutional series of 1302 patients with surgically resected CRLM[133].

Altogether, these data demonstrate that CRLM may be well-circumscribed, with a very low incidence of satellite nodules or micrometastases, suggesting a limited effect of minimal negative RM on recurrence or survival rates in selected patients[6,24]. Pawlik *et al*[134] have reported that OS and DFS, overall recurrence risk and site of recurrence were similar after resection of CRLM with margins of 1-4 mm, 5-9 mm, and ≥ 10 mm, suggesting that a predicted RM of < 1 cm should not contraindicate liver surgery. Other studies have confirmed that sub-centimetric tumour-free RM may have limited or no negative impact on the oncological outcome after LR for CRLM[135,136]. Recent meta-analyses however still suggest that the "1-cm rule" have an independent positive prognostic effect on OS and DFS and should be pursued whenever possible, even though a predicted sub-centimetric RM should no longer be considered a contraindication to surgical resection[137-139].

Microscopically positive RM (< 1 mm) is currently believed to significantly worsen overall oncological results of LR for CRLM, due to an increased risk of recurrence at the surgical margin[117,134,140] and of intrahepatic recurrence[140,141]. An increasing number of CRLMs has been associated with greater risk of R1 resection[133,135,142]. Tranchart *et al*[143] reported that R1 LR was an independent unfavourable predictor of OS and DFS, and that only administration of postoperative CHT predicted improved DFS after R1 LR. Further studies have confirmed either the adverse effect of R1 LR on survival[133,134,136,142] or the protective effect of postoperative CHT after R1 LR[141,144,145]. A favourable impact of NACHT on the oncological outcome of R1 LR has been also observed[146], especially in tumours responsive to CHT[147,148], but this point is still controversial[133,145]. The cessation of NACHT, however, regardless of previous response, may be followed by tumour regrowth, with clusters of viable tumour cells infiltrating the normal hepatic parenchyma for several millimetres at the periphery of the metastases, a phenomenon called "dangerous halo"[100]. Similarly, NACHT may determine irregular borders of metastatic lesions, especially after significant contraction, and sometimes discrete clusters of viable cancer cells are found outside of the main lesion, but near its peripheral margin[149]. Moreover, NACHT can alter the growth pattern of CRLM favouring the emergence of more aggressive patterns[99,100]. The possible progression of the dangerous halo is particularly worrying, and LR should achieve RM wide enough to reduce the risk of local relapse[100], particularly if CHT has been suspended for a relatively long time.

Recent studies suggest that also a submillimetric clear RM can be considered adequate for CRLM in certain circumstances[142]. The detachment of CRLM from intrahepatic vessels has been proposed as part of IOUS-guided PSLR[114]. Even though this procedure formally implies a R1 RM, the reported oncological results have been similar to those of R0 LRs, suggesting that tumour detachment from intrahepatic vessels can be safely achieved to expand resectability[150]. Other studies have questioned the role of R1 margin status as an independent predictor of survival since it was not related to survival after checking for competing risk factors on multivariate analysis[134,140,141]. Tumour biology has been suggested to play a determinant role on the long-term results, where R1 resections might not have a prognostic value per se, but rather reveal more aggressive disease[24,27,127,134,141,144]. Recent changes in the prognostic value of R1 LR might be partially related to the beneficial effect of perioperative CHT[143-147]. However, a recent multicentric retrospective cohort of 1784 hepatectomies confirmed the independent adverse effect of R1 LR compared to R0 LR, affecting both OS or DFS rates in patients with CRLM[151].

### Clinical and prognostic relevance of genetic mutations of CRLMs

The growing interest in genetic data and mutational status of primary and metastatic CRC is based on the increasing relevance of genetic mutation analysis of CRLM to prognosticate oncological outcomes of candidates for either systemic CHT or liver-directed therapies, including surgery[7-9,152-154]. The *RAS* oncogene (*KRAS*, *NRAS*, and *HRAS*) is involved in complex *RAS* signalling pathways that affect multiple cancer-driving processes. These include neoplastic drift of normal tissues, enhancement of tumour cell growth and suppression of cell death responses, and modulation of the tumour microenvironment by stimulating pro-angiogenic mechanisms and altering host-related immune responses, which finally promote local invasiveness and metastatic progression of tumour cells[152]. From 15% to 50% of patients receiving LR for CRLM have a *RAS* mutation[152], and the *KRAS* mutation accounts for 14% to 52% of the mutations in the *RAS* pathway in resectable CRLM[155]. *RAS* mutations have been associated with a higher prevalence of lung metastases and to specific patterns of recurrence after LR, especially at extrahepatic sites, and usually predict worse OS and DFS rates than wild-type tumours[9,152-156]. *RAS* mutations have been related to a higher incidence of positive margins after LR[157], and also the width of the RM has been suggested to have a different prognostic impact according to *RAS* mutational status[155]. Moreover, ARs determined better DFS and lower intrahepatic recurrence rates in patients with *RAS* mutations, suggesting that more extensive hepatectomies are required for more aggressive mutated CRLM[158]. *RAS* mutations determined worse oncological results also in candidates for repeat LR of recurrent resectable CRLM, in patients who received TSH for bilobar liver metastases, and in patients with synchronous liver and lung metastases undergoing liver surgery[152].

