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REVIEW

Simultaneous curative resection of double colorectal carcinoma with synchronous bilobar liver metastases

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Abstract

Synchronous colorectal carcinoma (SCRC) indicates more than one primary colorectal carcinoma (CRC) discovered at the time of initial presentation, accounts for 3.1%-3.9% of CRC, and may occur either in the same or in different colorectal segments. The accurate preoperative diagnosis of SCRC is difficult and diagnostic failures may lead to inappropriate treatment and poorer prognosis. SCRC requires colorectal resections tailored to individual patients, based on the number, location, and stage of the tumours, from conventional or extended hemicolectomies to total colectomy or proctocolectomy, when established predisposing conditions exist. The overall perioperative risks of surgery for SCRC seem to be higher than for solitary CRC. Simultaneous colorectal and liver resection represents an appealing surgical strategy in selected patients with CRC and synchronous liver metastases (CRLM), even though the cumulative risks of the two procedures need to be adequately evaluated. Simultaneous resections have the noticeable advantage of avoiding a second laparotomy, give the opportunity of an earlier initiation of adjuvant therapy, and may significantly reduce the hospital costs. Because an increasing number of recent studies have shown good results, with morbidity, perioperative hospitalization, and mortality rates comparable to staged resections, simultaneous procedures can be selectively proposed even in case of complex colorectal resections, including those for SCRC and rectal cancer. However, in patients with multiple bilobar CRLM, major hepatectomies performed simultaneously with colorectal resection have been associated with significant perioperative risks. Conservative or parenchymal-sparing hepatectomies reduce the extent of hepatectomy while preserving oncological radicality, and may represent the best option for selected patients with multiple CRLM involving both liver lobes. Parenchymal-sparing liver resection, instead of major or two-stage hepatectomy for bilobar disease, seemingly reduces the overall operative risk of candidates to simultaneous colorectal and liver resection, and may represent the most appropriate surgical strategy whenever possible, also for patients with advanced SCRC and multiple bilobar liver metastases.

Key words: Colorectal surgery; Synchronous colorectal liver metastases; Major hepatectomy; Parenchymal-sparing hepatectomy; Intraoperative ultrasonography; Simultaneous colorectal and liver surgery; Synchronous colorectal carcinoma; Ablative therapies

Core tip: Simultaneous colorectal and liver resection represents an appealing surgical strategy in selected patients with colorectal cancer and resectable synchronous liver metastases (CRLM). Synchronous colorectal carcinoma may represent an adequate indication to simultaneous resections, even though it may require more complex colorectal resections. In patients with multiple bilobar synchronous CRLM, major hepatectomies performed simultaneously with colorectal surgery have been associated with increased perioperative risks compared to major hepatectomies alone. Conservative or parenchymal-sparing hepatectomies reduce the extent of hepatectomy while preserving oncological radicality, and may represent the best option to reduce the perioperative risks of simultaneous colorectal and liver resection.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most frequent causes of cancer-related death in Western countries[1,2]. The development of at least two different neoplasms is defined as multiple primary CRC (MPCRC), which represents 5% to 10% of all CRCs[3,4]. Synchronous colorectal carcinoma (SCRC) indicates more than one primary CRC discovered in a single patient at the time of initial presentation, while neoplasms diagnosed some time after the resection and/or diagnosis of the first lesion are called metachronous CRC[3,4]. Compared with solitary CRC, SCRC possess distinctive features that need to be extensively investigated in preoperative evaluation to ensure adequate diagnosis and treatment[5]. SCRC account for 3.1% to 3.9% of CRCs[3,6], and may occur either in the same segment of the large intestine or separately in different colon segments[3,5]. Multiple factors, including inflammatory bowel diseases, hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome, and familial adenomatous polyposis (FAP)[3,7], predispose to CRC and have also been associated with a higher risk of SCRC, though predisposing factors only account for a minority of cases[8]. Patients with SCRC have in most cases an overall oncological prognosis similar to those with solitary CRC, at least when the pathological stages of tumours are comparable and the resections are curative[4-6,8-13]. Nonetheless, the accurate preoperative diagnosis of SCRC remains difficult and diagnostic failures may lead to inappropriate treatment and poorer prognosis[5]. The presence of SCRC or multiple neoplasms requires operative techniques tailored to individual patients, based on the number, location, and stage of the tumours. Patients with SCRC and established predisposing conditions such as HNPCC, FAP, and ulcerative colitis require extensive surgery, usually total colectomy or proctocolectomy. In the other cases the optimal surgical strategy is still debated. Conventional hemicolectomies or extended hemicolectomies can be indicated if multiple tumours are located in adjacent segments[12]. When SCRC are located in distant colonic segments, some authors suggest total or subtotal colectomy[14,15], while others suggest more conservative surgical strategies with resection of two intestinal segments, either open or laparoscopic-assisted[13,16-18], seemingly resulting in a higher risk of anastomotic dehiscence[6]. However, overall perioperative results of colorectal resections for SCRC seem to be worse than those of solitary CRC with more postoperative complications and reinterventions and longer hospital stays[6]. As a consequence, an accurate preoperative workup and adequate surgical strategies are required for SCRC especially when adjunctive simultaneous surgical procedures are needed to obtain potential cure.

Synchronous liver metastases (CRLM) are evident in nearly 15% to 25% of patients with CRC at the time of diagnosis[1]. Radical liver resection (LR) is presently considered the only curative therapy capable of achieving long-term survival with more recent series describing 5-year overall survival (OS) rates of 37% to 58% after hepatectomy[19,20]. Nonetheless, the management of patients who present with CRC and synchronous metastases is more complex because they are considered to have less favourable cancer biology and expected long-term results than those with metachronous liver disease[2,21]. The optimal timing for surgical resection in case of synchronous presentation of CRC and liver metastases is still controversial. Most surgeons usually prefer a staged approach with initial resection of the colorectal primary followed by hepatectomy[19], presuming that this strategy avoids increased perioperative complications associated with simultaneous procedures[20,22], and avoids also inappropriate hepatic surgery in patients with progression of the liver disease after colectomy especially if occurred during interval chemotherapy (CHT)[22]. More recently an increasing number of studies have shown satisfactory perioperative outcomes for simultaneous procedures comparable to those of staged strategies[19,23-30]. Simultaneous colorectal and liver procedures have the obvious advantage of avoiding a second surgical procedure, along with the chance of an earlier initiation of adjuvant CHT. However, an adequate evaluation of the cumulative risks of the two procedures is mandatory. In the last decade, the paradigm of surgical strategies for synchronous presentation of primary CRC and liver metastases is progressively changing, even though a consensus is far from being reached. Simultaneous colorectal resection and minor hepatectomy have perioperative results similar to minor hepatectomy alone, and are at present considered the treatment of choice in most patients with limited liver disease[19,23-30]. In patients requiring simultaneous colorectal and major LR the perioperative results are much more conflicting. Most investigators have reported worse perioperative outcomes than for major LR alone[20], while others remark that simultaneous colorectal and major hepatic resection can be performed safely in selected cases, with perioperative risks comparable to major LR alone[31-33]. Also simultaneous resection of rectal primaries and major hepatic resections have been considered reasonable in carefully selected patients[33,34].

Major hepatectomies have been traditionally preferred in the past to obtain radical resection of CRLM, especially in the case of large and/or multiple nodules. However, extensive hepatectomies have been associated with significant morbidity and mortality rates, usually related to posthepatectomy liver failure[35,36]. Several strategies have been developed to improve the feasibility of LR without increasing the risk of postoperative liver failure. Different systemic and locoregional chemotherapy protocols may significantly reduce the neoplastic burden in the liver with the aim of converting initially unresectable to resectable CRLM[37], but also of limiting the extension of LR[38]. Some technical innovations have permitted an increase in the amount of the future remnant liver (FRL) in candidates for major hepatectomy at increased risk of posthepatectomy liver failure based on the preoperative hyperplasia of the estimated remnant liver parenchyma, including preoperative portal vein embolization (PVE) and two-stage hepatectomy (TSH)[39]. An alternative strategy is to remove liver tumours with the minimum sufficient oncological margin to preserve as much non-tumourous liver parenchyma as possible, to limit the risk of liver failure in the perioperative period even for patients with advanced neoplastic liver disease[35], but also to preserve the major intrahepatic vessels whenever possible in order to increase the chance of reresection in case of hepatic recurrence (salvageability)[40,41]. In fact, reresection of relapsed CRLM has been widely demonstrated to have the potential for cure in selected patients with recurrent disease[20,42], with comparable morbidity and mortality rates than those of initial resection[43,44]. An accurate preoperative planning and an expert use of intraoperative ultrasonography (IOUS) are of paramount importance to achieve adequate oncological and surgical results. This strategy has been termed "conservative" or "parenchymal-sparing" liver resection (PSLR)[40,41]. A progressive shift toward more conservative hepatectomies has been observed in the last decade also for multiple and/or bilobar CRLM, and has been correlated with decreased morbidity and mortality rates and similar oncological results compared to major hepatectomies[45-47].

