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EARLY HEPATIC RECURRENCE AFTER COLORECTAL CANCER LIVER METASTASES SURGERY: A SINGLE PROSPECTIVE CENTRE STUDY

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1. INTRODUCTION

1.1 COLORECTAL LIVER METASTASIS AND THE EVOLUTION OF SURGICAL RESECTABILITY CRITERIA

Colorectal cancer is the third most common cancer[1]. Up to 70% of patients develop distant metastases during the progress of the disease, most commonly located in the liver; in 30–40% of these patients, the metastatic spread is confined to the liver[2]. Without treatment, the median survival of colorectal liver metastases (CRLM) is 6–8 months[3].

Hepatic resection is the only treatment modality associated with long-term survival in patients with CRLM, with 5-year survival rates ranging from 40 to 58% in selected patients[4]. The surgical management of CRLM has changed dramatically during the past three decades, leading to a marked improvement in overall survival, with a near doubling of the historical 5-year survival rate of 30% to 35%, in parallel with advances in surgical technique, better perioperative care, as well as more effective systemic chemotherapeutic agents[5].

Historically, major hepatectomy represented the treatment of choice in patients with CRLM. This paradigm has changed with the diffusion of the parenchymal-sparing liver resections (PSLR). Therefore, there has been an expansion in the criteria of resectability for colorectal liver metastasis and specifically, the number of metastasis, size of tumor lesion, and a mandatory 1 cm margin of resection are no longer considered absolute criteria for a curative surgical approach. The current definition of resectability includes the potential for complete resection with tumor-free margins (R0 resection), with preservation of at least two disease-free liver segments with viable vascular in-flow, outflow, and biliary drainage and an adequate future liver remnant (FLR) volume[6], that means at least 20% of the total estimated liver volume for normal parenchyma, 30%–60% if the liver is injured by chemotherapy, steatosis, or hepatitis, or 40%–70% in the presence of cirrhosis, depending on the degree of underlying hepatic dysfunction[7].

Nowadays, unresectable extrahepatic metastases or unresectable primary tumor, prohibitive anesthesiological risk, and medical contraindications to hepatectomy still constitute contraindications for resection.

Indeed, resection of the hepatic lesion should only be considered, however, when the extra-hepatic metastasis is surgically resectable or controllable via adjuvant therapies[8].

Nowadays, a greater number of parenchymal sparing strategies are being performed, which are considered by many the first-choice strategy because it preserves non-tumoral parenchyma, allows repeated resection in case of recurrence, and does not compromise oncological outcomes[9-11]. Indeed, parenchymal sparing resections might be particularly beneficial for patients with a high operative risk for major resection, who would otherwise not be candidates for resection. Intraoperative ultrasound (IOUS) has a key role in the modern hepatic surgery not only to better stage the disease, but above all as guidance to resection, as it is able to confirm and extend previous findings. The extensive use of IOUS allows to maximize the parenchymal sparing of healthy liver tissue, becoming essential for intraoperative decision-making[12].

However nearly 80% of patients with CRLM are not to be resectable at the time of diagnosis[13, 14]. These patients were traditionally considered for palliative chemotherapy. The advent of more effective chemotherapy and developments of surgical procedure and perioperative management have expanded the pool of resectable patients with CRLM, and a certain number of patients with initially unresectable CRLM can be converted to resectable[15, 16]. However, even with effective chemotherapy with or without targeted therapy, conversion rate is reported to be only 20%[16].

For patients with extensive bilateral multinodular CRLM, a single hepatectomy, even with specific procedures such as portal vein embolization (PVE) and local ablation therapy is sometimes not sufficient to remove all the tumors, even after significant downsizing by chemotherapy. In these cases, it is necessary to balance two conflicting objectives: (1) to achieve a complete tumor resection with curative intent (negative margins), and (2) to preserve as much liver parenchyma as possible to avoid liver failure. However, major hepatectomies are often required to achieve an R0 resection, and these are associated with substantial rates of morbidity and mortality[17]. Post-hepatectomy liver failure (PHLF) is the main cause of death after major hepatectomy and it is strictly related to the volume and quality of the future liver remnant (FLR)[18]. Several strategies have been developed in order to minimize the risk of PHLF and expand resectability.

So, in 2000, Adam et al. reported the concept of two-stage hepatectomy (TSH), based on two sequential procedures to remove multiple bilateral tumors impossible to remove by a single hepatectomy, and using the liver regeneration obtained after the first procedure[19].

Twelve years after the introduction of TSH, Schnizbauer et al.[20] reported a technical innovation to this important concept that undoubtedly represented a major breakthrough in surgery. This new approach, so-called associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), considerably accelerates FLR hypertrophy and drastically reduces the time interval between stages, therefore increasing resectability rates. As originally described, the technique consists in right PVL combined with in-situ splitting of liver parenchyma during the first stage, followed 7–10 days after by a second stage resecting the diseased hemi-liver.

1.2 THE PARADIGM SHIFT FROM LARGE TO PARENCHYMAL SPARING RESECTIONS AND THE IMPORTANCE OF THE SURGICAL MARGIN

Surgeons have progressively moved from the “1-cm” rule to the “1-mm” rule in the treatment of CRLM and a negative (≥ 1-mm) surgical margin is the present standard (Figure 1).

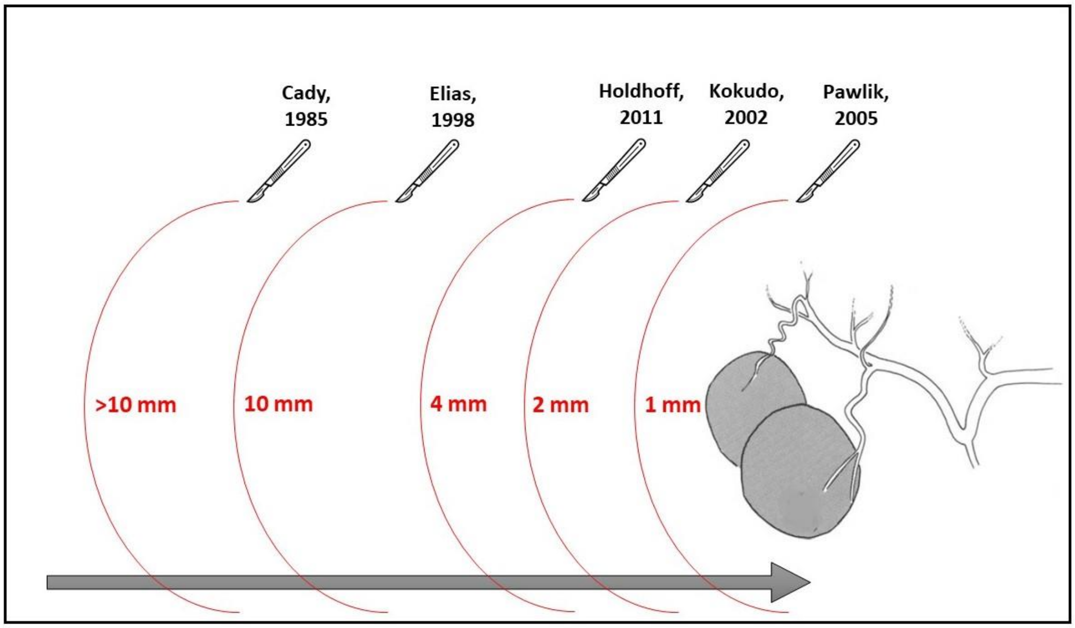


Figure 1. The paradigm shift from large to parenchymal sparing resections.

In the 1985, Cady et al. have reported that a surgical margin less than 1 cm was associated with a significantly shorter disease-free survival (DFS). As a result, major centers have adopted a 1-cm margin as a target during resection to minimize hepatic recurrence and improve survival after resection of CRLM. In fact, a 1-cm margin has been proposed as the minimally acceptable margin even for ablative techniques[21].