Similar to *RAS*, the *BRAF* oncogene interferes with signalling pathways involved in cell division and differentiation[152]. *BRAF* mutations occur in about 10% of patients with CRC and usually determine poor oncological outcomes[152]. *BRAF* mutations are present in a minority of patients with resectable CRLM, but have been associated with aggressive clinical behaviour and worse oncological outcome among candidates for LR, compared to both wild type *BRAF* and *KRAS* mutated tumours[8,152-156,159]. Other significant gene mutations, including *TP53*, *PIK3CA* and *SMAD4*, have been recently reported, with controversial conclusions about their prognostic impact in candidates for surgery of CRLM[8,152,153,155]. Triple mutation in *TP53*, *RAS* and *SMAD4* has recently been associated with worse OS and RFS rates after resection of CRLMs, compared to double mutations in any two of the three genes[7]. Moreover, in patients harbouring multiple CRLM, mutation heterogeneity for at least one gene across metastatic deposits determined worse prognosis after LR compared to homogeneous mutations, suggesting that worse oncological outcomes are associated with heterogeneous disease[160].

*RAS* mutation status may affect the oncological outcome even in candidates for percutaneous radiofrequency thermal ablation (RFTA)[152], hepatic arterial infusion, transarterial radioembolization and chemoembolization of CRLM[7,153,155]. Taken together, these data suggest that the mutational status of metastatic CRC might contribute in the future to appropriately select patients who can experience a survival benefit from LR, to define the optimal sequence of perioperative CHT, liver surgery and other effective loco-regional treatments, to identify patients at higher risk of recurrence after LR, and possibly to establish individualized therapeutic strategies[152-155].

### Therapeutic strategies for multiple bilobar liver metastases

In a series of 141 patients who received LR for CRLMs published in 1984, Adson *et al*[161] found similar 5-year OS rates between patients with single and those with multiple lesions. Subsequently, Ekberg *et al*[110] suggested that poor prognostic factors contraindicating surgery included > 4 lesions, impossibility to obtain a RM ≥ 1 cm and presence of extrahepatic disease. In the following years however radical LR of multiple (≥ 4) CRLM was confirmed to be compatible with long-term survival[162,163], with a beneficial effect of NACHT in case of multiple bilobar tumours[164] (Table 1). For patients with extensive bilobar disease, surgeons from the Paul Brousse Hospital proposed complex therapeutic strategies combining ablative techniques, PVE, TSH and NACHT[165-167]. In the same period, in a series of 183 Japanese patients who underwent LR for CRLM between 1980 and 2000, Kokudo *et al*[85] reported a 5-year OS of 41.9%, with an overall outcome of 21 patients with ≥ 4 CRLM similar to that of patients with ≤ 3 CRLM. These authors actually defined the following principles of conservative surgical strategies for multiple liver metastases: Careful preoperative assessment of the number of nodules and their contiguity to the major intrahepatic

vessels; meticolous intraoperative inspection, palpation and IOUS of the liver; multiple partial resections whenever possible, rather than extended hepatectomies; resection of large intrahepatic vessels only in case of neoplastic invasion; NAR even with minimal RM; and preoperative PVE whenever the calculated volume of the FRL was less than 40% in case of major hepatectomy. The remnant liver was the most common site of relapse in the overall series, and repeated LR was achieved in about half of these patients, with a 5-year OS rate of 44.7% starting from the first LR[85]. Torzilli *et al*[168] subsequently reported a similar approach to multiple (≥ 4) bilobar CRLMs in a small series of 29 patients where the operative strategy was based on tumour-vessel relationships and findings at colour Doppler IOUS, and concluded that one-stage IOUS-guided LR is safe and effective in selected patients with multiple bilobar CRLMs, decreasing the need for TSH.