There is growing evidence, at least in numerous experimental studies, that surgical procedures for primary and metastatic CRC can activate multiple local and systemic events, such as hypoxia, inflammation, immune depression, release of multiple factors after the resection of the primary tumour and/or the CRLM, and release of tumour cells during surgical manipulation[48]. These events can exert local tumour-promoting effects, such as favouring the implantation and the proliferation of the residual neoplastic cells (predisposing the patient to local recurrences), activating dormant tumour cells in distant organs, and/or establishing a pre-metastatic niche (predisposing the patient to the occurrence of distant metastases)[48]. The real impact of these events in the clinical setting is still uncertain. On the other hand, LR activates within few hours multiple molecular changes (upregulation of several cytokines and growth factors) with subsequent activation and proliferation of mature hepatocytes, hepatic progenitor cells, and non-parenchymal liver cells to restore the optimal liver volume. These specific regenerative factors determine a complex microenvironment, which has been demonstrated to promote either the proliferation of residual cancer cells or tumour propagation in the remnant liver and also at distant sites, at least in various experimental models[48-52]. In patients with multiple bilobar CRLM, extended hepatectomies are traditionally considered to achieve potentially curative LR. In selected patients, PVE with or without TSH is proposed to induce preoperative hyperplasia of the FRL and increase the resectability rate. As for liver regeneration, several experimental and clinical studies have demonstrated that also PVE promotes tumour progression, either through an upregulation of cytokines and growth factors or by haemodynamic changes in the blood supply to the liver, which may adversely influence the subsequent management of the neoplastic disease[49,53-55]. Taken together, these experimental and clinical observations support the theoretical advantages of simultaneous colorectal and liver resection, to prevent the drawbacks of multiple surgical procedures, and of conservative hepatectomies, to limit the impact of liver regeneration on tumour growth and metastatization.

The aim of the present review is to critically analyse the available data to determine whether complex colorectal resections for synchronous CRC are compatible with the simultaneous resection of CRLM, even in the case of multiple and/or bilobar CRLM.

SYNCHRONOUS COLORECTAL CARCINOMA

Epidemiology and predisposing conditions

The overall prevalence of SCRC ranges from 1% to 8% in different studies[3,6]. In four large multicentric studies including a study population between 13000 and 25000 patients with CRC, the prevalence ranged from 3.1% to 3.9%[6,10,11,56], while a recent systematic review pooling data from 39 series reported an overall prevalence of 3.5%[3]. In these series, SCRC had a higher male to female ratio when compared to solitary carcinoma, ranging between 1.5 and 2.2[3,6,10,11,56]. The mean age at presentation was 63 years in a systematic review pooling data from 32 series[3], usually higher than in patients with solitary CRC[3,6], even though this point is somewhat controversial[5,11]. Preferred locations of SCRC are still debated. Some authors have reported that many SCRC occur in the same segment of the large intestine, while others believe that most SCRC occur separately in different colon segments[3,5]. Moreover, SCRC are located in the ascending colon probably more often than described for solitary CRC[3,5,6], but also this point is controversial[5]. A minority of patients develop more than two SCRC[7,16], with a maximum of seven simultaneous colorectal lesions described in a single patient[56].

Possible predisposing factors, including inflammatory bowel diseases, HNPCC or Lynch syndrome, and FAP, to CRC have also been associated with a higher risk of SCRC[3,7]. SCRC has been diagnosed in up to 20% of patients with CRC associated with inflammatory bowel disease[57,58] (more frequently ulcerative colitis than Crohn's disease[59]), and in 21% of patients with CRC associated with FAP[57]. Patients with known predisposing factors might account for about 12% of SCRC[8]. Dysplasia induced by chronic inflammation and adenomas are involved in the development of SCRC in these patients[8,60]. Colorectal serrated polyps have more than a two-fold increase risk of detection of advanced CRC, with proximal and large serrated polyps having the highest risk[61]. Also the serrated neoplastic pathway may predispose to MPCRC[62]. Higher incidence rates of associated benign neoplasms have been described for SCRC than for single cancers[5,11,13]. The higher incidence of mucinous carcinoma in SCRC is still controversial[3,7]. Metachronous CRC can also occur after resection of SCRC, especially in patients with inflammatory bowel disease[59].

Mechanisms of carcinogenesis and molecular biology

MPCRC usually develop on a common etiologic substrate, either hereditary or environmental. Multiple recent studies on molecular carcinogenesis have demonstrated that chromosomal instability, microsatellite instability, and gene methylation are all mechanisms implicated in multiple lesions or events predisposing to SCRC. This may be due either to familial predisposition or more frequently to individual factors (mainly environmental exposure). Factors involved in the development of MPCRC have been recently reviewed[3-5,62]. CRC has a substantial heritable component[63]. Based on multicentric data derived from almost 45000 pairs of twins, the estimated effect of heritability on CRC is up to 35%[64], even though involved genetic factors are still incompletely understood. Well-known hereditary CRC syndromes, including HNPCC and FAP (which account for 3% to 5% of all CRC[65]), present germline mutations and promote the development of several neoplasms over time[8]. Other diseases and conditions, such as inflammatory bowel diseases, may extensively involve colorectal mucosa, thus promoting the formation of multiple foci of dysplasia and cancer[57]. In most cases however, the origin of SCRC is unknown, likely due to the coexistence of genetic predisposition and environmental factors[4]. As for other neoplasms, also for SCRC the concept of a field defect has been proposed to explain tumour multiplicity through a generalized cellular or molecular disorder in the entire colorectal mucosa[66]. Because only a minority of all SCRC are related to hereditary diseases, an important proportion of SCRC lack a clear basis of inheritance[4,9], being possibly related to individual predisposition to MPCRC. As for sporadic CRC, the prevalence of SCRC increases with age[9,10], indicating the possible role of cumulative environmental damage, even though this point has not been confirmed in other studies[8,11]. Alcohol intake and tobacco smoke, which consists of different genotoxic substances, have been related to an augmented risk of MPCRC[4,5].

Molecular biology and mechanisms of development of SCRC are heterogeneous. The majority of CRC follows the classical adenoma-carcinoma sequence of tumour progression, and dysplastic adenomas are the most common form of premalignant precursor lesions[63,67]. However, more than 15% of sporadic CRC develop through alternative pathways of molecular events, including cancers originating from serrated precursor lesions[63,68]. Molecular pathways of development of SCRC have been recently reviewed[3,5,9,66,68-70] and are out of scope for this review. Nonetheless, the complex mechanism of carcinogenesis involved in the development of SCRC is still largely unknown and only partially related to known genetic mutations commonly found in CRC.

Prognosis

The prognosis of patients with SCRC compared to solitary CRC is still debated. Even though the first prospective study on the outcome of SCRC reported worse long-term results than solitary CRC[15,69], most recent studies could not demonstrate different survival rates between SCRCs and CRCs when the pathological stages of tumours were matched and the resections were curative. However, some authors have reported marginal survival benefits of patients with SCRC[3,5,6,8-13].

Diagnosis

The preoperative diagnosis of multiple SCRC remains difficult (Table 1). Additional tumours may be ignored or missed at the time of diagnosis of the first cancer, with diagnostic failure leading to inappropriate treatment and poorer prognosis[5]. Routine preoperative colonoscopy is mandatory to identify synchronous neoplasms[71]. Because preoperative evaluation of the colon during colonoscopy is often incomplete due to bowel obstruction, poor bowel preparation, or technical reasons, double-contrast barium enema and computed tomographic (CT) colonography, magnetic resonance (MR) colonography, and/or positron emission tomography/computer tomography (PET/CT) colonography are advisable[5,63,72-74]. Also the use of intraoperative colonoscopy has been recommended in selected cases[5,16,75]. At the time of operation, it is also important to palpate the entire colon and check pathological specimens thoroughly[5,16]. An adequate combination of these imaging techniques with the traditional colonoscopy usually permits an accurate definition of number and location of synchronous colorectal neoplasms and an appropriate plan of the optimal surgical procedures[6]. Patients with mid and low rectal adenocarcinoma should routinely receive endorectal ultrasound and pelvic magnetic resonance imaging because the quality of preoperative imaging for local staging is essential to pursue an appropriate therapeutic strategy[76-78], which includes perioperative chemoradiotherapy and surgical resection for locally advanced extraperitoneal tumours[77,78].

Surgical treatment strategies

The standard surgical procedure for the treatment of rectal cancer is total mesorectal excision consisting of the removal of the rectum together with the mesorectum, which contains most of the involved lymph nodes and tumour deposits, and the mesorectal fascia[76] along with clear circumferential margins[77]. The appropriate removal of the rectal cancer reduces the risk of local recurrence and the development of distant metastases[77,78]. Surgical procedures for colon cancer entail resection of the tumour with the corresponding lymph nodes. The extent of colonic resection is determined by the tumour location and the supplying blood vessels. The presence of SCRC or multiple neoplasms requires operative techniques tailored to individual patients based on the number, location, and stage of the tumours. Patients with SCRC and established predisposing conditions such as HNPCC, FAP, and ulcerative colitis require extensive surgery, usually total colectomy or proctocolectomy. In the other cases, the optimal surgical strategy is still debated. Early-stage lesions can be removed during colonoscopy with endoscopic mucosal or submucosal resection. Hemicolectomy or extended hemicolectomy can be indicated if multiple tumours are located in adjacent segments[12]. When SCRC are located in distant colonic segments, some authors suggest total or subtotal colectomy to remove synchronous tumours or polyps eventually undetected at preoperative imaging and to prevent the development of metachronous neoplasms[14,15]. In the same circumstances, other authors suggest more conservative surgical strategies, with resection of two intestinal segments (either open or laparoscopic-assisted)[13,16-18] and two anastomoses, seemingly resulting in a higher risk of anastomotic dehiscence[6].

Perioperative results of colorectal resections for SCRC are also debated. In a multicentric study of 884 patients who were operated for SCRC between January 2009 and December 2011 and were registered in the Dutch Surgical Colorectal Audit[6], extended surgery (*e.g.*, subtotal colectomy, proctocolectomy, or combined resection) was performed in more than 35% of cases. The application of neoadjuvant chemoradiation for rectal tumours was lower for synchronous than for solitary CRC (20% *vs* 38%), laparoscopic resections were less frequent, and more (permanent and deviating) stomas were constructed during surgery than for solitary tumours. Overall, the perioperative outcomes of SCRC were worse than for solitary CRC: postoperative complications, reinterventions, 30-day mortality, and time of hospital stay were significantly increased in patients with SCRC. After adjustment for patient- and tumour-related factors, having SCRC was still associated with a higher risk of severe postoperative complications and reinterventions, but not with higher 30-d mortality. The authors concluded that the higher risk of unfavourable perioperative outcomes could be explained by the more extended surgical resection often required for SCRC. Holubar *et al*[17] reported 69 patients who underwent multiple colonic anastomoses, laparoscopic-assisted in ten (17%) cases, with a 44% conversion rate. Length of stay was seven (5-10) days, overall 30-day morbidity was 36% without anastomotic leaks or fistulas, and 30-day mortality was 3%. Li *et al*[18] examined a personal series of 11 patients and 52 adjunctive patients collected from six previous reports of the literature who underwent laparoscopic-assisted combined bowel anastomoses for SCRC, and concluded that combined bowel anastomoses are potentially feasible and safe procedures for SCRC when performed by experienced surgeons.