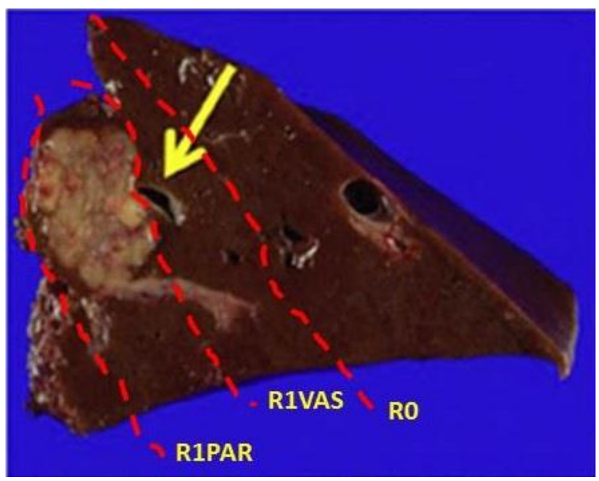
Later on, considering that the use of 1-cm rule for resection could exclude a large number of patients from the only therapeutic interventions able to affect long term survival, not reaching this margin became not a contraindication but a strong recommendation[22]. In 1998, firstly Elias stated that the “one-centimeter free margin” concept should not be rigidly adhered to. For the author, it is justifiable to undertake resection of liver metastases from colorectal cancer, provided it is curative and safe, even in the face of what would classically be considered poor prognostic factors.

In 2011, Holdhoff evaluated the resection margin through a combination of histopathologic and genetic analyses and found that tumors with a significant radiologic response to chemotherapy were not associated with any increase in mutant tumor DNA in beyond 4 mm of the main tumor, supporting the clinical evidence that a negative (R0) margin may be sufficient. Furthermore, authors did not find evidence of residual tumor DNA in the region in which the tumor likely existed prior to chemotherapy, suggesting that tumors which respond to chemotherapy likely do so in a concentric fashion[23].

In the last 15 years, various authors have shown comparable results with narrower margins and even with positive microscopic margins (R1). In 2002, Kokudo et al. reported that micrometastases around liver tumors were mostly confined to the immediate vicinity of the tumor border and so hypothesized that the minimum surgical margin for successful liver resection without cut-end recurrence may lie somewhere between 0 mm and 10 mm. Indeed, a surgical margin of 2 mm appears to be a clinically acceptable minimum requirement, carrying an approximately 6% risk of margin-related recurrence. Kokudo's study represents the first multicenter report to examine the effect of surgical margin status after resection of hepatic CRM on both margin recurrence and survival[24].

In 2005, for the first time in literature, according to Pawlik et al., a positive margin was considered to be a margin less than 1 mm, defining as the presence of exposed tumor along the line of transection or the presence of tumor cells at the line of transection detected by histologic examination. Although a positive surgical margin was associated with an increased risk of margin recurrence (11%), the width of the margin was not significant. Patients with a margin of 1 mm to 4 mm did have a slightly increased rate of margin recurrence compared with patients who had wider margins; this did not reach statistical significance. In conclusion, this study demonstrated that the width of a negative surgical margin does not affect survival, recurrence risk, or site of recurrence[25].

Similarly, detachment of CRLM from major intrahepatic vessels if they have not been infiltrated (R1 vascular resection) was recently shown to have an excellent outcome. In fact, in 2016, Viganò et al. tried to clarify the clinical relevance of R1 resection for CRLMs in a large, recent, single-center series, with a focus on the distinction between tumor exposure along the transection plane (standard R1) and CRLM detachment from intrahepatic vessels that is called R1 vascular (R1Vas) (Figure 2). Instead of R1 parenchymal (R1Par), representing an independent negative prognostic factor of overall survival, conversely R1vascular surgery achieves outcomes equivalent to R0 resection. So, CRLM detachment from intrahepatic vessels can be pursued to increase patient resectability and resection safety[26].



R1PAR: R1 parenchymal; R1VAS: R1 vascular

Figure 2. Representation of the different types of section margins

In conclusion, after Pawlik'study, the paradigm shift from large to parenchymal sparing resections had really achieved, leading to a modification of the oncological concept of safe resection margins.

Because the current consensus is that the thickness of the margin does not modify survival, the aggressive indications for CRLM and complexity of surgical procedures corresponded to high R1 resection rates. In the most experienced hepatobiliary units, R1 resection occurs in 10 to 30%[27] of patients, reaching 30 to 60% of patients with multiple bilobar CRLM or with initially unresectable disease[28].

However, the adequate width of the surgical margin is still a matter of debate, as the outcomes of R1 resection is associated with higher local recurrence rate and worse survival and several pathological data support the inadequacy of R1 surgery.

Actually, in 2008, Adam et al. first reported no negative prognostic impact of positive surgical margins. Some recent studies have shown that perioperative chemotherapy may reduce or even cancel the relevance of R1 surgery[29].

Later on, subsequent several recent studies had denied any negative prognostic role of R1 resection in the era of aggressive and effective perioperative chemotherapy[30, 31].

Finally, in 2015, the EGOSLIM (Expert Group on OncoSurgery management of Liver Metastases) group convened and published a brief but clear statement; ‘‘safe resection margins are still a goal of therapy; a minimal surgical clearance margin of 1 mm has been suggested as sufficient.’’ Nonetheless, the optimal surgical margin for CRLM remains unknown[32].

Considering that several evidences is still in favor of R0 surgery, a reappraisal of R1 resection is needed.

1.3 RECURRENCE AFTER LIVER RESECTION FOR COLORECTAL LIVER METASTASIS

Advances in surgical and medical oncology have resulted in prolongation of survival for patients with colorectal liver metastasis. However, many patients still develop recurrent disease. Studies addressing overall recurrence have reported rates ranging from 60 to 85% at one year[33, 34]. Specifically, hepatic recurrence occurs in 50% of patients during follow-up, with 2.8% to 13.9% presenting with surgical margin recurrence[33, 34].

However, data on rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis are limited. In fact, most studies reporting on outcomes following surgical management of colorectal metastasis have exclusively focused on overall survival rather than recurrence[33]. Unfortunately, to date, most series on the topic of pattern of recurrence for colorectal metastasis have been limited by small sample sizes and the few largely single-institution studies were published in an era prior to more effective systemic chemotherapy.

One of the most frequently used scoring systems is the clinical risk score (CRS) developed by Fong et al.[33]. This system categorizes patients into “low risk” and “high risk” groups for disease recurrence, with low scoring patients having an overall median survival of 74 months and high-scoring patients having an overall median survival of 22 months. CRS was calculated as 1 point per criterion met: node positive primary, >1 preoperative liver lesion, largest preoperative liver lesion >5 cm, preoperative CEA >200 pg/L, and time between removal of primary and appearance of liver metastases <12 months. Since a clinical risk score of this kind was important for the accurate care of colorectal cancer patients, after its publication in 1999, the CRS has seen longstanding and pervasive use in surgical practice. Nevertheless, the improvements in clinical care may have modified the accuracy of this scoring system and probably, today it would be necessary to reassess and modernize the score, adding some factors now relevant for the management of CRLM and that may improve the prognostic power of the CRS in the modern era of liver resection[35].

For example, blood loss and need for a transfusion remain a significant concern that can impact both immediate and long-term outcomes. Allogeneic red blood cell transfusions and their transfusion-related immunomodulation effects have been recently suggested as a cause for early cancer recurrence and worse overall outcomes[36].

Then, numerous intra-operative strategies have been developed to limit blood loss. Of these, portal pedicle clamping (PPC), first described by Hogarth Pringle for liver trauma, is one of the only strategies proven effective to reduce intra-operative blood loss in randomized controlled trials. Portal pedicle clamping has also been recently employed in regular hepatobiliary practice and its effects on survival and recurrence has been investigated. De Carlis et al. found that patients who received intermittent hepatic pedicle clamping, comparing with those who did not, had similar 5-year overall survival rate, but the 5-year recurrence-free rate was significantly higher. Noteworthy, the study was limited by the exclusion of patients with higher-risk disease according to CRS[37]. Conversely, other results are consistent with the lack of a difference in overall survival and recurrence-free survival[38].

Moreover, in the last decade numerous studies have investigated factors associated with recurrence after hepatectomy in CRLM (Table 1).

Several clinicopathologic and morphological factors are now considered to be independent prognostic factors associated with recurrence and hepatic recurrence. Primary colorectal tumor stage, differentiation and lymph node metastasis of primary colorectal tumor, time interval to the appearance of metastasis, number and size of metastases, preoperative CEA level, neoadjuvant/adjuvant chemotherapy and the status of the resection margin have been established as important determinants of tumor recurrence in CRLM[30, 34, 36, 39-50].