In recent years, ablative techniques that achieve local tumour destruction by heating, comprising RFTA and microwave ablation, have become increasingly widespread as an attractive option to treat primary and metastatic liver tumours, alone or in combination with LR[8]. Ablative techniques for CRLM have usually shown significantly lower complications, but also higher recurrence rates and lower OS when compared to LR[169-171]. The efficacy of RFTA is considered equivalent to liver surgery for small (≤ 2 cm) CRLM[170], and an ablation margin > 1 cm has been associated with better oncological results[7]. Therapeutic strategies combining LR with intraoperative ablation techniques proved to be effective in increasing resectability of multiple bilateral CRLM[26], with overall oncological results comparable to those of bilateral LR or TSH. They can therefore represent an effective choice for successfully pursuing parenchymal-sparing treatments for extensive disease in selected patients[7,26,67,172-174], also in case of laparoscopic procedures[126]. The choice between RFTA and microwave ablation should be based on the features of the liver tumours and their anatomical relationship with the main intrahepatic vessels[26].

Actually, a progressive shift toward more conservative procedures for bilobar CRLM, eventually including intraoperative ablations, has been recently reported by surgeons traditionally inclined to more extensive LR[32]. The beneficial results of PSLR were also documented in a retrospective multicentric series of patients with multiple (> 3) bilobar CRLM comparing PSLR to non-PSLR, defined as the resection of ≥ 3 consecutive hepatic segments[33]: PSLR was associated with lower complications and a shorter stay in the intensive care unit, while OS and DFS were similar between groups. The beneficial impact of PSLR for the treatment of multiple bilobar metastases has been confirmed by others, questioning also the consolidated role of TSH[31,67]. Also selected patients with a large number of liver metastases are potential candidates for liver surgery. In a bi-institutional series comparing 736 patients with 1-3, 4-7 and ≥ 8 CRLM, respectively, multivariate analysis revealed that decreased survival was associated with positive lymph node metastasis of the primary cancer, extrahepatic disease, tumour size > 5 cm, and tumour exposure during LR, indicating that the number of CRLM may have less impact on the prognosis than other prognostic factors[175]. In another series of 849 patients receiving LR for CRLM[176], 743 patients with 1-7 metastases were compared to 106 with ≥ 8 metastases: In the latter group, multivariate analysis recognized three preoperative adverse prognostic factors, including primary rectal cancer, no response to preoperative CHT and extrahepatic disease; patients with ≥ 2 risk factors had very poor outcomes, while those without risk factors had survival rates comparable to patients with 1-7 metastases. In a series of 529 patients with ≥ 10 CRLM derived from the LiverMetSurvey registry, a macroscopically complete (R0/R1) LR was obtained in 72.8% of patients and was correlated with a 3- and 5-year OS of 61% and 39%, respectively, being the strongest favourable factor of OS at multivariate analysis[177]; other independent favourable factors were age < 60 years, preoperative MRI, maximal tumour size < 40 mm, and adjuvant CHT. Therefore, the authors concluded that the number of CRLM per se should not contraindicate surgery, which gives the only hope of prolonged survival.

### *The impact of PSLR on simultaneous resection*

The perioperative outcomes of simultaneous colorectal and minor liver resection, including mortality, severe morbidity, hepatic-related morbidity and blood transfusion requirements, are comparable to those observed for minor LR alone[2,4,12]. Results are much more conflicting for patients eligible for simultaneous colorectal and major LR. Some authors reported that combined procedures including major LR adversely impact on perioperative morbidity and mortality rates compared to major LR alone[3,76], while others did not observe added perioperative risks in these cases[19,20]. Currently, most authors suggest simultaneous procedures in case of uncomplicated, easily accessible CRC with liver disease requiring minor LR[13,14,178], while more

extended criteria should be reserved to units specialized in both hepatobiliary and colorectal surgery[11]. Actually, the planned extent of LR seems to represent the most important determinant of whether colorectal and hepatic procedures should be performed simultaneously[4,12,73,179] (Table 1). Since PSLR substantially decreases the need for major LR and the related perioperative risks, it may represent the most appropriate surgical strategy to associate a colorectal procedure with the resection of multiple and/or bilobar SCRLM[180]. In a small series of 39 patients who underwent simultaneous curative colorectal and liver resection for CRLM, Tanaka *et al*[73] reported that only the mean volume of the resected liver was a significant risk factor for perioperative complications (350 *vs* 150 g; $P < 0.05$); simultaneous procedures included 38.5% of low anterior resections and 5 major hepatectomies. The systematic application of PSLR criteria have been associated with higher rates of feasibility of combined resections also in case of multiple CRLM. In a series from the University of Tokyo, Minagawa *et al*[181] found that a simultaneous resection was feasible in 142 out of 148 evaluated patients (96%), regardless of the site of the primary tumour and the extent of CRLM, without perioperative mortality; half of the patients had rectal cancer, while only 11.3% of patients required a hemi-hepatectomy, based on their policy of PSLR[85]. In a more recent series of 150 patients[182] the feasibility of a simultaneous resection was 84.7%, with low postoperative major complications (18.2%), few anastomotic leaks (1.6%), and nil mortality; the 5- and 10-year OS rates were 64% and 52%, respectively. Similarly, in a small series of 45 patients who received elective resection of primary CRC and SCRLM[74], a simultaneous CRR with anastomosis and one-stage PSLR was feasible in 34 (75,6%), none of them requiring a right hepatectomy.