Table 1 Diagnostic evaluation of synchronous colorectal cancer

Local tumour staging
Preoperative colonoscopy with histological assessment of all colorectal lesions
CT of the abdomen and pelvis
In case of rectal cancer include
Endorectal ultrasound
Pelvic magnetic resonance imaging
If preoperative evaluation during colonoscopy is incomplete (bowel obstruction, poor bowel preparation, technical reasons, *etc.*)
Double-contrast barium enema
CT colonography, if available
MRI colonography, if available
PET–CT colonography, if available
Intraoperative assessment
Intraoperative colonoscopy
Palpation of the entire colon
Thorough examination of pathological specimens
Evaluation of metastatic disease
CT of the chest, abdomen, and pelvis
MRI of the chest, abdomen, and pelvis, in selected cases
18FDG-PET–CT, in selected cases
Patient performance status
Thorough evaluation of coexisting morbidities
Pulmonary function tests, in selected cases
Echocardiography, in selected cases

CT: Computer tomography; MRI: Magnetic resonance imaging; PET-CT: Positron emission tomography/computer tomography.

SURGICAL STRATEGIES FOR SYNCHRONOUS CRLM

Surgical strategies in patients with resectable CRC and upfront resectable synchronous metastases limited to the liver have been widely debated in the last decades. The traditional "staged" or "classic" approach with resection of the colorectal tumour followed by hepatectomy is probably still favoured in most cases because the risks of the colorectal and the liver surgery are not cumulated[20,22,79,80], and CHT can be selectively administered between the two procedures[22]. In the case of large synchronous CRLM and uncomplicated primary tumour, a reversed therapeutic strategy with LR followed by colorectal resection has been proposed, to minimize the risk of progression of the metastatic liver disease to unresectability. This strategy is termed "reverse" or "liver-first" approach[22,81,82] and has become more widely used, either in patients with borderline resectable liver involvment and uncomplicated primary tumour or in patients with resectable CRLM and locally advanced rectal cancer that can be treated with neoadjuvant chemoradiotherapy and subsequent rectal surgery[22,81,83-85]. Moreover, in a small proportion of patients, a complete clinical, endoscopic, and radiological response of the primary tumour to chemoradiotherapy subsequent to initial radical LR has been reported, thus delaying or even avoiding bowel surgery[85]. However, simultaneous colorectal and liver resection remains the most appealing approach and is obtaining a growing consensus due to the advances in oncological concepts and continued development of anaesthesia, critical care, radiological imaging, and techniques of hepatobiliary surgery favouring the expansion of resectability criteria[40]. Simultaneous resections have clear advantages because the patient experience is improved and psychological stress is limited by decreasing the time to removal of the disease, the total number of surgical procedures, the duration of perioperative CHT[19,29]. Also the cumulative costs of hospitalization are substantially decreased in selected cases[86]. Nonetheless, the real impact on the oncological outcome and on the perioperative results are still debated[2,20].

Preoperative assessment

The accurate preoperative staging of advanced CRC is of paramount importance (Table 2) and can be obtained with cross-sectional imaging by CT or MRI[1,2,87,88]. The current guidelines of the North American National Comprehensive Cancer Network (NCCN) suggest the use of CT or MRI of the chest, abdomen, and pelvis. 18FDG-PET–CT imaging is reserved for patients who may undergo potentially curative surgical resection[2]. Preoperative liver imaging should be accurately evaluated to define the number and the site of CRLM, the tumour-vessels relationship, the pattern of intrahepatic vasculature, the presence of anatomical variations, and the FRL volumes[35,89-91]. Recent studies underline the favourable impact of preoperative MRI on the overall oncological outcome of patients with multiple CRLM[92]. The accurate assessment of patient performance status is mandatory to determine suitability for more complex therapies, especially those including liver surgery. Coexisting morbidities and liver steatosis should be

Table 2 Diagnostic evaluation of synchronous colorectal liver metastases

Local tumour staging
CT and/or MRI of the liver, to evaluate
Number and location of CRLM
Tumour-vessels relationship
Pattern of the hepatic vasculature
Presence of anatomical variations
Future remnant liver volumes
Intraoperative assessment
Intraoperative ultrasonography
Evaluation of metastatic disease
CT of the chest, abdomen, and pelvis
MRI of the chest, abdomen, and pelvis, in selected cases
18FDG-PET–CT
Patient performance status
Thorough evaluation of coexisting morbidities
Pulmonary function tests
Echocardiography
In the case of suspected liver disease/steatosis include (elderly patients, metabolic syndrome, previous systemic CHT, *etc.*)
Liver function tests
Evaluation of the grade of steatosis, in selected cases

CT: Computer tomography; CRLM: Colorectal cancer and synchronous liver metastases; CHT: Chemotherapy; MRI: Magnetic resonance imaging; PET-CT: Positron emission tomography/computer tomography.

adequately assessed. Accurate stratification of the perioperative risks should include liver function tests with evaluation of the grade of steatosis in selected cases, and pneumological and cardiological evaluation with pulmonary function tests and echocardiography[88]. Even though up to 70% of the normal adult human liver can be removed, previous systemic CHT may seriously alter liver function and the consequent ability to tolerate extended resections[93-96]. Oxaliplatin-based regimens are associated with augmented risks of vascular lesions, including the sinusoidal obstruction syndrome (SOS), which has been reported to increase morbidity after major LR, especially after administration of more than six cycles[97]. Irinotecan-based regimens are associated with the occurrence of various degrees of steatosis up to the chemotherapy-associated steatohepatitis (CASH), which may worsen perioperative morbidity and mortality rates after LR[97]. The impact of adding targeted molecular therapies, including cetuximab or bevacizumab, to conventional systemic chemotherapy on perioperative morbidity or mortality rates after hepatectomy is still controversial[97].

Simultaneous vs staged colorectal and liver resection

Many recent systematic reviews and meta-analyses have compared the perioperative and long-term outcomes of simultaneous versus delayed hepatectomy for synchronous CRLM. In a systematic review of the literature including 16 controlled trials comparing simultaneous resection of synchronous CRLM and of the primary cancer with a staged approach, where the metastases were resected at a later stage, there was a tendency towards shorter hospital stays and lower perioperative morbidity after simultaneous resection[23]. Perioperative mortality seemed to be lower with the staged approach, and five-year survival rates seemed to be similar in the two groups. The authors underlined that all studies were retrospective and had a general bias because staged procedures were significantly preferred in patients with left-sided primary CRC and larger, more numerous and bilobar metastases. They concluded that simultaneous resections might be selectively undertaken. In a meta-analysis evaluating 14 comparative studies comprising 2204 patients[24], those undergoing simultaneous resection had similar operative time and intraoperative blood loss, shorter hospital stay, and lower morbidity rate. One-, three- and five-year survival rates were similar between groups. The authors concluded that simultaneous resection is a safe and effective treatment for patients with synchronous CRLM and might be considered as the preferred treatment in appropriately selected patients. Another systematic review and meta-analysis of 19 non-randomized controlled trials including 2724 patients came to similar conclusions[25]. Yin *et al*[26] conducted a systematic review and meta-analysis of 17 retrospective studies including 2880 patients, of whom 1015 with simultaneous resection and 1865 with delayed resection. The simultaneous group had lower postoperative complications, whereas postoperative mortality within 60 d and overall and recurrence-free survival (RFS) were similar between groups. Moreover, the authors proposed precise selection criteria for patients suitable for a simultaneous resection, including LR of no more than three segments, colon resection (especially the right-sided colectomy), age < 70 years, and exclusion of severe comorbidities.

Somewhat different conclusions were drawn in a wider meta-analysis including 24 studies published between 1991 and 2010, which comprised 3159 patients, of whom 1381 had simultaneous resections and 1778 had delayed resections[27]. Significantly fewer patients received neoadjuvant CHT in the simultaneous resection group. The bilobar distribution (P = 0.01), the size of CRLM (P < 0.001), and the proportion of major LR (P < 0.001) were found to be higher in the delayed resection group. Operative blood loss and length of surgery were similar between groups, and length of hospital stay was significantly reduced in simultaneous resections (P = 0.007). Post-operative complications, OS, and disease-free survival (DFS) were similar between groups. The authors concluded that delayed resections may result in better outcomes because patients undergoing delayed resection had intraoperative parameters, postoperative complications, and survival rates comparable to those of patients undergoing simultaneous resection, despite more extensive metastatic liver disease. A subsequent meta-analysis evaluating 4494 patients from 22 studies published between January 2000 and April 2013[28] questioned the reliability of some previously published meta-analyses because important biases of the examined retrospective studies, mainly the fact that significantly more patients with mild conditions underwent simultaneous procedures, were not corrected. Summarized baseline analyses to find imbalanced factors between simultaneous and staged groups showed that patients were more likely to undergo simultaneous resection when they had less CRLM (single nodule, P = 0.002; ⩽ 3 nodules, P < 0.0001), of smaller size (diameter ⩽ 5 cm, P = 0.04; smaller mean diameter, P < 0.00001), with unilobar distribution (P = 0.0002), requiring minor LR rather than major LR for curative resection (P < 0.00001), and a right-sided CRC rather than left-sided (P = 0.0006). After correction of baseline imbalance, simultaneous and staged resections had comparable safety and efficacy, with similar postoperative morbidity and mortality, and overall and disease-free survivals. Similar results were found in another recent systematic review and meta-analysis of 30 studies including 5300 patients, of whom 2235 patients received simultaneous resections and 3065 patients received staged resections[26]. Patients undergoing delayed surgery were more likely to have received neoadjuvant treatment, have bilobar disease, or undergo major LR. Parameters relating to safety and efficacy were similar between the two groups. The average length of hospital stay was six days shorter with the simultaneous approach (P < 0.001). Long-term survival was similar for the two approaches.