Among these several prognostic factors for recurrence, the surgical margin status or resection margins (RMs) is a technical, operative variable that is directly dependent upon the surgeon’s technique and it has also been traditionally associated with long-term prognosis[51]. However, as previously mentioned, the importance of the surgical margin achieved during liver resection, as prognostic factor to predict the development of local recurrence and long-term outcome, remains controversial.

Table 1. Factors associated with recurrence after hepatic surgery for colorectal liver metastasis. Literature between 2012 -2018.

Authors	N	Median age [years]	Type of study	Median FU [months]	Factors related to recurrence	Type of recurrence	Incidence [%]
Jung S.W. 2016[34]	279	65.5	Perspective	6	(univariate) Poorly differentiate CRC, synchronous metastasis, ≥5 cm of liver mass, preoperative CEA≥50 ng/mL, positive liver resection margin, and surgery alone without perioperative chemotherapy (multivariate) poorly differentiated CRC, ≥5-cm metastatic tumor size, positive liver resection margin, and surgery alone without perioperative chemotherapy	ER	10.8
Akyuz M. 2015[39]	206	62	Retrospective	29	(univariate) Tumor size CEA pre-op, margin status (multivariate) Positive margin status increased 3-6 folds risk of SMR	SMR	15.5
Hallet J. 2016[41]	2320	63	Retrospective	27	Node-positive primary, No. of lesions>3, Size of largest lesion>4 cm	Overall Intrahepatic Extrahepatic Intra and extra hepatic	47 46.2 31.8 (54 lung) 22
Viganò L. 2013[43]	6025	>70y 25,4%	LiverMetSurvey	34.4	T3–4 primary tumor; synchronous CRLM; > 3 CRLM; 0 mm margin liver resection; associated intraoperative radiofrequency ablation Protective factors: preoperative chemotherapy and response to pre-operative chemotherapy	Overall ER	45.4 10.6
Ayez N. 2012[30]	264	62	Retrospective	34	T stage primary tumor; positive lymph node in primary tumor; >4 CRLM; no neoadjuvant chemotherapy No difference in DFS and OS between R0/R1	Overall Intrahepatic Extrahepatic Intra and extra hepatic	65 20 33 11
Bhogal, R.H. 2015[42]	243	66	Retrospective	58	For liver recurrence: male sex and advanced primary tumors (Dukes C) For any recurrence: Number of metastases, largest tumor size	ER (18 months) Liver Overall	38 11 27
Angelsen J.H. 2014[52]	253	66	Prospective and retrospective	60	RMs do not impact hepatic recurrence, whereas extrahepatic recurrence was more frequent compared to no recurrence with RMs <5 mm	SMR Intrahepatic Extrahepatic	16.5 21.5 32.6
Mao R. 2017[45]	255	56	Retrospective	28.6	CEA ≥ 30 ng/ml, primary tumor lymph vascular invasion (LVI), number of metastases ≥ 4, R1 resection, initially unresectable disease	ER Overall	34 65
Imai K. 2016[44]	846	61	Retrospective	24	(Univariate) Age, primary tumor stage, bilobar distribution of liver metastases, preoperative chemotherapy cycles and lines, response to last-line chemotherapy, tumor number and size at hepatectomy, CEA and CA19-9 at hepatectomy, PVE, major hepatectomy, two-step approach, surgical margin status of liver metastases, and concomitant extrahepatic disease (Multivariate) Age ≤57 years, preoperative chemotherapy line, progression of disease during last-line chemotherapy, 3 tumors at hepatectomy, and CA19-9.60 U/mL at hepatectomy	ER*	43
Lin J. 2018[48]	307	57.5	Retrospective	31.7	(Univariate) Node-positive primary tumor and metastatic diameter > 3 cm (Multivariate) Node-positive primary tumor and metastatic diameter > 3 cm	ER • intrahepatic • extraepatic • unknown	16,0 57,1 30.6 12.2
Angelsen J.H. 2015[40]	311	66.1	Retrospective	4.2	Number and size of metastases, ASA score and synchronous disease. Perioperative chemotherapy	Overall (4yr) intraepatic extraepatic intra and extra hepatic	67.4 43.1 28.2 28,7
de Jong M.C. 2009[46]	1669	61	Retrospective	30	(Univariate) Node-positive primary tumor, synchronous hepatic metastasis, history of RFA, and receipt of chemotherapy, the clinical risk score, tumor size >5, preoperative CEA level, surgical margin status were not associated (Multivariate) rectal primary tumor site, disease-free interval >12 months, history of RFA, receipt of chemotherapy, the clinical risk score	Overall Intraepatic Extraepatic intra hepatic + lung intra hepatic + other extraepatic	56.7 43.2 35.8 11.6 9.4
Gomez D. 2014[47]	259	≥65y 68%	Retrospective	28	Higher tumor number, presence of perineural invasion and R1 resection	Overall	53.3
Kim Y. 2019[49]	68	57.1	Retrospective	2	Resection margin of the metastatic tumor and ypN		NA
Schierge T.S. 2015[36]	106	64.5	Retrospective	29	blood loss; comorbidities; tumor load, and positive resection margins, transfusion		NA
Kuo I.M 2015[50]	159	58.5	Retrospective	38.5	(Univariate) Centrally located metastasis, primary tumor in the transverse colon, metastasis in regional lymph nodes, initial extrahepatic metastasis, synchronous liver metastasis, multiple lesions, poorly differentiated tumor, and resection margin <10 mm (Multivariate) inadequate resection margin and centrally located liver metastasis	Overall ER	77 21

Parau A. 2015	70	≥ 53 y 49%	Retrospective	NA	(Univariate) Age >53 years, advanced T stage of primary tumor, moderately- poorly differentiated tumor, positive and narrow resection margin, preoperative CEA level >30 ng/ml, DFS <18 months (Multivariate) Perioperative chemotherapy and achievement of resection margins beyond 1 mm		NA

Abbreviations: SMR Surgical margin recurrence; ER: early recurrence (within 6 months after liver resection; * within 8 months after liver resection); CEA carcinoembryonic antigen level; CRC colorectal cancer; CRLM colorectal liver metastasis; RFA radiofrequency ablation; NA not available.

Actually, the prolonged overall survival observed with submillimeter margins is likely a microscopic surrogate for the biologic behavior of a tumor rather than the result of surgical technique[53]. In fact, the potential aggressiveness of colorectal cancer is readily evident when relapses occur early after resection of the primary tumor, when it recurs in the liver with large or bilobar metastases, and when there is little or no measurable response to chemotherapy[54, 55].

Indeed, in 2006 Takahashi et al. showed that time to recurrence after liver resection for CRLM strongly correlated with prognosis and especially patients with disease recurrence within 6 months after liver resection have the poorest outcome[56]. According to these data, early recurrence was defined as any recurrence occurring within 6 months after liver resection and the same time interval was adopted by Malik et al. in their study about early recurrences after liver resection for CRLM[57]. Interestingly, in this study the author found that the presence of eight or more metastases was the only significant predictor of early disease recurrence on multivariable analysis. In addition, the presence of numerous hepatic metastases was also a predictor of extra-hepatic recurrences and unresectable recurrent disease, suggesting that early recurrence is a marker of aggressive tumor biology[57].

In 2004, Tanaka et al. had already reported that short tumor doubling time in CRLM is a poor prognostic factor for both overall and DFS[55]. The authors demonstrated that only doubling time was retained as independent predictive factors for remnant liver recurrence and a doubling time of 45 days or less was associated with multiple, early remnant liver recurrences, precluding repeat hepatectomy and resulting in a poor prognosis. Interestingly, only tumor size and the prognostic nutritional index (PNI) based on the peripheral blood lymphocyte count and serum albumin concentration were significantly related to tumor doubling time, suggesting how doubling time would be determined by the interplay of both tumor characteristics and the patients' immune and nutritional status.