## MINI-INVASIVE COLORECTAL AND LIVER SURGERY

### *Mini-invasive colorectal surgery*

Laparoscopic surgery is presently considered the standard approach for surgical treatment of colon cancer[34,35], while its role for rectal cancer is still somewhat controversial (Table 2). Despite the longer operative time, laparoscopic rectal resection has shown superior short-term outcomes than open surgery, but pathological and oncological outcomes are equivocal. Vennix *et al*[37] reviewed 14 RCTs comparing laparoscopic to open rectal resection, and reported that the number of resected lymph nodes, surgical margins, long-term OS and DFS, and local recurrence rates were similar between groups. Similarly, a recent multicentric Japanese study analyzed 1500 patients operated for low rectal cancer and found significantly better perioperative results after laparoscopic than open surgery, while the 3-year OS and RFS rates were similar between groups[38]. On the contrary, a meta-analysis of 14 RCTs from Martínez-Pérez *et al*[39], comparing 1697 patients with laparoscopic rectal resection to 1292 patients with open rectal resection, found that the circumferential resection margin involvement, distal resection margin involvement, mean number of lymph nodes retrieved, mean distance to the distal and radial margins were similar between groups, but the risk of non-complete (nearly complete or incomplete) mesorectal excision was significantly higher in patients undergoing laparoscopic resection (13.2% *vs* 10.4%, $P = 0.02$). Likewise, in a subsequent meta-analysis of 14 RCTs, Nienhüser *et al*[183] found better oncological outcome for complete resection rate and the number of resected lymph nodes in favour of the open rectal surgery compared to laparoscopic surgery, but the long-term oncological outcome was similar between groups. The real impact of these histopathologic results on OS and DFS, however, is uncertain since long-term results of the ongoing RCTs are still awaited.

The role of robotic surgery in the treatment of rectal cancer is still to be established. A recent meta-analysis referred to 5 RCTs including 334 robotic and 337 laparoscopic surgery cases[36] showed that robotic surgery was associated with significantly lower conversion rate, but significantly longer operating time compared to laparoscopic surgery; perioperative mortality, rate of circumferential margin involvement, incomplete mesorectum, and mean number of harvested lymph nodes were similar between the groups. The authors noted however that, although patients were all operated by skilled surgeons, the rate of incomplete mesorectal excision was 23.5% for the robotic group and 25.6% for the laparoscopic group, comparatively higher than described in the current literature for open and conventional laparoscopic rectal resection[39]. Some recent small series suggest that robotic surgery could improve the quality of total mesorectal excision for rectal cancer compared to laparoscopic procedures[184], but these conclusions have not been confirmed by the available RCTs[36]. For all these reasons robotic surgery for rectal cancer can be selectively used,

**Table 2 Controversial issues involving mini-invasive (laparoscopic and robotic) surgical strategies for colorectal cancer with synchronous resectable liver metastases**

| Controversial issue | Advantages | Disadvantages |
|---|---|---|
| Mini-invasive *vs* open colorectal surgery | Achieves better perioperative results; achieves similar oncological results | In case of rectal resection, may determine a higher risk of suboptimal oncological results at histopathology; in case of rectal resection, its overall impact on oncological outcomes is still uncertain |
| Mini-invasive *vs* open liver surgery | Achieves better perioperative results; achieves at least similar oncological results; rapid technological evolution; rapid growth of surgical experience and skill | Usually preferred for limited disease, in favourable locations and selected patients; may determine more complex and longer procedures; may determine more extended hepatectomies; less frequently used for major LR, including TSH and ALPPS, and for CRLM in postero-superior segments and in the caudate lobe; may determine higher costs |
| Mini-invasive *vs* open simultaneous colorectal and liver resection | Achieves better perioperative results; achieves similar oncological results | Usually preferred for limited liver disease, in favourable locations, and higly selected patients; may determine more complex and longer procedures; may determine higher costs |
| Mini-invasive *vs* open PSLR | Achieves better perioperative results; achieves similar oncological results; rapid technological evolution; rapid growth of surgical experience and skill | The principles of PSLR are time-consuming and rather difficult to apply during mini-invasive procedures; usually preferred for limited disease, in favourable locations and selected patients; may determine more complex and longer procedures; may determine higher costs |
| The impact of PSLR on mini-invasive simultaneous resection | May achieve better perioperative results; may achieve similar oncological results | May determine more complex and longer procedures; may have very limited indications |