The discordant results of the numerous meta-analyses published in recent years is due to the limitations intrinsic to meta-analysis of retrospective studies, mainly due to the fact that compared to RCTs retrospective studies are not randomized. As a consequence, experimental and control groups are often poorly comparable, and the baseline imbalances may significantly compromise the accuracy of the results. Without adequate correction of baseline imbalances before pooled analyses, ideally using methods based on the individual patient data analysis (which however is not always available), meta-analyses can only improve the precision, not the accuracy, of the pooled results, which should be interpreted and applied with great prudence[28]. The copious studies comparing simultaneous and classical staged resections, where the colorectal resection is followed by hepatectomy usually with interval CHT, must be interpreted cautiously because at least two major confounding factors are usually present. Candidates to simultaneous resection were usually younger, in better clinical conditions, with right-sided primary cancer, and more limited liver involvement usually necessitating minor hepatectomies[23,26-30]. On the other hand, patients enrolled in the staged groups included significantly more patients who received preoperative CHT[27-29], and only those who had received successful staged resections, while patients who developed progressive liver disease during the interval were excluded. For these reasons, the overall survival of patients selected for staged approaches could be overestimated by including only patients with more favourable cancer biology or responsive to perioperative (neoadjuvant and/or interval) CHT. Future studies should avoid this selection bias by including patients with progressive metastatic disease after colorectal resection that missed the subsequent hepatectomy[28].

More recent studies have compared all the available surgical strategies, the staged primary-first *vs* the staged liver-first *vs* the simultaneous resection. In a small series of 57 patients with rectal cancer and synchronous CRLM, the authors compared the traditional staged resections with the simultaneous resections and the liver-first approach[98]. The overall morbidity rate was 24.6%, without in-hospital mortality. The median in-hospital stay was significantly shorter for the simultaneous approach. The five-year OS rate was 38%, with an estimated median survival of 47 mo. The authors concluded that long-term survival can be achieved using an individualized approach in patients with rectal cancer and synchronous CRLM and that simultaneous procedures as well as the liver-first approach are attractive alternatives to traditional staged procedures. In another series of 156 consecutive patients with synchronous CRLM, Brouquet *et al*[81] compared the results of the three different surgical strategies, and found comparable three- and five-year OS rates. The only factors independently associated with the OS were a liver tumour size > 3 cm and the cumulative perioperative morbidity. Similar conclusions have been drawn in a multi-institutional study including over 1000 patients from four major hepatobiliary centres[82]. The median OS was 50.9 mo and the cumulative one-, three- and five-year survivals were 89%, 60%, and 44%, respectively, without significant differences between simultaneous and staged surgical procedures. The cumulative recurrence rate was 57%, and was similar between patients undergoing simultaneous and staged procedures. Independent factors of worse long-term prognosis were being male, a rectal primary, and combined LR plus ablation. The authors concluded that tumour biology rather than surgical strategy was the main effector of the oncological outcome. A systematic literature review of 18 studies comparing the different surgical approaches in patients with synchronous CRLM concluded that none of the three surgical strategies appeared inferior to the others[99]. Similarly, a network meta-analysis review of 3605 patients comparing classic staged, simultaneous, and liver-first surgical strategies could not demonstrate significant differences of 30-day mortality, postoperative complications, and five-year OS rates[100]. In a systematic review of three cohort studies comprising a pooled population of 1203 patients who underwent surgical treatment of CRC with synchronous CRLM between 1982 and 2011 and where the different treatment modalities were reported separately[101], 62.2% of patients received bowel-first surgery, 6.2% of patients received liver-first surgery, and 31.6% of patients received simultaneous surgery. Perioperative outcomes were similar between the three methods with low overall treatment-related mortality and similar survival rates.

Neoadjuvant CHT in resectable liver disease

Strategies including different CHT protocols to augment resectability in the case of initially unresectable synchronous CRLM are out of scope for this review. The role of neoadjuvant CHT in patients with resectable CRLM is still controversial. The EORTC Intergroup trial 4098386 was a randomized comparison of perioperative oxaliplatin-based CHT administered either before or after LR *vs* LR alone in patients with limited CRLM ($\leqslant$ 4) classified as resectable at baseline assessment[102]. Thirty-five percent of patients had synchronous disease. The overall results revealed an absolute increase in the rate of progression-free survival at three years in the patients randomized to receive perioperative CHT, but significantly more frequent reversible postoperative complications in the same group. However, the absolute differences in outcomes observed between groups were small and the study received much criticism[28,30]. Moreover, a long-term follow-up report of this trial could not find any difference in survival between the groups[103]. A systematic review of 23 trials evaluating the clinical response and outcomes of neoadjuvant systemic CHT for resectable CRLM suggested that preoperative CHT may achieve objective response with improvement in DFS[104]. However, also this study was considered to have enough limitations to affect the final conclusions[30]. Another systematic literature review concluded that, while combination regimens resulted in enhanced tumour response and resectability rates in up to 30% for unresectable CRLM, studies on neoadjuvant CHT failed to convincingly demonstrate a survival benefit for resectable lesions, with most reports describing increased postoperative complications in a subset of patients due to parenchymal alterations associated with CHT[97]. A recent analysis of a multi-centric cohort from the LiverMetSurvey International Registry, which included patients who had received curative LR for synchronous CRLM, compared 693 patients who received neoadjuvant CHT prior to liver surgery with 608 patients treated by surgery alone, and could not find any survival advantage between the groups[105]. Discouraging results were also obtained associating the targeted molecular agent cetuximab with conventional neoadjuvant CHT protocols[106].

CONSERVATIVE OR PARENCHYMAL-SPARING LIVER SURGERY

Resectability of CRLM has significantly improved over the last decades. The traditional criteria related to the features of liver tumours to evaluate resectability have been replaced by an accurate preoperative estimation of what remains after LR. Tumours should be considered resectable if complete liver tumour excision can be obtained with curative intent (macroscopically uninvolved surgical margins), in the absence of unresectable extrahepatic disease, and the estimated FRL parenchyma is sufficient to prevent liver failure[107]. Major liver resections, including conventional major hepatectomies and more recently described two-stage procedures, with or without PVE, are traditionally preferred by most surgeons to obtain radical resection of CRLM, especially in the case of large and/or multiple nodules. However, extensive hepatectomies have been associated with significant morbidity and mortality rates, usually related to posthepatectomy liver failure[35,36]. "Conservative" or "parenchymal-sparing" hepatectomies are based on the expert use of IOUS, which permits removal of liver tumours with the minimum sufficient oncological margin to preserve as much non-tumourous liver parenchyma as possible, to limit the risk of perioperative liver failure[35], but also to preserve the major intrahepatic vessels whenever possible with the aim of increasing salvageability in case of hepatic recurrence[40,41]. The progressive diffusion of conservative strategies of LR is related to at least three factors: The increasing evidence that CRLM have different intrahepatic diffusion patterns than hepatocellular carcinoma, so that anatomical resections per se have no impact on the oncological outcome; the evolution of the concept of adequate surgical resection margin (RM), where the "1-cm rule" proposed by Ekberg *et al*[108] has been progressively abandoned in favour of the concept of "negative margin" without considering margin width; and the increasing evidence that also patients with large numbers of CRLM are potential candidates for curative liver surgery in the context of multimodal treatment strategies of advanced CRC.

Anatomic vs non-anatomic resection

Adequate resection of liver tumours should involve resection of the tumour with enough margin to prevent recurrence and to achieve potentially curative treatment. Hepatocellular carcinoma has a high propensity for vascular invasion and metastatic spread through the portal venous system. As a consequence, anatomic resection (AR) is considered the optimal surgical strategy because it eradicates portal tributaries close to the tumour, possibly reduces the risk of local tumour spread, and may ultimately determine a survival benefit compared to non-anatomic resection (NAR)[35,109]. Multiple surgical strategies which limit the extension of LR while respecting the segmental or subsegmental distribution of intrahepatic vessels have been described over the last 30 years and successfully performed due to the expert use of IOUS, either for primary or for metastatic liver tumours[40,110-114]. Metastatic tumours can spread within the liver by different pathways. Neoplastic cells might disseminate within and outside the liver through portal and hepatic veins, lymphatic vessels, bile ducts, and perineural spaces[115]. Sasaki *et al*[116] defined portal vein, hepatic vein, and bile duct invasion as the growth of cancer cells into blood vessels or bile duct branches in the liver parenchyma, and defined intrahepatic lymphatic invasion as the growth of cancer cells in luminal structures located in the portal spaces and lined by endothelial cells. Korita *et al*[117] described intrahepatic lymphatic invasion as the presence of isolated cancer cells or cell clusters within vessels with immunoreactivity for D2-40 antibody[117,118]. Other studies about the prognostic role of different patterns of intrahepatic diffusion of CRLM did not describe the method used to define vascular invasion, so that differentiation between invasion of blood vessels and of lymphatic vessels was uncertain[115]. With these limitations, the prognostic role of the portal vein and the hepatic vein invasion is still uncertain[115,118], while migration of tumour cells from CRLM through intrahepatic lymphatic vessels has a documented adverse impact on survival[116-119]. For these reasons, AR including portal tributaries close to the tumour and the corresponding liver parenchyma should not be theoretically justified for CRLM, and NAR with adequate surgical margin is presently considered an appropriate surgical strategy[35,90,120-125]. A recent meta-analysis of seven non-randomized controlled studies including 1662 patients with CRLM, compared 989 patients who underwent AR and 673 who underwent NAR[121]. NAR reduced the operation time and blood transfusion requirements whereas postoperative morbidity and mortality were similar between groups. Also oncological outcomes, including surgical margins, OS, and DFS survival were similar between the groups. Another systematic review of 12 studies included 2005 patients, who underwent either PSLR (1087 patients) or AR (1418 patients) for CRLM[122]. Most studies included a large subset of patients with solitary tumours and a reported median tumour number of one to two regardless of surgical strategy. While there was considerable inter-study variability regarding RM status, there was no difference in the incidence of R0 resection between groups. Median postoperative length-of-stay was similar; also OS was similar after PSLR (five-year OS: mean 44.7%, range 29%-62%) and AR (five-year OS: mean 44.6%, range 27%-64%). The authors concluded that PSLR had comparable safety and efficacy profiles compared with AR without compromising oncological outcomes.