Nowadays, indicators of tumor biology and how they might influence outcome are of increasing interest. Mutation of the KRAS gene may be an indicator of biological aggressiveness. In this perspective, Cucchetti1et al. stratified a cohort of patients who underwent resection for only metachronous disease in three subgroup according to a mathematical model to estimate CRLM doubling times: the fast-growing CRLMs, doubling time less than 48 days; the intermediate-growing CRLMs, doubling time 48–82 days and the slow-growing CRLMs, doubling time more than 82 days. The study demonstrated that the tumor doubling time was shorter in patients with more advanced primary tumor stages, with mutant KRAS and in those who did not receive chemotherapy. In addition, for the fast-growing group, the risk of recurrence was highest within the first postoperative year and was about 7 per cent per month[54].

Several studies had showed that histopathologic factors of primary CRC were related to liver metastasis. Conversely, few studies, focusing on the histopathology of metastatic lesions as a predictive marker of tumor recurrence have been performed. Histopathological studies of liver metastases have resulted in the description of three histological growth pattern (GP). These are: *desmoplastic* GP, where a rim of collagen surrounds the tumor tissue and separates the liver parenchyma from the cancer cells; *pushing* GP, where tumor cells push the liver parenchyma aside, encompassing pressure on the hepatocytes at the tumor margin; and *replacement* GP, where tumor cells replace the hepatocytes hereby maintaining the trabecular architecture of the liver parenchyma (Figure 3)[58]. CRLMs grow according to different GPs with different angiogenic properties. In a recent study that enrolled 205 patients from 1995 to 2005, who were resected for liver metastasis and followed for 2 years, a pushing GP was the only independent predictor of poor survival, suggesting that this pattern is characterized by a more aggressive tumor biology in comparison to patients with desmoplastic or replacement GP[59]. Similarly, in a second prognostic study by Nielsen et al., survival was related to GPs, and desmoplastic growth was associated with small tumor size, dense lymphocytic infiltration and a more favorable prognosis in term of overall survival[60]. A more recent study considered also the effect of the therapeutic approach, comparing chemo-naive patients and patients receiving neo-adjuvant therapy[58]. Authors found that desmoplastic GP in resected liver metastases predicts a reduced risk of recurrence in comparison to other GPs, while the patients resected for pushing metastases tended to have earlier recurrence. Interestingly, the prevalence and impact of desmoplastic GP was independent of whether or not neo-adjuvant chemotherapy had been given[58]

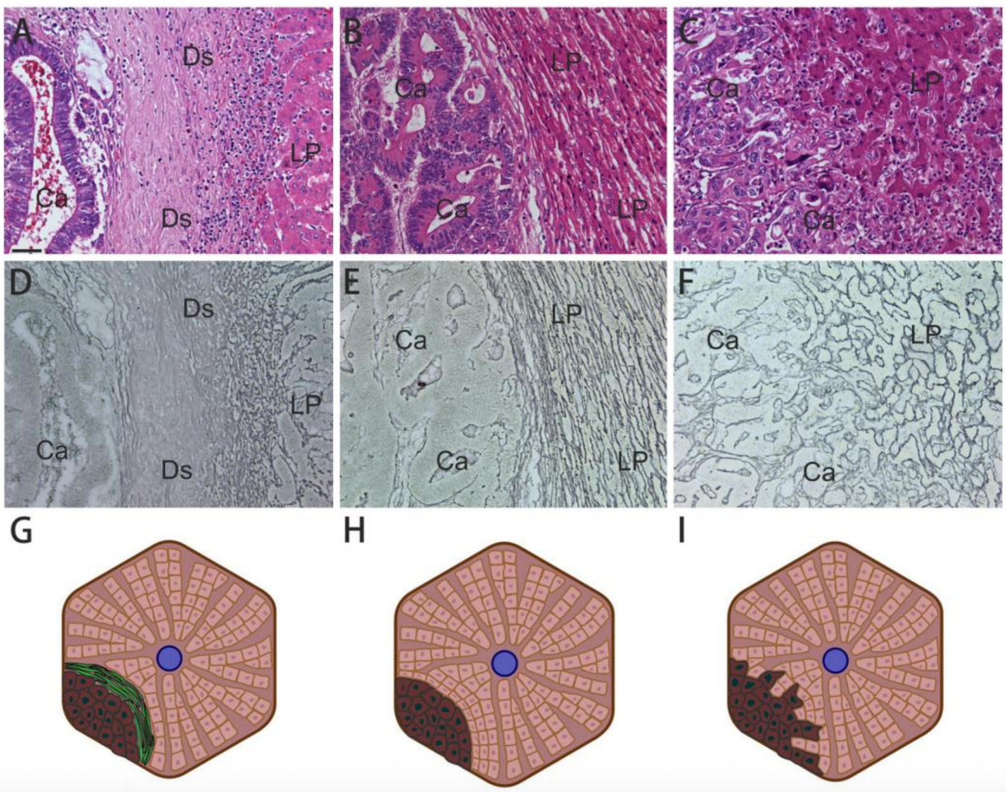


Figure. 3 Illustration of growth patterns in colorectal liver metastases. The different growth patterns are illustrated in a, b, g (desmoplastic growth pattern), b, e, h (pushing growth pattern) and c, f, i (replacement growth pattern). The mixed growth pattern is not shown, but is usually a mixture of two patterns, often including a pushing component[58].

Finally, data on the prognostic implications of vascular, biliary, perineural and lymphatic invasion in patients with CRLM are limited. Gomez et al, identified three independent predictors of DFS, mainly tumor number, perineural invasion, and resection margin. In addition, the presence of perineural invasion was the only independent predictor of poorer overall survival on multivariate analysis[47]. More recently, Park et al. found that tumor infiltrating inflammation and presence of dedifferentiation of metastatic lesion were independent risk factors for tumor recurrence after hepatic resection in CRLM[61].

In other words, the pathophysiological mechanisms behind overall and hepatic recurrence may not simplistically include inadequate margin resection, but rather they could represent the expression of cancer aggressiveness and the natural progression of micrometastatic disease from the primary tumor.

Further elucidation of the mechanisms and biological pathways involved in and responsible for the differences in GP between CRC liver metastases in different patients might lead to therapeutic agents and strategies and may contribute to a histology-based prognostic biomarker for patients with colorectal liver metastases.

Therefore, the relationship between the growth rate of CRLMs and biological features of colorectal cancer may provide additional information related to outcome pathologic prognostic markers of hepatic tumors predicting the prognosis of these patients have been identified.

2. THE STUDY

2.1 AIMS OF THE STUDY

The aim of this study was to investigate the impact of margin width resection on early liver recurrence and DFS after hepatic resection for colorectal metastasis in a consecutive series of patients from a single institution. The hypothesis of the present study was that margin width resection (R0 or R1) does not influence oncological outcomes after resection for CRLM.

In addition, the study aimed to identify other clinicopathologic prognostic factors predictors for early recurrence (defined as recurrence within 6 months of CRLM resection) and for DFS.

Moreover, the study sought to examine the pattern of early and late recurrence (intra- or extra-hepatic recurrence) of patients who were managed with curative intent resection.

2.2 MATERIALS AND METHODS

2.2.1 STUDY DESIGN AND PATIENTS' SELECTION

This is a prospective observational study, performed at the Oncological Surgery, Hospital Policlinic San Martino, Genoa, Italy from 1st April 2014 to the 1st June 2019. The study was approved by the Local Ethical Committee and met the guidelines of the local Govern-mental Agency. Patients provided written informed consent before inclusion.

Patients undergoing primary hepatic resection for colorectal liver metastasis with curative intent and having a minimum follow-up period of 6 months were included.

The selection criteria for surgery in our center included a sufficient remaining tumor-free liver volume[6, 7] with adequate blood perfusion and bile drainage, and absence of: a) non-resectable extrahepatic metastases, and/or b) no disseminated disease as evaluated pre-operatively.

Exclusion criteria for this study were patients who underwent repeat hepatic resections, who colorectal resection was not performed in our center, patients with R2 resections or Dindo-Clavien V and patients who underwent combined resection with radiofrequency ablation (RFA).

2.2.2 PREOPERATIVE EVALUATION

Before surgery, all patients were evaluated with a baseline history and physical examination, serum laboratory tests, and appropriate imaging studies. Preoperative investigations included computed tomography (CT) scan of the chest and abdomen/pelvis, and tumour marker analysis (CEA: carcinoembryonal antigen). In cases with an inconclusive CT scan, magnetic resonance imaging (MRI) of the liver, contrast-enhanced ultrasound and 18 F-fluorodeoxyglucose 18(FDG)-positron emission tomography (PET)/CT scan were performed.