LR: Liver resection; TSH: Two-stage hepatectomy; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; CRLM: Colorectal liver metastases; PSLR: Parenchymal-sparing liver resection.

giving appropriate consideration to the extra cost and time requirements[40].

### *Mini-invasive liver surgery*

The use of minimally invasive techniques of LR, including LLR and robotic-assisted LR, has rapidly increased in the last decade[41,43] (Table 2). Nevertheless, the acquisition of adequate experience in mini-invasive LR is difficult, requires specific complex training with a prolonged learning curve, and may be accompanied by a significant increase of costs per procedure[42,43]. As for conventional open liver surgery, also mini-invasive techniques are evolving toward more complex procedures. However, at present, the vast majority of mini-invasive LR are minor and mainly involve anterior and inferior liver segments (segments S2, S3, S4b, S5 and S6)[43,44]. Major LR including 3 or more segments, and resection of the postero-superior segments (S4a, S7 and S8) and caudate lobe are still considered challenging, although increasingly performed in most experienced centers[41-43,45,46]. Mini-invasive procedures have been successfully proposed also for TSHs, including ALPPS[47,48]. Hand-assisted or hybrid approaches are selectively adopted in difficult procedures[42,43]. Multiple recent studies have underlined the advantages of mini-invasive LRs. In an extensive literature review examining the comparative benefits of laparoscopic *vs* open LR in 2473 patients[49], LLR had better perioperative results, without differences in complication rates, survival and total hospital costs. Besides, the long-term oncological results of LLR for primary or metastatic liver malignancy are believed to be similar to those of open procedures[41,50]. Likewise, a random-effects meta-analysis of 8 case-matched series by Schiffman *et al*[51] comparing LLR to open LR for CRLM, found significantly better perioperative results in the LLR group, with comparable operative times, and similar 5-year DFS and OS rates. Although a wider and more recent meta-analysis including 4591 patients confirmed previous results[52], the authors underlined that, given the selection bias in the examined series, their results might only be referred to highly selected patients with few, small, peripherally located, and unilobar CRLM. To limit the confounding effects of selection bias in nonrandomized trials comparing LLR *vs* open LR, Zhang *et al*[53] have recently conducted a meta-analysis of 10 studies with propensity score-based analysis including 2259 patients with CRLM; two studies included patients with simultaneous colorectal and liver resection, and 3 studies included > 40% of major hepatectomies in both laparoscopic and open groups. Perioperative results were better in the laparoscopic group, although with significantly longer operative time; mortality rates, R0 resection, tumour recurrence and 5-year OS were similar between groups. However, a recent meta-analysis of individual patient data from 2 RCT and 13 propensity-score matched studies have raised the question of the oncological outcome of mini-invasive compared to open liver surgery for

CRLM[185]: The authors examined 3148 patients who received LLR ($n$ = 1,275) or open LR ($n$ = 1,873), and found a survival benefit in favour of LLR at 3 ($P$ = 0.0030), 5 ($P$ = 0.0025), 10 ($P$ = 0.0035) and 15 ($P$ = 0.0048) years from surgery, respectively; the survival advantage was not evident for patients undergoing simultaneous colorectal and liver resections; furthermore, no survival advantage was found when the meta-analysis was limited to the 473 patients included in the 2 RCTs. The authors cautiously concluded that the unexpected long-term survival benefit in favour of LLR suggests that laparoscopy is at least not inferior to the standard open LR for CRLM. A survival advantage of LLR for CRLM at 3 years from surgery was also found in the meta-analysis reported by Parks *et al*[186], while LLR was associated with better 3-year OS but similar 5-year OS than open LR in the previously cited meta-analysis by Zhang *et al*[53]. These differences in the OS rates were not confirmed in other studies, including multicentric series[50] and meta-analyses[51,52], so that the question of the overall oncological outcome of mini-invasive techniques compared to open surgery for CRLM remains controversial. Robotic LR is currently considered an effective alternative to LLR[155,188]. Compared to laparoscopic procedures, robotic-assisted LR has been associated with longer operative times, higher rates of Pringle manoeuvre, higher intraoperative blood loss and higher costs, while the other perioperative outcomes are comparable[54,189]. Oncological outcomes, including margin status, DFS and OS rates, were similar in a recent multicentric study comparing the two mini-invasive techniques[54].