Since the early 2000s, the systematic use of conservative procedures of LR, either for primary or for metastatic liver tumours, has been considered of paramount importance in some Japanese studies to achieve zero mortality and low morbidity rates. Meticulous attention to the balance between the hepatic functional reserve and the hepatic volume to be removed, the routine use of NAR with adequate surgical margin for resection of liver metastases whenever possible, and the attitude to perform simultaneous colorectal and liver resections for synchronous CRLM were among the most important criteria to perform safe hepatectomies without perioperative mortality[35]. Kokudo *et al*[123] retrospectively evaluated 115 patients with unilobar single or double tumours undergoing major AR (64 patients) or limited NAR (51 patients) and found that survival rates were similar between the groups. Anatomical major hepatectomy was unnecessary in 80.4% of the cases if the tumours were resectable by limited NAR, and 90% of the ipsilateral recurrence, which could have been avoided if the first operation was anatomical hemihepatectomy, could undergo a second hepatectomy with a five-year survival rate of 58.3%. The authors concluded that limited NAR should be a basic surgical procedure for CRLM to minimize surgical stress and operative risks. Mise *et al*[124] have recently evaluated a series of 300 patients with a solitary CRLM ⩽ 30 mm undergoing PSLR (156 patients) or more extended hepatectomy (144 patient), including right hepatectomy, left hepatectomy, or left lateral sectionectomy. The rate of PSLR increased during the 20-year study period. PSLR did not negatively impact OS, RFS, and liver-only recurrence-free survival compared to non-PSLR. Repeat LR was more frequently performed in the PSLR group (68% *vs* 24%, $P < 0.01$). Subanalysis of patients with recurrence limited to the liver revealed better five-year OS from initial LR (72.4% *vs* 47.2%; $P = 0.047$) and from hepatic recurrence (73.6% *vs* 30.1%; $P = 0.018$) in the PSLR group. Upon multivariate analysis, non-PSLR was an independent significant risk of non-candidacy for repeat hepatectomy. The authors concluded that conservative resections did not increase recurrence in the liver remnant while increasing the opportunity of salvage reresection and the five-year survival rate in case of recurrence. These results have been subsequently confirmed in a multicentric cohort of 1720 patients from the LiverMetSurvey registry, with a single CRLM ⩽ 30 mm located in the right hemiliver[125]. Eight-six percent of patients underwent PSLR and fourteen percent underwent right hepatectomy. PSLR was associated with lower major complication rates (3% *vs* 10%; $P < 0.001$) and 90-day mortality rates (1% *vs* 3%; $P = 0.008$). Hepatic recurrence was similar between groups (20% *vs* 22%; $P = 0.39$), as well as the five-year OS and RFS rates. However, in patients with liver-only recurrence, repeat LR was more frequently performed after PSLR than after right hepatectomy (67% *vs* 31%;

P < 0.001), and the five-year OS rate was significantly higher after PSLR than after right hepatectomy (55% *vs* 23%; *P* < 0.001). Taken together, these results indicate that a combination of conservative NAR followed by liver reresection in the case of recurrence limited to the liver offers superior oncological benefits than major LR in most patients with limited hepatic disease, and should be considered at present the most appropriate surgical strategy[123-125].

Similar results have been recently reported in patients with two or more CRLM. Karanjia *et al*[126] evaluated 283 consecutive patients who underwent successful LR for CRLM over ten years and compared 128 patients who had right and extended right hepatectomy with 155 patients who had other types of LR. Operative mortality was 3.9% and 0.7% after right hepatectomy and after other types of LR, respectively (*P* = 0.04). Morbidity was 31.3% and 18% after right hepatectomy and after other types of LR, respectively. The one-, three- and five-year OS rates were 84.1%, 54.3%, and 38.9% after right hepatectomy and 95.4%, 65.9%, and 53.3% after other types of LR, respectively (*P* = 0.03). The one-, three- and five-year DFS rates were 69.5%, 34.4%, and 25.5% after right hepatectomy and 68.4%, 34.91%, and 34.91% after other types of LR, respectively (*P* = 0.46). The authors concluded that in patients with CRLM, right and extended right hepatectomy have greater operative morbidity and mortality and significantly worse OS compared to all other types of LR. In a more recent series of 917 consecutive patients who received LR for CRLM from 2000 to 2010, Lordan *et al*[127] compared 238 patients who underwent PSLR case-matched with 238 patients who had major hepatectomy using a propensity scoring system. Fewer PSLR patients received perioperative blood transfusions (*P* < 0.0001). PSLR patients had a lower incidence of complications (*P* = 0.04), grade Ⅲ/Ⅳ complications (*P* = 0.01), 90-day mortality (*P* = 0.03), and a shorter hospital stay (*P* = 0.04). OS and DFS rates were similar. The authors concluded that patients with resectable CRLM should be offered PSLR if technically feasible because PSLR is safer than major hepatectomy without compromising long-term survival. Parenchymal-sparing hepatectomies are effective also for CRLM deeply placed where major hepatectomies have been traditionally preferred. Matsuki *et al*[128] evaluated 63 patients who received first curative LR for deeply placed CRLM whose centre was located > 30 mm from the liver surface. PSLR and major hepatectomy were performed in 63% and 37% of patients, respectively. Resected volume was smaller after PSLR than after major hepatectomy (251 g *vs* 560 g) (*P* < 0.01). Total operation time, amount of blood loss, rate of major complications, and positive operative margins were similar. OS, RFS, and liver recurrence-free survivals did not differ between the two groups. The authors underlined that direct major hepatectomy without PVE was unfeasible in 40% of the PSLR group because of the small FLR and concluded that PSLR for deeply placed CRLM can be performed safely without compromising oncologic radicality and can also increase the number of patients eligible for a direct surgical treatment by limiting the resection volume.

Resection margin

There has long been controversy over the impact of the width of the resection margin on the oncological outcome of LR candidates for CRLM. Since the 1980s surgeons have advocated for R0 resection margins of 10 mm or greater, the so-called "1-cm rule", in order to prevent local recurrence and optimize overall survival[38,108,129]. The presence of residual microscopic deposits of neoplastic cells after removal of metastatic nodules is considered an important source of remetastasis and a significant factor of adverse prognosis[115,129]. As for the primary tumour, micrometastases may occur in CRLM. Intrahepatic micrometastases are defined as detectable microscopic tumour nests within the liver parenchyma or portal tracts surrounding the dominant tumour, but separated by a rim of non-tumourous parenchyma, are predominant within 4 mm to 10 mm of the tumour margin, and are considered the morphological expression of remetastasis from existing liver metastases[40,119,130,131]. Their role as a prognostic factor in the oncological outcome of patients with CRLM is however still controversial. One study reported that patients with intrahepatic micrometastases had higher incidence of intrahepatic recurrence and worse survival, with ten-year survival rates of 21.9% compared to 64.3% for patients without micrometastases[132]. In another study, intrahepatic micrometastases were less frequently detected in patients treated with neoadjuvant CHT than in those untreated[133]. A 2 mm RM is however considered acceptable to significantly reduce the incidence of local recurrence in the series where the role of intrahepatic micrometastases has been evaluated[119,130]. In a small series based on the detection of tumour-specific mutant DNA in liver tissue surrounding metastases, mutant DNA was detectable in surrounding liver tissue within 4 mm of the tumour border, while biopsies at 8 mm, 12 mm, and 16 mm from the macroscopically visible margin were free from microscopically visible tumour cells and detectable mutant DNA, even in patients whose tumours were larger before CHT[131]. Also the presence of fibrotic tissue between the tumour and the surrounding hepatic parenchyma has been recognized as a favourable prognostic factor in CRLM and may be relevant in the evaluation of the RM. Yamamoto *et al*[134] reported that the five-year survival rate was 71% in patients with a thick pseudocapsule, 63% in those with a thin pseudocapsule, and only 19% in the absence of a pseudocapsule. Similar results were reported in the study by Okano *et al*[135], where five-year survival rates were 88% in patients with a thick pseudocapsule, 64% in patients with a thin pseudocapsule, and 31% in those without a pseudocapsule. Taken together, these data show that CRLM are usually well circumscribed, with very low incidences of satellite nodules or micrometastases, so that limited negative resection margins may have a limited impact on recurrence and survival rates, even though RM width of 10 mm should be achieved whenever possible[38].