Each patient was discussed in a multidisciplinary team meeting with surgeons, oncologists and radiologists and also geriatric evaluation in patients 65-year-old and older.

Preoperative chemotherapy was administered for patients with initially unresectable CRLM in the conversion setting or patients with synchronous (diagnosed before, during, or within 3 months after colorectal resection) or marginally resectable CRLM in the neoadjuvant setting.

Standard demographic and clinicopathologic data were collected for each patient including sex, age, ASA score, CEA level, comorbidity (with particular attention to chronic liver disease and cirrhosis, staging through MELD and Child-Pugh Score), as well as treatment related variables including history of preoperative chemotherapy, number of cycles.

Data were also collected on primary tumor characteristics, specifically on primary tumor location, date of resection (primary), TNM stage, genotype mutations (KRAS, NRAS, BRAF), microsatellite instability. Furthermore, the Lymph nodes ratio (LNR), defined as the ratio between positive lymph nodes and the total number of retrieved lymph nodes, was also collected for each colorectal surgical procedure. Then, date of detection of CLM and presentation (synchronous vs. metachronous), number, size and location of CLM were recorded. In the present study, diagnosis of liver metastasis within three months were considered as metachronous, even though up-to-date there is no consensus on the defining time point for synchronous/metachronous disease[62].

2.2.3 SURGICAL PROCEDURES

All patients underwent conventional open liver resection with curative intent, and to achieve complete resection (R0) while preserving as much normal functional liver parenchyma (with adequate vascular inflow, outflow, and biliary drainage) as possible. Resection of three or more segments was considered a major hepatic resection. The presence of extrahepatic tumors was not considered a contraindication to hepatic resection if the lesions were limited and resectable. Extrahepatic disease identified in the abdominal cavity was resected at the same time as hepatic resection. For extrahepatic disease located outside the abdomen, resection was performed 2–3 months after hepatectomy if the disease remained controlled with interval chemotherapy.

The operations were performed by two different surgeons. Intraoperative ultrasound of the liver was carried out in all patients. A central venous pressure less than 5 mm Hg was maintained during parenchymal transection and monitored by central venous access.

All patients received therapeutic liver resection and hepatic hilar lymph node dissection was not performed routinely. Anatomical resection was characterized as complete anatomical resection based on Couinaud’s classification (segmentectomy, sectionectomy, and hemihepatectomy or extended hemihepatectomy) in patients with an acceptable liver reserve[63]. Non-anatomical resection (atypical resection) was the first-choice type of resection, according to the concept of parenchyma spearing, but if it is not suitable, a two-stage hemihepatectomy approach, as ALPPS, has been performed. As regard synchronous metastases, primary tumor resection was combined to metastases resection balancing patient's clinical conditions and fitness for surgery and the burden and extension of metastatic disease.

Pringle maneuver had always been carried out. Intermittent portal pedicle clamping was used at the discretion of the operating surgeon (no longer than 15 minutes clamped with 5 minutes unclamped).

In general, the hepatic parenchymal transection was performed through the clamp-crush technique. Once the parenchyma is crushed, the exposed vessels and bile ducts were divided through absorbable suture or non-absorbable suture ligation. Alternatively, vascular clips for larger caliber vessels and bipolar energy device (bipolar forceps or Aquamantys®) for smaller caliber vessels were used.

When hemostasis on the liver section area is not convincing, a flap of sealant matrix of human fibrinogen/human thrombin is applied.

As regarding resection margins (RM), RM <1 mm were defined as positive (R1), in accordance with Pawlik et al[25]. In addition, RM status was obtained from the microscopic measurements in the histological reports, in which the closest distance was measured between the tumor edge and the transection surface of the liver parenchyma. Microscopically and in line with the histological reports, the widths were stratified as coincidental margins if the tumor was in contact with the surgical margin (0 mm); widths of less than, or equal to, 1 mm or greater than 1 mm.

2.2.4 POSTOPERATIVE PERIOD AND FOLLOW-UP

Postoperative complications were graded according to the validated classification criteria described by Dindo Clavien Classification[64] and the Comprehensive Complication Index (CCI®-Calculator)[65] and major complications were defined as any complication of grade III or higher.

Adjuvant chemotherapy was recommended routinely, using the same protocol as that applied before surgery.

All patients were followed up every three months for the first two years, with a physical examination, carcinoembryonic antigen (CEA) measurement, and abdominal ultrasonography. Every six months, patients underwent computed tomography scan of the abdominal/thoracic/pelvic region (enhanced MRI could replace CT) to detect any intrahepatic or distant recurrence. In accordance with previous reports[56, 57], early recurrence was defined as any recurrence (liver recurrence (LR) or extrahepatic recurrence) occurring within 6 months after liver resection.

Patient characteristics and details of surgical treatment, as margin resection width, and perioperative chemotherapy were analyzed to identify predictive factors of early recurrence.

At last date of follow-up date overall survival (OS) and DFS were also collected.

2.2.5 STATISTICAL ANALYSIS

Patients' data were collected from a prospective computerized database. The descriptive analysis for quantitative variables was expressed as median or mean and standard deviation (SD).

The association between categorical data was performed with the two-tailed Pearson $\chi 2$, or Fisher's exact test when appropriate. Student's t-test was used to analyze any significant clinical pathological differences among patients who developed early recurrence when compared to the remaining cohort.

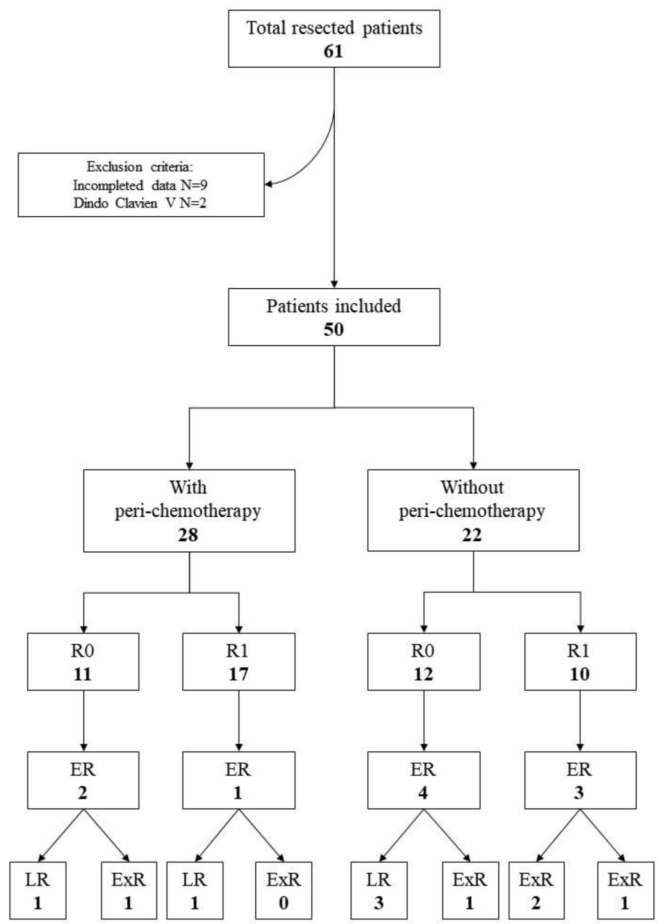
Recurrence and DFS were estimated using the Kaplan-Meier method, and any significant difference between the sub-groups noted by univariate analysis was compared using the log-rank test.

All statistical analyses were performed using the SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL, USA).

2.3 RESULTS

2.3.1. PATIENTS' DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

During the study period, 61 patients underwent primary hepatic resection for CRLM. Two patients died postoperatively within 30 days. Nine patients were excluded due to uncompleted collection data. Thus, a total of 50 patients were ultimately included in the study (Figure 4).



ER Early recurrence; LR liver recurrence; ExR extra-hepatic recurrence

Figure 4. Flow diagram of eligible patients included and excluded in the study and pattern of early recurrence.