It should be underlined however that in these series, patients undergoing mini-invasive LR were in most cases highly selected with regards to tumour size, number of liver lesions and tumour location, so it seems inappropriate to generalize their perioperative and oncological results to the current population of patients with resectable CRLM, who frequently have more severe liver disease. In recent multicentric series where case-matched analyses were adopted to obtain well-balanced cohorts and appropriately compare outcomes, the unmatched initial cohorts of patients with open LR had significantly more advanced metastatic disease than those with LLR[50,55,56], as reflected by more frequent preoperative CHT, higher incidence of concomitant extrahepatic disease, bilobar distribution, and a higher number of tumours and larger tumour size. Besides, the surgical procedures were substantially different, since patients with open LR underwent more limited resections, multiple resections, with more use of preoperative PVE, hepatic pedicle clamping, or combined treatments with RFTA. Also in case of CRLM located in the postero-superior liver segments, still considered challenging locations for mini-invasive procedures, LLR has been selectively adopted for superficial, solitary, and small CRLM (up to 30 mm), not proximal to major vessels[57]. Taken together, these data demonstrate that most surgeons still consider mini-invasive procedures for highly selected patients with limited liver disease in favourable locations, which in fact represent a minority of potential candidates for curative resection of CRLM.

### *Mini-invasive vs open simultaneous colorectal and liver resection*

Based on the growing consensus toward simultaneous resection of CRC and SCRLM, mini-invasive techniques have been applied also for simultaneous procedures (Table 2), even including major LR[58,60,61]. In a recent meta-analysis, the authors compared 164 mini-invasive to 213 open simultaneous resections of CRC and SCRLM[62]: The mini-invasive approach resulted in lesser surgical blood loss and shorter length of postoperative stay, while operating time, operative blood transfusion, intestinal function recovery time, postoperative complications, OS and DFS rates were similar between the groups. In another meta-analysis involving 502 patients with CRC and SCRLM[63], 216 receiving a mini-invasive procedure and 286 an open procedure, mini-invasive surgery was associated with less intraoperative blood loss and blood transfusion, faster recovery of intestinal function and diet, and shorter postoperative hospital stay; operation time and overall postoperative complication rates were similar between groups, as were the OS and DFS rates, respectively. However, also these series mainly included patients with limited liver disease, since mean/median tumour size of CRLM was 19 to 55 mm, and mean/median number of nodules was 1.0 to 2.0. Therefore, as previously discussed for mini-invasive LR, also for simultaneous resections the perioperative and oncological outcomes of mini-invasive procedures cannot be extended to the current population of candidates for simultaneous colorectal and liver resection, which frequently includes patients with more advanced neoplasms or requiring more complex procedures. The attitude to select patient with limited liver disease and favourable location of CRC for mini-invasive simultaneous procedures is confirmed by a recent multicenter study[64] of 142 patients treated by combined laparoscopic resection of CRC and SCRLM: patients with solitary lesions of < 50 mm,

located in segments S2 to S6 were considered as more suitable to LLR; even though 40.8% of patients had rectal cancer, only 3.5% had preoperative CHRT, suggesting that patients with low rectal cancer and SCRLM were not usually considered for simultaneous resection; simultaneous rectal and major liver resection was performed in 4.2% of patients. Moreover, the authors pointed out that the average contribution of each institution to the overall series reached approximately one patient per year and per institution, that is the evident consequence of the strict selection criteria for simultaneous mini-invasive procedures. The same authors subsequently compared this series of 142 patients with laparoscopic simultaneous procedures to 241 patients who received open simultaneous resections in the same period and concluded that appropriate candidates for simultaneous laparoscopic procedures were patients without severe comorbidities, presenting with one, small (up to 30 mm) CRLM resectable by a wedge resection or a left lateral sectionectomy[65]. Mini-invasive simultaneous resections have similar oncological outcomes than open procedures[62,63,65]. In a very recent unicentric series from South Korea, 109 patients out of 126 undergoing simultaneous laparoscopic resection were compared, by propensity score matching, with 109 out of 318 undergoing an open approach between 2008 and 2016[61]: The 3-year OS and DFS rates were similar between groups, despite some perioperative advantages for the laparoscopic group. The authors however suggested among the limitations of their retrospective study, a natural selection bias for more simple cases to undergo LLR.