R1 resection

The presence of residual macroscopic or microscopic tumour on RM after surgery for CRLM is traditionally considered a significant factor of adverse prognosis[108] due to increased local and intrahepatic recurrence as well as decreased OS and DFS. As a consequence, the adequate evaluation of the RM is of paramount importance to define the postoperative oncological prognosis. However, the accurate assessment of margin status depends on multiple factors. Different techniques of liver transection create different extensions of tissue loss[38]. The thermal effects of energy devices and of the argon-beam coagulation on the cut surface of the liver causes extensive cell killing within 2-5 mm of the RM[130,136]. Also pathologic assessment of the exact distance between the excised tumour and the end of the liver parenchyma has multiple limitations[137]. With these limitations, there is strong evidence that microscopically positive RM (R1) negatively impacts overall oncological results. R1 resection has been associated with an increased risk of recurrence at the surgical margin[119,131,138-140] and of intrahepatic recurrence[139,141]. Tranchart *et al*[142] found that R1 resection was an independent adverse predictor of OS and DFS, and the use of postoperative CHT was the only independent predictor of improved DFS in patients with R1 resection. The adverse effect of R1 LR on survival has been confirmed by other studies[138,143,144]. However also the protective effect of postoperative CHT after R1 resection has been recently confirmed[141,145].

The role of neoadjuvant CHT on the oncological outcome of R1 resection is controversial. Ayez *et al*[146] found that R1 resection remained an adverse prognostic factor in OS and DFS in patients receiving LR for CRLM not treated with neoadjuvant CHT, but not in those who had undergone neoadjuvant CHT. Different results were obtained in a study of 378 patients treated with neoadjuvant CHT and subsequent LR, where the effect of positive margins on OS was analysed in relation to response to CHT[147]. Fourteen percent of resections were R1 (tumour-free RM < 1 mm). The five-year overall survival rates were 55% for patients with R0 resection (tumour-free RM ⩾ 1 mm) and 26% for those with R1 resection (P = 0.017). R1 resection and a minor pathologic response to CHT at histology were independently correlated with worsened survival upon multivariate analysis. The survival advantage correlated with negative resection margins (R0 *vs* R1 LR) was higher in patients with suboptimal morphologic response at CT scans after CHT (five-year OS: 62% *vs* 11%; P = 0.007) than in those with optimal response (three-year OS: 92% *vs* 88%; P = 0.917), and higher in patients with a minor pathologic response at histologic evaluation (five-year OS: 46% *vs* 0%; P = 0.002) than in those with a major response (five-year OS: 63% *vs* 67%; P = 0.587). The authors concluded that with the current neoadjuvant CHT protocols, negative resection margins still represent a crucial prognostic factor and should remain the principal purpose of LR, and that the adverse influence of positive RM is most evident in the presence of suboptimal response to neoadjuvant CHT. In a similar study of 227 patients who received neoadjuvant oxaliplatin and/or irinotecan and 5-FU and subsequent curative LR[148], positive margins (tumour-free RM < 1 mm) significantly increased the risk of death without postoperative CHT (P = 0.0077), but not with postoperative CHT. Negative RM sizes of ⩾ 1– < 5, ⩾ 5– < 10, and ⩾ 10 mm were not significant predictors of OS. The authors concluded that patients undergoing LR for CRLM should receive postoperative CHT if negative margins cannot be achieved, and that negative margins wider than 1 mm do not improve OS for patients receiving neoadjuvant CHT. It should be noted however that when neoadjuvant CHT is interrupted, regardless of previous response, regrowth may occur at the periphery rather than in the centre of the metastasis, with clustering of viable cancer cells infiltrating the liver tissue for several millimetres at the periphery of the metastasis, irrespective of any signs of response in its centre, a phenomenon called "dangerous halo"[136]. Similarly, it has been found that neoadjuvant CHT may determine irregular borders of CRLM, particularly evident in lesions with significant contraction, and sometimes discrete islands of viable tumour cells outside of the main tumour, but all close to the peripheral margin of the tumour mass[149]. The possible progression of the dangerous halo is particularly worrying, and the planned surgical margin should be wide enough to limit the risk of local recurrence, especially if CHT has been interrupted for a relatively long time. It has been suggested that the argon-beam coagulation of the cut surface of the liver might reduce the risk of recurrence by providing a layer of necrosis of 2 mm to 5 mm[136].

Also submillimetric clear margins have been considered adequate for resection of CRLM. A total of 2368 patients undergoing LR for CRLM at Memorial Sloan Kettering Cancer Center between 1992 and 2012 were examined to evaluate the impact of margin width on OS[144]. The median OS of the R1, 0.1-0.9 mm, 1-9 mm, and ⩾ 10 mm groups was 32 mo, 40 mo, 53 mo, and 56 mo, respectively (P < 0.001). Compared with R1 LR, all RM widths, together with submillimetric margins, were associated with increased OS (P < 0.05). The significant association of RM width and OS remained when adjusted for all the other pathological and clinical factors of prognosis. The authors concluded that RM width is independently predictive of better survival rates, so that adequate margins should be obtained whenever possible. However, LR should be performed also in patients where narrow RM are anticipated because submillimetric margin clearance may improve survival. The authors also suggested that the favourable outcome observed with submillimetric margins could be the expression of the biological behaviour of the tumour rather than the result of the surgical technique. Detachment of CRLM from intrahepatic vessels has been proposed as part of IOUS-guided PSLR[113,150]. Even though this kind of resection implies formally R1 resection margins, oncological outcomes seem to be similar to those described for R0 resections. In a recent series of 627 resection areas in 226 consecutive patients with CRLM, Viganò *et al*[151] compared the outcomes of R1 surgery (RM < 1 mm), distinguishing standard R1 resection and R1 resection with detachment of CLM from major intrahepatic vessels (R1 vascular). Five percent of recurrences at surgical RM occurred in 12.4% of patients. Local recurrence risk was similar between the R0 and R1 vascular groups but increased in the standard R1 resection group ($P < 0.05$ for both). Standard R1 resection had a higher rate of hepatic-only recurrences ($P = 0.042$) and was an independent negative prognostic factor of OS on multivariate analysis ($P = 0.034$). Conversely, R1 vascular resections had oncological outcomes similar to those of R0 resections suggesting that CRLM detachment from intrahepatic vessels can be safely pursued to increase resectability. Similar strategies of conservative IOUS-guided LR sparing intrahepatic vessels have been used in simultaneous colorectal and liver resection of advanced CRC with synchronous CRLM to limit the extension of LR with the aim of reducing the overall risk of the simultaneous procedures[91].

The data on whether R1 margin status is an independent predictor of survival have been conflicting because some authors have found that R1 margin status was not associated with survival after controlling for competing risk factors on multivariate analyses[138,139,141]. Tumour biology might play a determinant role in the impact of RM status on oncological outcome, where R1 resections could not have a prognostic value per se but reflect a more severe disease[38,40,129,138,141,145]. Recent changes in the prognostic value of R1 resections could reflect in part the beneficial effect of perioperative CHT[142,145-148]. In a recent series of 1784 hepatectomies analysed from a multicentric retrospective cohort of hepatectomies performed for CRLM in 32 French centres from January 2006 to December 2013[152], positive primary tumour lymph nodes at colorectal resection ($P = 0.02$), operative time > 240 minutes ($P = 0.05$), synchronous CRLM ($P = 0.02$), clamping of the hepatic pedicle > 40 min ($P = 0.001$), tumour size > 50 mm ($P = 0.001$), recurrent hepatectomy ($P = 0.001$), > 3 nodules (P=0.0001), and bilateral nodules ($P = 0.0001$) were recognized as risk factors for R1 resection upon multivariate analysis. After a propensity score matching according to Fong criteria, however, R1 resection still maintained an adverse impact on OS and DFS, with one-, three-, and five-year OS of 94%, 81%, and 70% in R0 LR *vs* 92%, 75%, and 58% in R1 LR, respectively ($P = 0.008$), and with one-, three-, and five-year DFS of 64%, 41%, and 28%in R0 LR versus 51%, 28%, and 18% in R1 LR, respectively ($P = 0.0002$).

R0 resection: the optimal free resection margin

Determining the optimal free RM in surgery of CRLM is much more controversial, since the traditional 1-cm rule to consider oncologically adequate the RM has been widely debated in the last decades. Pawlik *et al*[138] in 2005 demonstrated that OS, DFS, recurrence risk, and site of recurrence were not significantly different among patients undergoing resection of CRLM with RM of 1-4 mm, 5-9 mm, and ⩾ 10 mm, and suggested that predicted margin of < 1 cm after LR should not contraindicate LR. A similar study including 1019 patients from the Memorial Sloan Kettering Cancer Center showed that patients undergoing LR with RM > 10 mm had better survival than those with RM < 10 mm. However, within the latter group there was no significant difference in survival when stratified according to RM width, and patients with subcentimetric RM had an overall survival of 42 months (significantly better than similar patients treated with systemic CHT or ablative therapies)[153]. In another multicentric study of 2715 patients who received primary resection of CRLM, a 1-mm tumour-free RM was sufficient to obtain 33% five-year overall DFS, while extra RM width did not further increase DFS. After the propensity case-match analysis, the authors did not find a statistical difference in DFS between patients with negative narrow RM and wider RM clearance[143]. Recent meta-analyses however support the need of achieving adequate resection margins whenever possible. Dhir *et al*[154] examined 4821 patients with negative RM from 18 studies and found that the five-year OS for the ⩾ 1 cm negative RM subgroup was 46% when compared with 38% for < 1 cm negative RM subgroup ($P = 0.009$). In another meta-analysis based on 18 studies including 6790 patients[155], R1 resection had a negative impact on OS and DFS rates and was associated with more frequent recurrences. The use of current protocols of CHT did not alter the adverse oncological outcome of R1 resection. Notably, ⩾ 1 cm negative RM obtained the best overall survival rates. Margonis *et al*[156] evaluated 34 studies including a cohort of 11147 LR. Wider RM (> 1 cm *vs* < 1 cm) was significantly associated with improved OS and DFS at three years, five years, and ten years. Also > 1 mm *vs* < 1 mm RM was significantly associated with improved OS. Meta-regression analyses did not reveal any significant impact of perioperative CHT. The authors concluded that even though a > 1 mm RM determines better prognosis than a submillimetric RM, obtaining a RM > 1 cm may determine even better oncologic results and should be attempted whenever possible. Taken together, these data suggest that the 1-cm rule still has prognostic importance in the oncological outcome of resection of CRLM and should be pursued whenever possible. However, the likelihood of local and intrahepatic recurrences seem to be frequently independent of margin width, where tumour biology seems to be a more decisive predictive factor of both intrahepatic recurrence and poorer long-term survival. Even though R1 resections should be avoided, the actual margin width of R0 resections seems to have a limited impact on the postoperative oncological outcome. For all these reasons, failure to comply with the 1-cm rule should no longer contraindicate liver resection of colorectal metastases.