There were 34 (68%) men and 16 (32%) women, and the median age at the time of surgery was 70 (range 38 to 86); 18 patients (35% of the sample) were age 75 or older.

More than 82% of patients had one or more comorbidities and 50% of patients had multimorbidity (i.e. CRLM plus two or more comorbidities), with a median number of drugs of 4. The most common comorbidities were diabetes, hypertension, heart failure and COPD. So, that most of patients were classified as ASA 3 (38%) or ASA 2 (42%).

Patients' clinical characteristics are illustrated in Table 1.

Table 1. Patients' demographic and clinical characteristics.

VARIABLES	**N**	**%**
MEDIAN AGE (range)	70,5 (38–86 y)	
GENDER:		
Female	16	32
Male	34	68
ASA SCORE		
1	10	20
2	21	42
3	19	38
NUMBER OF DRUGS Median (range)	4 (0-9)	
COMORBIDITY		
Diabetes	12	23
Hypertension	26	50
Heart failure	12	23
Kidney disease	1	2
COPD	6	11
Thyroid pathologies	2	4
HCV	2	4
HBV	2	4
CHILD (N=37)		
A5	32	86
A6	5	14
MELD (N=42) Median (range)		7 (6-20)
MARKERS		
CEA > 200 μg/L	6	11
CA 19.9 > 33,0	18	36
PERI-CHEMOTERAPY	28	56
• pre-operative	18	36
• Adjuvant	18	36
• Pre + adjuvant	8	16

Overall, 18 patients (36%) underwent neoadjuvant chemotherapy before liver surgery, including 83% who received neo-adjuvant fluoropyrimidine-based cytotoxic chemotherapy. In detail, 8 patients received neo-adjuvant 5FU ± oxaliplatin; 5 patients neo-adjuvant 5FU ± oxaliplatin + bevacizumab or + panitumumab (n=2). Only a minority of the patients (n = 3) received fluoropyrimidine-based treatment ± irinotecan ± cetuximab (EGFR inhibitor). Then, biologic agents such as bevacizumab, cetuximab, and panitumumab were used in 9 patients (50%). Preoperative chemotherapy included ≥ 4 cycles in all 18 patients (100 %) while ≥ 6 cycles in 13 (72%) patients.

2.3.2 CLINICOPATHOLOGIC CHARACTERISTICS OF THE PRIMARY AND METASTATIC TUMORS

Table 2 illustrates primary and metastatic tumor characters. With respect to primary colorectal cancer characteristics, almost 54% of the sample had a primary colon tumor, while 46% had a primary rectal tumor. In terms of pathologic stage, most patients had T3–T4 tumors (n = 48; 96%), lymph node metastasis (n = 28; 56%). During the primary resection, the median number of lymph nodes removed per patient was 20 (range: 9–55).

Thirty-three patients (69%) had moderately differentiated colorectal tumors (G2), while 8 (16%) poorly differentiated tumors (G3 e 4).

In 36 patients were available the genotype analysis of KRAS and BRAF mutation. KRAS and BRAF mutations were detected in 30.5% and 0.5% of the cases, respectively. Indeed, all patients reported microsatellite stability (MSS).

In 33 patients (66%), the presentation of liver metastasis was synchronous with the primary while 17 patients (34%) had metachronous liver metastasis with a median disease-free time of 11 months.

The median number of liver metastasis was 1 (range 1 to 10). Sixty-three per cent of patients had a solitary liver tumor, while 19 patients (37%) had ≥ 2 tumors and 73% of patients had tumors measuring <5 cm.

Most patients had bilobar hepatic disease (68%) while six patients confined to only one hemi-liver (32%). Indeed, the most prevalent growth pattern distribution were the pushing GP (39%), the mixed GP (39%) and the replacement (18%).

Table 2. Clinicopathologic characteristics of the primary and metastatic tumors

PRIMARY TUMOR	**N**	**%**
LOCATION		
Ascending Colon	17	34
Descending Colon	10	20
Rectum	23	46
NODE STATUS		
Positive	28	56
Negative	22	44
GRADING (N=48)		
Gx	7	15
G1	0	0
G2	33	69
G3	7	15
G4	1	1
METASTASES		
NUMBER median	1 (range 1-14)	
1	33	66
2-4	13	26
>5	4	8
TIMING		
Synchronous*	33	66
Metachronous	17	34
TUMOR SIZE (cm)		
<5 cm	37	74
>5 cm	13	26
DISTRIBUTION (N=19)		
Unilobar	6	32
Bilobar	13	68
CRS FONG		
0	5	10
1	12	24
2	15	30
3	14	28
4	4	8
5	0	0
GROWTH PATTERN (N=33)		
Desmoplastic	1	4
Pushing	13	39
Replacement	6	18
Mixed	13	39

*diagnosis of liver metastasis within three months

2.3.3 SURGICAL RESECTIONS AND POSTOPERATIVE RESULTS

Surgical treatment was conventional open liver resection with curative intent in all patient. The distribution of type of hepatic resections is shown in Table 3.

Patients undergoing combined surgery were 16 (32%), one patient was submitted to staged liver resections and underwent portal vein embolization. The most common surgical resections performed in this series were single and multiple wedge resection, counting for the almost 80% of the total procedures.

The blood transfusions were made only in two cases during surgery, while during the postoperative period seven patients were treated with antiplatelet agents.

The Pringle maneuver was used in all patients, and when needed, the median of time of application was 38 min (5-80 min).

The median length of hospital stay was 9 days (range 6 to 27). Intensive care admission after surgery was needed in 13 (26%) patients, but only for the first 24 hours.

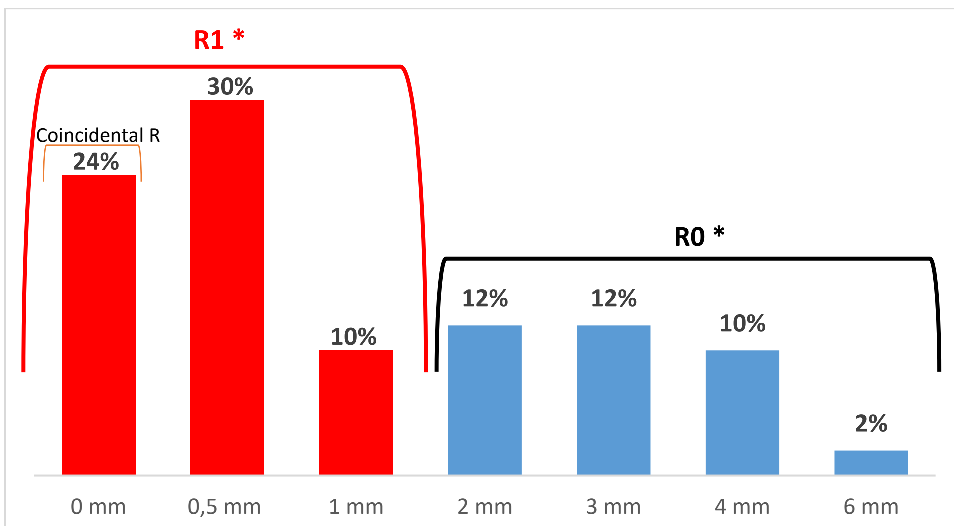
As regarding resection margins, the mean resection margin in all patients was 1.4 mm ± 1.5 mm, which reflects a parenchyma-sparing operative approach. Margin status was unknown only in one patient. The distribution of RMs, defined as positive (R1) if ≤ 1 mm according to Pawlik et al.[25] was represented in Figure 5. An R0 resection was achieved in in 23 (47%) patients and an R1 resection occurred in the remaining 26 (53%) patients. Histological reports categorized 24% patients as coincidental margins (0 mm); 40% with margins greater than 0.1 mm to 1 mm; 36% with margins greater than 1 mm; and no patients with margins greater than 1 cm.

Table 3. Types of surgery and resection margin status.