### *Mini-invasive vs open PSLR*

Although PSLR with negative resection margins is now accepted as the standard of care for CRLM[126], there is some concern that mini-invasive LR may sometimes involve larger procedures resecting more liver parenchyma, since smaller PSLR may be more complex with laparoscopic approaches[42,43,66,67,126]. This might be the case especially for multiple and/or bilobar tumours and for tumours located in the postero-superior liver segments. In a small series of 35 patients undergoing LLR for CRLM, 54% of patients underwent major LR, even though the median number of nodules was one, with mean tumour size of 40 mm[190]. Likewise, in a multicentric series of 176 patients with LLR[55], 45.5% of patients underwent a major LR even though patients had a mean tumour number of 2.2 nodules, with bilobar distribution in 18.2% and maximum tumour size > 50 mm in 6.8% of the cases. In another series of 133 patients undergoing LLR for CRLM[191], the authors reported 65 (48.9%) major hepatectomies in a patient population where the size of the biggest lesion was > 5 cm in 15.8% of the cases, and the tumours were solitary in 40.6%, bilobar in 26.3% and with a postero-superior location in 37.6% of the cases, respectively. Altogether, these data suggest that candidates for mini-invasive LR of CRLM frequently receive major hepatectomies despite limited liver disease. This situation is not really surprising when we consider that all the principles of parenchymal-sparing LR[85] are time-consuming and rather difficult to apply during mini-invasive procedures: The careful intraoperative inspection and palpation of the liver is possible only for hand-assisted or for hybrid laparoscopic procedures[192]; the assiduous use of IOUS is more time-consuming during laparoscopy[192,193]; multiple partial resections instead of extended hepatectomies, and NAR even with a minimum surgical margin, are complex procedures also for expert laparoscopic surgeons, especially when tumours are located centrally or in postero-superior segments[126]; and detachment of tumours in contact with large intrahepatic vessels is hazardous because of the problematic control of major intraoperative bleeding during mini-invasive procedures[126]. Actually, patients with relatively limited liver disease are being more frequently addressed with mini-invasive major LR or staged hepatectomies[43,66], while in recent years open procedures are evolving toward more complex parenchymal-sparing resections[31,114,120-122].

However, even though the preservation of functional hepatic volume may be more difficult during LLR, and mini-invasive LR is less frequently performed for tumours in difficult locations[44,45], an increasing number of reports demonstrate that technological advances and growth of surgical experience and skill are favouring the development of mini-invasive parenchymal-sparing approaches[126,193], although the transection planes require expert use of IOUS to delimit segments, define the anatomy of intrahepatic vessels, and prevent bleeding[126], and the transection areas are larger and more difficult to manipulate than those of hemi-hepatectomies[43]. In a series of 62 IOUS-guided laparoscopic segmentectomies reported by Ishizawa *et al*[68], laparoscopic resection of the postero-superior segments (S1, S4a, S7 and S8) was performed in 26 patients with satisfactory results, but determined longer operation time and increased blood loss than the other laparoscopic segmentectomies. Other series have reported limited anatomic LLR in case of liver tumours deeply located in the postero-superior