Surgical strategies for multiple bilobar metastases

In 1984 Adson *et al*[157] reported a study of 141 patients who had resection of CRLM between 1948 and 1982 and found similar five-year survival rates between patients with single metastases and those with multiple lesions. They concluded that removal of multiple hepatic metastases was advisable in selected cases. This study was contradicted by Ekberg *et al*[108] in a series of 72 LR for CRLM between 1971 and 1984, where poor prognostic factors contraindicating surgical resection of CRLM included more than four lesions, impossibility to achieve a RM ⩾ 1 cm, and evidence of extrahepatic disease. These data were confirmed by Hughes *et al*[158] in a series of 100 patients who survived for more than five years after resection, where patients with ⩾ 4 metastases were considered to be contraindicated for LR. The considerable improvements achieved in the 1990s in the knowledge and treatment of colorectal metastases led to substantial changes in the surgical strategies for multiple CRLM[89]. In 1995 Scheele *et al*[159] reported their experience with 32 patients undergoing LR of ⩾ 4 CRLM. According to their study, five or more independent metastases had an adverse effect on resectability. However, if a radical excision of all detectable disease could be obtained, the number of metastases (1-3 *vs* ⩾ 4) was not significantly predictive of either OS or DFS. Subsequently Weber *et al*[160] reported a study of 155 patients who received LR for ⩾ 4 CRLM with a five-year OS of 23%. As the number of tumours increased, the five-year survival rate diminished from 33% to 14%. However, in this study there were twelve five-year survivors, including two patients with nine or more nodules. Also the potential benefits of neoadjuvant CHT were delineated. Tanaka *et al*[161] reported 71 patients who had received LR for ⩾ 5 bilobar CRLM and compared the outcome of 48 patients who received neoadjuvant CHT followed by LR with that of 23 patients treated by LR alone. Patients with neoadjuvant CHT experienced better three- and five-year survival rates from the time of diagnosis than those without CHT (67.0% and 38.9% *vs* 51.8% and 20.7% respectively; P = 0.039), and required fewer extended LR (four segments or more) (81.3% *vs* 100.0%; P = 0.027) Multivariate analysis demonstrated that neoadjuvant CHT independently predicted survival. The authors concluded that in patients with bilateral multiple CRLM, neoadjuvant CHT before LR was associated with improved survival.

For patients with extensive bilobar disease, multiple strategies combining TSH and neoadjuvant CHT were described by the surgeons from the Paul Brousse Hospital[162-164]. In selected patients with multiple CRLM not eligible for a curative one-stage resection, even when downstaged by CHT, after PVE, or combined with local ablation techniques, Adam *et al*[162] proposed a TSH strategy, where the highest possible number of nodules was resected in a first non-curative procedure, and the remaining tumours were resected after an adequate period of hepatic regeneration. The three-year survival rate of the 16 patients who completed the procedure was 35%, with four patients (31%) disease-free at 7 mo, 22 mo, 36 mo, and 54 mo. The same group subsequently examined a series of 33 patients with bilobar CRLM where a right or extended right LR was planned. The first-stage hepatectomy consisted of a clearance of tumours of the left FRL by resection or radiofrequency ablation (RFTA) to prevent the growth of metastatic nodules in the estimated FRL after PVE, followed by a right PVE to induce atrophy of the right hemiliver and hyperplasia of the left hemiliver. The second-stage hepatectomy, a right or extended right hepatectomy, was performed in patients with adequate left FRL hyperplasia and without disease progression. The one- and three-year survival rates were 70.0% and 54.4%, respectively, in the 25 patients in whom the procedure was completed[164].

In all these Western studies, patients with multiple CRLM were candidates for major or extended hepatectomies in most cases. In the same period the surgeons from the Cancer Institute and the University of Tokyo were following a different approach to multiple CRLM[35,89,130]. Kokudo *et al*[89] reported a series of 183 patients who received LR with curative intent for CRLM from 1980 to 2000 with five-year OS of 41.9%. The overall outcome of 21 patients who had ⩾ 4 tumours in the liver was not significantly different from that of patients with ⩽ 3 tumours. In the same study the authors delineated the principles of conservative LR strategy for multiple CRLM: Accurate preoperative evaluation of the tumour number and their proximity to the major intrahepatic vasculature, careful intraoperative inspection and palpation of the liver and use of IOUS, multiple partial resections whenever possible instead of extended hepatectomies, with resection of large intrahepatic vessels only if tumour invasion was present, non-anatomical resection even with a minimum surgical margin, and preoperative PVE when the estimated volume of the remnant liver was under 40% in case of major hepatectomy. In the overall series the remnant liver was the most common site of recurrence, and repeated liver resection was carried out in approximately half of the patients after recurrence, with a five-year survival rate of 44.7% starting from the first hepatectomy. With these diagnostic and therapeutic strategies the same group performed over 1000 hepatectomies without mortality[35]. A similar approach to multiple bilobar CRLM was reported by Torzilli *et al*[165] in a series of 29 patients with multiple (≥ 4) bilobar CRLM where the surgical strategy was based on tumour-vessel relationships at IOUS and on findings at colour-Doppler IOUS. Tumour removal was feasible in 89.7% of patients. There was no in-hospital mortality and the overall morbidity rate was 23%. After a median follow-up of 14 mo (range 6-54), three patients had died from systemic recurrence, twelve were alive without disease, and eleven were alive with recurrence. However, no local relapses were observed at the surgical RM. The authors concluded that IOUS-guided resection based on strict criteria allows one-stage LR in selected patients with multiple bilobar CRLM, and thus decreasing the need for a TSH.

In the past decade, ablative techniques, including RFTA and microwave ablation (MWA), have emerged as an appealing option for the local treatment of primary and metastatic liver tumours, including CRLM, alone or in combination with LR. The role of ablation in patients with CRLM is unclear since ablative techniques have usually shown significantly lower rates of complications, but also lower survival rates and higher rates of recurrence as compared to LR[166-168], even though RFTA might have a role equivalent to liver surgery in the treatment of small (≤ 2 cm) CRLM[167]. Recent studies have shown that LR combined with intraoperative ablation techniques is effective in the treatment of multiple bilateral CRLM, with adequate perioperative outcomes and without compromising overall oncological results compared with bilateral resection or with TSH. It may represent an excellent option to pursue effective parenchymal-sparing treatments for extensive CRLM[169-172].

A progressive shift toward more conservative hepatectomies for bilobar CRLM has been reported also by surgeons traditionally inclined to more extensive LR. In a series of 443 LR in 440 patients who received resection of bilateral CRLM at the Memorial Sloan-Kettering Cancer Center[45], a major hepatectomy including three segments, hemihepatectomy or more extended resection in most cases, was performed as part of 380 operations. Major complications were 29% and 90-day mortality was 5.4%. Estimated five-year disease-specific and recurrence-free survivals were 30% and 18%, respectively. However, the surgical technique changed over time toward parenchymal-sparing techniques based on the wider use of multiple simultaneous liver resections, wedge resections, and local ablations, which correlated with decreased mortality rates without changes in disease-specific survival or liver recurrence. The authors concluded that resection of bilateral CRLM can be achieved with reasonable morbidity, mortality, and oncologic results, and that increased use of parenchymal-sparing approaches is associated with decreased mortality without compromising oncological outcomes. The favourable results of PSLR have been recently confirmed in a multicentric retrospective series of patients who had received LR for multiple (> 3) bilobar CRLM, comparing 331 patients who had received PSLR with 360 who had received non-PSLR, defined as the resection of three or more consecutive liver segments, excluding TSH[46]. PSLR was associated with lower complications (25% *vs* 34%; P = 0.04) and fewer Dindo-Clavien grade Ⅲ and Ⅳ complications (10% *vs* 16%; P = 0.03). Liver failure was less frequent after PSLR (2% *vs* 7%; P = 0.006), with a shorter ICU stay (0 days *vs* 1 day, P = 0.004). OS and DFS were similar between the two groups. The authors concluded that PSLR for multiple bilobar CRLM represents an appropriate alternative to non-PSLR in selected patients, with lower morbidity and comparable oncological outcomes. Recent studies have further demonstrated the positive impact of PSLR in the treatment of multiple bilobar CRLM, bringing into question also the consolidated role of the TSH in these cases[47]. A bi-institutional study compared the outcome of patients with multiple bilobar CRLM who had received TSH or PSLR. The inclusion criteria were ≥ 6 CRLM, ≥ 3 CRLM in the left liver, and ≥ 1 lesion with vascular contact. A total of 74 TSH and 35 PSLR were compared. Drop-out rate of TSH was 40.5%. PSLR had significantly lower blood loss, overall morbidity, severe morbidity, and liver-specific morbidity than TSH. R0 resection rate was similar between groups. PSLR and completed TSH had similar five-year OS (38.2% *vs* 31.8%), three-year RFS (17.6% *vs* 17.7%), and recurrence sites. The authors concluded that parenchymal-sparing hepatectomies are a safe alternative to TSH for multiple, bilobar, deeply located CRLM, and that PSLR should be preferred whenever achievable because of better safety and oncological results comparable to completed TSH without the drop-out risk.