SURGERY	**N**	**%**
Segmentectomy	7	14
Single wedge resection	25	50
Multiple wedge resection	14	28
Subsegmentectomy	1	2
Hemihepatectomy	2	4
Two stage hemihepatectomy-ALPPS	1	2

SIMULTANEOUS CRC RESECTION	16	32
OTHER SURGERY	21	42
• colecistectomy	12	24
• intestinal resections	2	4
• abdominal wall surgery	5	10
• stoma closure	3	6
ONLY LIVER SURGERY	15	30
IBL (mL)		
≤ 250	40	80
250-500	6	12
>500	4	8
IBL Median (range) [ml]	125 (15-800)	
MARGIN STATUS (N=49)		
0 mm	10	20
0 - 1 mm	16	33
≥ 1 mm	23	47
OPERATING TIME MEDIAN (range) [min]	162 (55-345)	
Liver section time Median [min]	50 (10-120**)**	
HOSPITAL STAY Median (renge) [day]	9 (6-75)	

Abbreviations: CRC colorectal cancer; IBL intra-operative blood loss



Abbreviations: R: resection; * according to Pawlik[25].

Figure 5. Histograms of distribution of margin resection width that were recorded in pathology reports.

Within 30 days of surgery, 36 patients (72%) developed ≥1 medical or surgical complication, either during the hospitalization or after discharge, without leading to readmission (Table 4). The most common complications were minor (50%), or even classified as I -II grade according to Dindo-Clavien classification[64]. Actually, although resection may be associated with liver-related complications such as hemorrhage, bile leak and liver insufficiency, these complications were uncommon and only 22% were major complication (> III grade). Bile leak and abscess at the resection site were the most frequent (8% and 6% respectively) and they required to be treated with percutaneous drainage placement. Reoperation occurred in three cases but as complication related to colorectal surgery (2 patients who developed anastomotic leak and one patient whit obstruction bowel). Indeed, no bleeding occurred in this series and the median perioperative blood loss was 100 ml (15-800). Nevertheless, most complications in this series were pulmonary (14%) and renal (18%).

Although there seemed to be an increased length of hospital stay in parallel with the degree of severity of the complications according to Dindo-Calvien classification (Figure 6), these difference did not reach the statistically significance (no complications 8.4 days; I-II grade 10.6 days and III-IV grade 13.3 days; $p<0.2$).

The distribution of complicated patients according to Comprehensive Complication Index (CCI) is shown in Figure 7, in which each complication grade is designated to prefixed scores (grade I = 8.7, grade II = 20.9, grade IIIa = 26.2, grade IIIb = 33.7, grade IVa = 42.4, grade IVb = 46.2). As the majority of grade I and grade II complicated patients showed a single complication, the median CCI was 12.2 (range 0-62.9). Indeed, high CCI scores were positively correlated with prolonged hospital stay (Pearson correlation $t = 2.15$, $df = 36$, p-value <0.03; 95%CI: 0.02 - 0.59; cor 0.33) (Figure 8).

Table 4. Incidence and severity of all postoperative complications.

	N of patients [n=50 (%)]
Postoperative morbidity by severity	
No complications	14 (28)
Minor complications	25 (50)
Major complications	11 (22)
Complication grade (Dindo-Clavien classification)	
I	13 (26)
II	12 (24)
IIIa	8 (16)
IIIb	1 (2)
IVa	2 (4)
Comprehensive complication index (CCI)	12.2 (0-62.9)
Types of post-operative morbidity	
Pulmonary	

Pleural effusion	5 (10)
Pneumonia	2 (4)
Gastrointestinal	
Bile leak	4 (8)
Abscess	3 (6)
Bowel obstruction	1 (2)
Leakage anastomotic	2 (4)
Hiccup	1 (2)
Systemic	
Delirium	7 (14)
Sepsis	2 (4)
Cardiac	
Heart failure	3 (6)
Dysrhythmias	2 (4)
Urogenital	
Acute renal failure	9 (18)
Urinary retention	7 (14)
Wound	
Infection	2 (4)
Perioperative blood loss [ml]	100 (15-800)
HOSPITAL STAY Median (range) [days]	9 (6-75)
Length of hospital stay [days]	
≤ 6	4 (8)
> 6	46 (92)
Reoperation	3

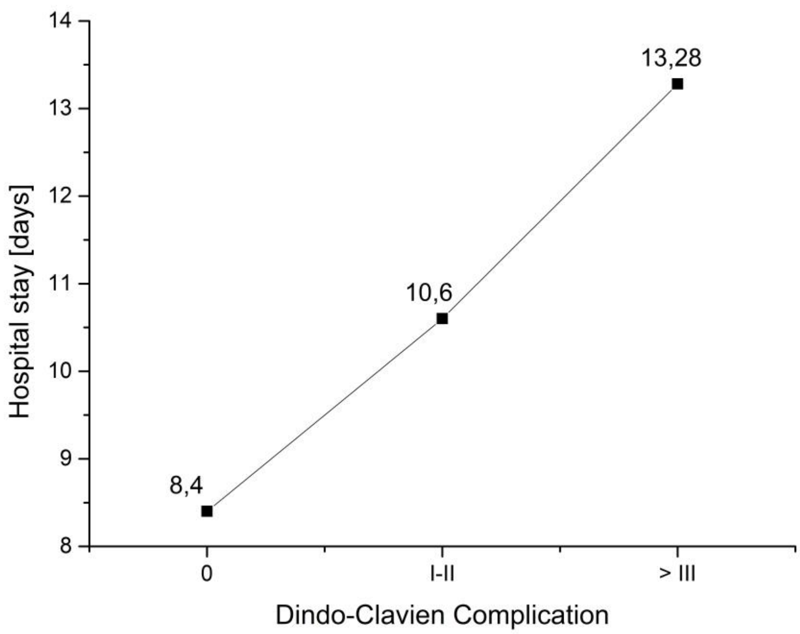


Figure 6. Distribution of the mean length of stay according to Dindo-Calvien Classification.

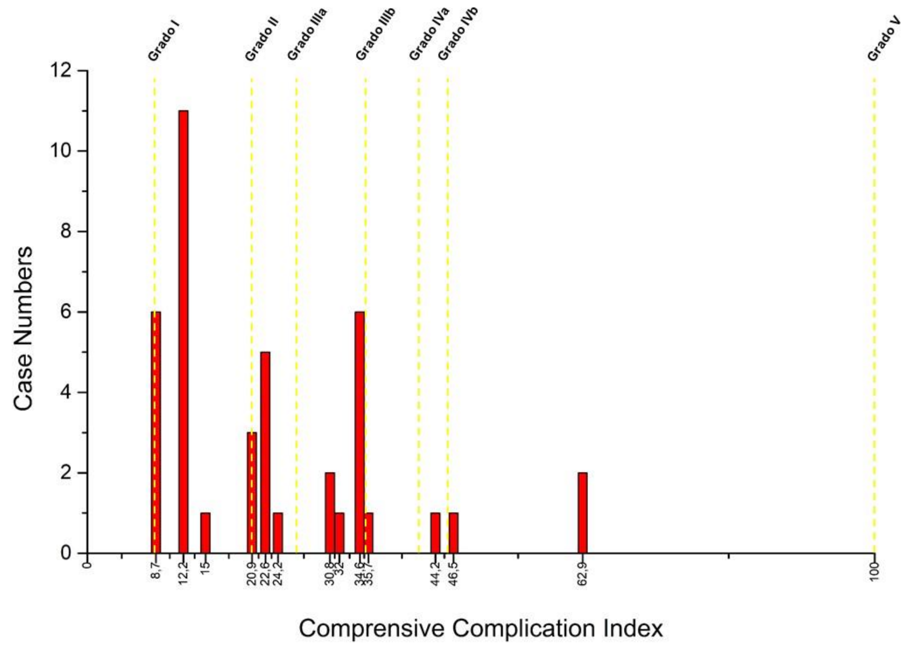


Figure 7. Overview of comprehensive complication index (CCI).

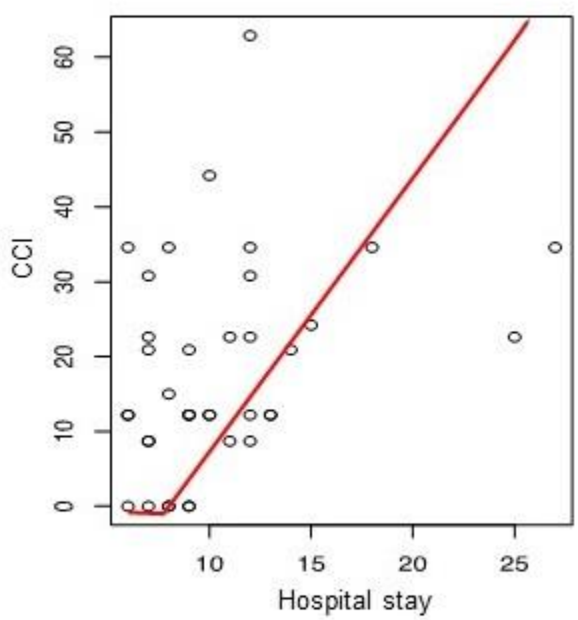


Figure 8. Correlation between length of stay in days and Comprehensive Complication Index (CCI).