segments[45,66,68,193], in the central segments[69], in the caudate lobe[45,70,71], and for centrally located tumours proximal to major intrahepatic vessels[72]. These reports, however, mainly come from skilled laparoscopic surgeons and usually refer to patients with single lesions, smaller than 30 to 40 mm[45], so that the reported perioperative and oncological results cannot be generalized to patients with more severe liver disease. Two RCT have recently compared the outcome of patients undergoing mini-invasive and open PSLR, respectively. In the OSLO-COMET RCT[193], 280 patients with resectable CRLM were recruited between 2012 and 2016, to compare mini-invasive ($n$ = 133) and open ($n$ = 147) LR; patients were included if the CRLMs could be radically resected by a PSLR, including repeat LR; exclusion criteria included, among others, the need of concomitant RFTA, vascular or biliary reconstruction, simultaneous colorectal and liver resection; patients selection resulted in a mean (SD) number of CRLMs of 1.5 (1.1) and 1.6 (1.1) in the laparoscopic and open group, respectively, while the median (interquartile range) pathology weight of resected specimen was 83 g (38-185) and 64 g (31-204) in the laparoscopic and open group, respectively. There were no differences in blood loss, operation time, and RMs; postoperative complications were lower and the postoperative hospital stay was shorter for LLR, respectively; mortality was similar between groups; although the cost of the procedure was significantly higher for LLR, in a 4-mo perspective the costs were equal. In the LapOpHuva RCT[192], 193 patients with resectable CRLMs were enrolled between 2005 and 2016, to compare mini-invasive (96 patients) and open (97 patients) PSLR, among 540 patients operated for CRLMs in the same period; exclusion criteria included, among others, high tumour load with multiple and bilobar metastases, huge liver metastases > 10 cm, metastases close to major vessels, metastases requiring non-standardized surgical techniques, including repeated LR, simultaneous colorectal and liver resection, right/extended right/extended left hepatectomy, TSH. There were no differences regarding surgical time, blood loss and transfusion requirement between groups; LLR group required more frequently a Pringle manoeuvre; LLR group showed lower global morbidity, but similar severe complications and mortality; OS and DFS rates were similar between groups. In both studies however the patient selection was quite stringent, and the laparoscopic procedures were performed by very experienced laparoscopic surgeons. In the LapOpHuva trial, 195 patients among 540 (36.1%) were finally considered resectable by laparoscopy, while 179 (33.1%) were excluded because required complex resection of single or multiple metastases, including repeat LR and simultaneous colorectal and liver resection, and the others because of more complex LR. These figures represent the real-life experience of a reference Liver Unit, and probably depict the actual limits of mini-invasive liver surgery.

### *The impact of PSLR on mini-invasive simultaneous resection*

PSLR may have a positive impact also in simultaneous laparoscopic procedures (Table 2), since major hepatectomies have been associated with worse perioperative results. However, simultaneous colorectal and conservative liver resection may require very long operative times with sometimes complex liver procedures already with conventional open surgery. Tanaka *et al*[73] reported a series of 39 simultaneous procedures including 38.5% of patients with rectal cancer requiring low anterior resection; the CRLM were bilobar in 35.9% of patients; LR included 23 partial resections, 3 segmentectomies, 8 sectionectomies, 4 left hepatectomies and 1 right hepatectomy; the median (SD) duration of operation was 510 (154) min. In another recent series of 38 patients who received simultaneous PSLR and restorative CRR[74], low anterior resection was performed in 44.7% of patients, after preoperative neoadjuvant CHRT in 21.1%; 47.7% of patients had bilobar CRLM and 28.9% had multiple (≥ 4) bilobar CRLM; a simultaneous major LR (≥ 3 segments) was performed in 13.2% of patients; the mean (SD) duration of the surgical procedure was 382 (139) min in patients without hepatic pedicle clamping and 564 (122) min in patients requiring intermittent hepatic pedicle clamping because of more extended liver disease and more complex LR. In a recent series of 145 patients with rectal cancer and SCRLM, who received a simultaneous resection[21], LR included 41% wedge resections, 39% segmentectomies and 21% major resections (≥ 3 segments), while a pump for adjuvant chemotherapy was placed in 20% of patients; the mean (SD) duration of operation was 354 (96) min. We should consider if these complex procedures, eventually including low or ultra-low rectal resection, major hepatic resections, atypical or anatomic segmental LRs, intraoperative ablations during the same procedure, are presently feasible with mini-invasive approaches, or if we need further technological advances and surgical expertise to pursue PSLR for complex surgical situations.

## CONCLUSION

In conclusion, simultaneous resections in selected patients with resectable CRC and SCRLM have postoperative risks comparable to staged resections, may reduce the length of perioperative CHT and usually decrease the overall costs of cure. A staged approach is still advisable in patients requiring urgent CRR because of complicated CRC. All the other patients can be theoretically considered for simultaneous resection. In the case of rectal cancer, preoperative CHRT should be considered according to the tumour stage and its potential benefits. However, simultaneous resections should be reserved for surgical teams experienced in both fields. Concerning the LR, a systematic approach using IOUS to pursue oncological radicality while reducing the extent of hepatectomy may represent the best choice to reduce the perioperative risks of simultaneous procedures. Mini-invasive approaches have a standardized role in oncological colorectal surgery, while LLR is still usually reserved for limited tumours in favourable locations. Conservative LRs, that may be considered standard of care for CRLM, especially in case of simultaneous procedures, are more complex with mini-invasive approaches, notably for larger or multiple tumours in difficult locations. It remains to be established if the available surgical strategies of simultaneous colorectal and liver resection are presently feasible with mini-invasive procedures, or if conventional open procedures are still safer and more effective, at least for more complex tumours, while awaiting for further technological advances and surgical expertise in mini-invasive surgery.

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