Recent reports have demonstrated that also patients with large numbers of CRLM are potential candidates for liver surgery. In a bi-institutional Japanese study of 736 patients who underwent LR for CRLM over a 16-year period[173], the authors compared 493 patients with 1-3 tumours, 141 with 4-7 tumours, and 102 with ≥ 8 tumours. Major hepatectomies had been performed in a minority of patients (21.6%). The five-year OS and DFS rates were 51% and 21%, respectively, for the entire patient cohort, 56% and 29% for patients with 1-3 tumours, 41% and 12% for those with 4-7 tumours, and 33% and 1.7% for those with ≥ 8 tumours. Positive lymph node metastasis of the primary CRC, the presence of extrahepatic metastases, a maximum tumour size > 5 cm, and tumour exposure during LR were associated with decreased survival upon multivariate analysis. The authors concluded that in patients with multiple CRLM, the number of CRLM has less prognostic impact than other factors, and that complete LR may offer a chance of cure even in patients with numerous CRLM, including those with eight or more nodules. In another bi-institutional study of 849 patients undergoing LR for CRLM[174], 743 patients with 1-7 metastases were compared to 106 with ≥ 8 metastases. The overall perioperative mortality rate was 0.4%. Patients with 1-7 metastases had higher five-year OS (44.2% *vs* 20.1%; P < 0.001) and DFS (28.7% *vs* 13.6%; P < 0.001) rates. In patients with ≥ 8 metastases, OS and

DFS were similar for patients with 8-10, 11–15, or > 15 metastases. In this group, multivariate analysis identified three preoperative factors of adverse prognosis, including extrahepatic disease (P = 0.010), no response to preoperative CHT (P = 0.023), and primary rectal cancer (P = 0.039). Patients with two or more risk factors had very poor outcomes, while those with no risk factors had survival rates similar to patients with 1-7 metastases (five-year OS rate 44.0% *vs* 44.2%). The authors concluded that LR is safe in selected patients with ≥ 8 metastases, and offers reasonable five-year survival independent of the number of metastases. A recent French multicentric study examined the outcome of 529 patients undergoing liver surgery for ≥ 10 CRLM from 2005 to 2013, prospectively collected in the LiverMetSurvey registry[92]. The five-year OS was 30%. A macroscopically complete (R0/R1) resection was achieved in 72.8% of patients and was associated with a three- and five-year OS of 61% and 39%, compared to 29% and 5% for R2/no resection patients (P < 0.0001). Upon multivariate analysis, R0/R1 resection resulted as the strongest favourable factor of OS (P < 0.0001). Other independent favourable factors were maximal tumour size < 40 mm (P = 0.02), age < 60 years (P = 0.005), preoperative MRI (P = 0.007), and adjuvant CHT (P = 0.04). Of the 346 patients who underwent R0/R1 resection, 74.6% had developed a recurrence at last follow-up, with three- and five-year primary DFS rates of 23% and 7%, respectively. When hepatic recurrence and extrahepatic recurrence were surgically treated, the secondary DFS rates (taking into account the impact of repeat surgery) at three years and five years were 42% and 31%, respectively. The authors concluded that, even though the oncological outcome of patients with ≥ 10 CRLM is obviously worse compared to patients exhibiting fewer lesions, surgery remains the only hope of prolonged survival, especially if complete resection can be performed, and that the number of CRLM should not be considered per se as contraindication to surgery.

The impact of PSLR on simultaneous colorectal and liver surgery

Simultaneous colorectal resection and minor hepatectomy have perioperative results similar to minor hepatectomy alone, and are at present considered the treatment of choice in most patients with limited liver disease suitable for minor LR[1,19,24]. The results are much more conflicting in patients requiring simultaneous colorectal and major LR because most investigators have reported worse perioperative outcomes than for major LR alone also in experienced hepatobiliary centres[20,79,80,82,175], while others remark that simultaneous colorectal resection and major hepatectomy can be performed safely in selected cases with perioperative risks comparable to major LR alone[31-33]. Most studies comparing simultaneous and staged procedures are retrospective, with patients undergoing simultaneous procedures having more limited hepatic involvement, which could explain these discordant outcomes[19,22,26]. At present, most authors suggest combined resections in the case of easily accessible, uncomplicated colorectal tumours with CRLM requiring minor hepatectomies[26,27,176], while these criteria could be selectively extended in units experienced in both hepatobiliary and colorectal surgery[23]. In a recent survey reporting the opinion of colorectal and liver surgeons about simultaneous resection of CRC and liver metastases[177], most surgeons of both groups perceived that simultaneous procedures were appropriate in adequately selected patients, especially in candidates to any type of colorectal surgery with minor LR. Restorative rectal resections coupled with a major LR were considered inappropriate due to the risk of leakage of the colorectal anastomosis. Some concern did exist as well, especially among liver surgeons, about the risk of leakage also for colo-colic anastomoses if combined with major LR.

As a matter of fact, even though surgeons experienced in colorectal and hepatobiliary surgery should carefully select candidates to simultaneous resection to minimize perioperative complications, the planned extent of LR seem to represent the most important determinant of whether simultaneous procedures are individually appropriate for CRC with synchronous CRLM[19,24,178,179]. As previously discussed, IOUS-based conservative techniques of liver surgery substantially decrease the need for major hepatectomies also for multiple bilobar CRLM, with a substantial reduction of perioperative related risks and may represent an appropriate solution even for potential candidates to simultaneous colorectal and liver resection for bilobar synchronous CRLM. In a small retrospective series of 39 consecutive patients with synchronous CRLM, who underwent curative simultaneous "one-stage" hepatectomy and resection of the colorectal primary, Tanaka *et al*[178] observed that only the volume of the resected liver was a significant risk factor for postoperative complications (350 g mean resected liver volume in patients with postoperative complications *vs* 150 g in those without complications; P < 0.05). The systematic application of the criteria of conservative liver surgery have been associated with higher rates of feasibility of simultaneous colorectal and liver resections also in patients with multiple hepatic nodules. Minagawa *et al*[180] in 2006 reported 148 patients admitted with CRC and synchronous CRLM since January 1989, evaluated for simultaneous resection regardless of the location of the primary cancer and the extent of CRLM. A simultaneous resection was performed in 142 cases (feasibility rate 96%), without perioperative mortality. Fifty-one percent of patients had the primary tumour located in the rectum. With the systematic application of their principles of conservative IOUS-based liver surgery[89], only 11.3% of patients required a hemihepatectomy, while the others received limited resections (74.6%) or the resection of one or two segments (14.1%). In a more recent study of 150 patients who underwent resection of primary CRC and synchronous CRLM between 1993 and 2011[181], the proportion of simultaneous resections was 84.7%. Among the 127 patients who had received a simultaneous colorectal and hepatic resection, there was no postoperative mortality, postoperative complications were 61.4%, major complications were 18.2%, and anastomotic failure occurred in 1.6% of patients. The three-, five- and ten-year OS was 74%, 64%, and 52%, respectively. In a small series of 45 patients who underwent elective resection of primary CRC and synchronous CRLM, a simultaneous colorectal resection with anastomosis and conservative one-stage LR was feasible in 75.6% of patients. It was possible to avoid a right hepatectomy in all the patients undergoing simultaneous restorative colorectal resection[91]. Seven patients had synchronous CRC at presentation (unpublished data), and two of them had rectal cancer within diffuse colorectal poliposis and received restorative proctocolectomy with ileoanal J-pouch and temporary diverting loop ileostomy. One patient with multiple CRLM of the right hemiliver underwent the restorative proctocolectomy after neoadjuvant CHT, with a subsequent resection of liver segments S6–S7–S8. The other had a single metastasis in segment S8 and underwent simultaneous restorative proctocolectomy and liver segmentectomy. Two patients had a simultaneous cancer proximal to a rectal cancer, with multiple bilobar CRLM. One received neoadjuvant chemoradiotherapy and subsequent resection of the sigmoid colon and of the rectum with simultaneous one-stage PSLR. In the other patient a TSH was planned to treat the hepatic disease. The patient received neoadjuvant chemoradiotherapy and a subsequent rectal resection with a first-stage LR consisting of multiple wedge resection in the left hemiliver with right portal vein ligation. At re-exploration for the second-stage LR a massive diffusion of the cancer at the hepatic hilum was found and the planned right hepatectomy was not performed. Finally, three patients had SCRC in distant colonic segments, and we opted for a restorative subtotal colectomy. One patient underwent simultaneous liver bisegmentectomy of S2-S3 with splenectomy and interaortocaval lymphadenectomy because of splenic and interaortocaval lymph node metastases. The other two underwent PSLR for multiple bilobar CRLM, associated with intraoperative RFTA in one patient. Therefore, five patients received simultaneous potentially curative colorectal and one-stage liver resection without postoperative mortality and complications requiring reoperation.

CONCLUSION

In conclusion, simultaneous procedures represent an attractive surgical option in selected patients with resectable CRC and resectable synchronous CRLM. Simultaneous resections should only be considered by surgical teams experienced in both fields. Staged procedures are still advisable in the case of complicated CRC requiring urgent colorectal resection. In all other cases, simultaneous resections should be theoretically considered whenever possible, including patients with SCRC. In these cases, if the synchronous tumours are located in distant colorectal segments, an extended restorative colectomy should be considered to prevent the risks related to multiple colorectal anastomoses, especially if prolonged hepatic pedicle clamping is planned for extensive PSLR and/or CRLM adjacent to major intrahepatic vessels. When rectal cancer is diagnosed, the indication to preoperative chemoradiotherapy and its potential benefits should be adequately considered. A systematic approach to liver resection that focuses on the need of reducing the extent of hepatectomy while preserving oncological radicality may represent the best strategy to limit the perioperative risks in candidates to simultaneous colorectal and liver resection.

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