2.3.4 DISEASE RECURRENCE AND OVERALL SURVIVAL.

The overall median follow-up period in this study sample was 23 months (range: 2-70 months).

At the end of the follow-up, as of January 2020, 34 (68%) patients were alive, of which 21 (61%) disease-free. Sixteen (32%) patients died, of which 6 (37,5%) died of cardiovascular causes while 10 patients reported cancer related death. In these letter cases, the mean DFS and OS were 13 ± 8 months and 25 ± 17 months, respectively.

During the follow up period, recurrence after liver resection was documented in 24 patients (48%) (Appendix A). Recurrence rate within the first year was 38% (19 patients) (Figure 9), and only 2 recurrences were found after the second year from liver surgery. One-year and two-year mortality were 12% and 22%, respectively.

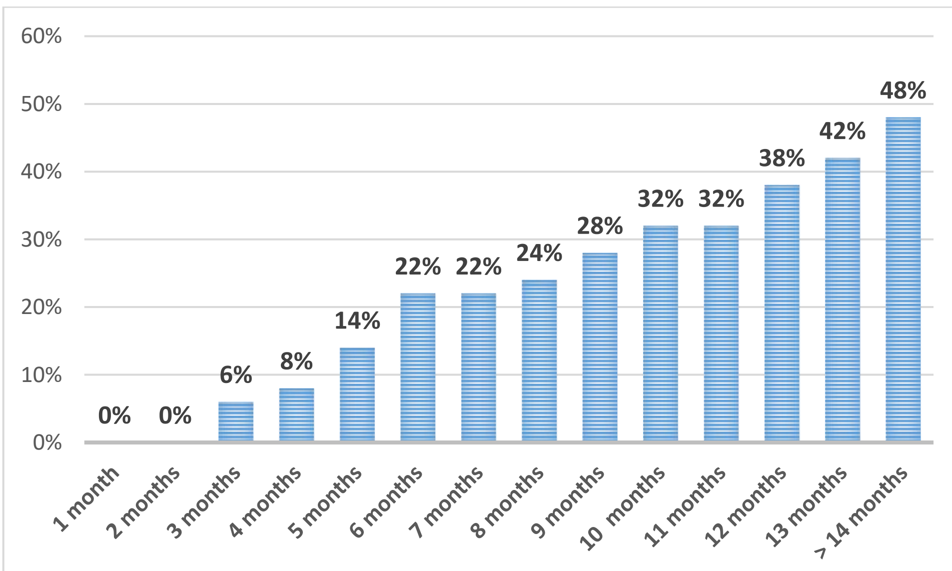


Figure 9. Distribution of rate of recurrence during the follow up period.

Early recurrence (within 6 months after liver resection) occurred in 11 patients (22% of the sample and 46% of the total recurrences), including 4 patients (36%) with liver-only recurrence and 7 patients (63%) with systemic recurrence (with or without liver recurrence) (Figure 10).

There was no difference in hepatic recurrences in the early recurrence group than in the late recurrence group (50% vs. 50%; p =0.8), neither in extra-hepatic recurrences.

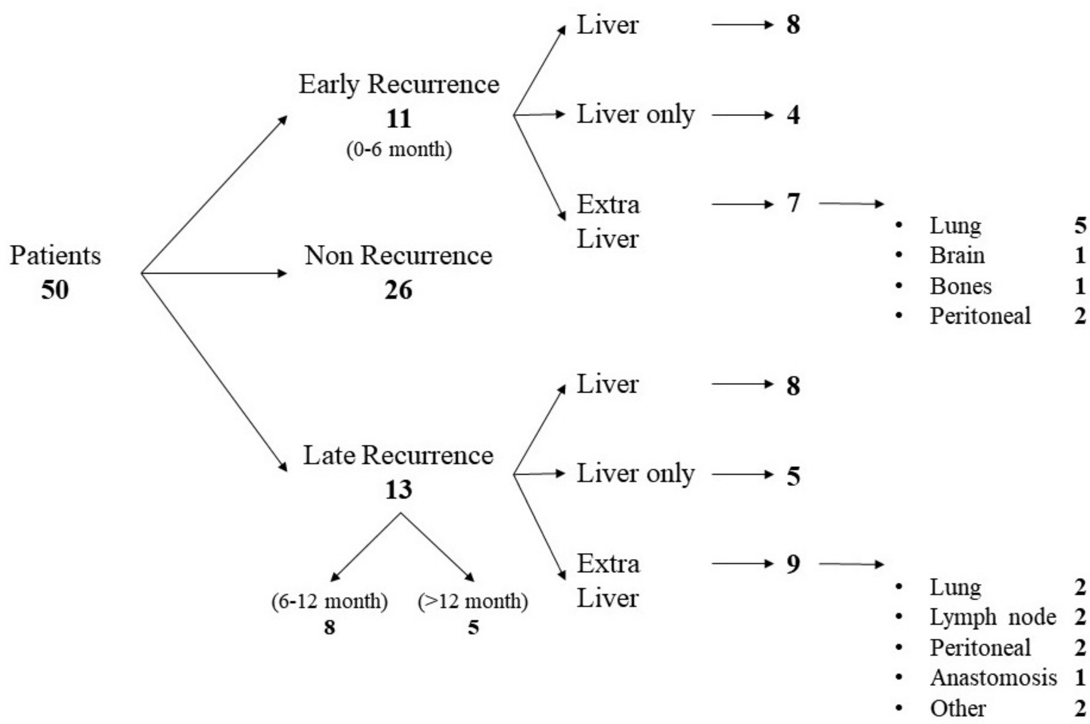


Figure 10. Pattern of early and late recurrence.

2.3.5 FACTORS ASSOCIATED TO EARLY RECURRENCE AND DISEASE-FREE SURVIVAL: UNIVARIATE ANALYSIS

Clinical characteristics of the involved patients and results of the performed univariate analysis of registered clinical factors are shown in Table 5. According to univariate analysis, no significant differences were found in early recurrence and DFS between gender, location of the primary tumor, number and size of resected liver metastases, growth pattern and KRAS wild type.

Time of diagnosis of liver metastases was the only significant prognostic factor for both DFS and for early recurrence.

Moreover, histological grade of primary tumor (G2:33% vs. G3:86% vs. G4:100%; p<0.040) and synchronous presentation of liver metastases (80% vs. 20%; p<0.037) were associated with shorter DFS.

There was a slightly significant association between the severity of postoperative complication and the occurrence of a recurrence disease (p<0.08; Table 5). Indeed, patients who developed severe postoperative complications (grade III and IV Dindo-Clavien) reported a mean DFS of 479 days versus 312 days in the subgroup of patients who had complication grade I-II (p<0.06) (Figure 11).

Table 5. Univariate analysis of prognostic factors on early recurrence and DFS.

Parameter	**DFS [n (%)]**	***p* value**	**ER [n (%)]**	***p* value**
Gender		0.269		0.900
Male	14 (42)		7 (63)	
Female	10 (58)		4 (37)	
Location of the primary tumor		0.950		0.307
Ascending Colon	9 (36)		3 (27.3)	
Descending Colon	5 (20)		4 (36.4)	
Rectum	11 (44)		4 (36.4)	
Primary tumor staging		0.232		0.625
I	1 (4)		0 (0)	
IIA	4 (16)		3 (27.5)	
IIB	0 (0)		0 (0)	
IIIB	7 (28)		1 (9)	
IIIC	0 (0)		0 (0)	
IVA	11 (44)		6 (54.5)	
IVB	2 (8)		1 (9)	
Primary Regional lymph node metastasis		0.08*		0.425
Negative	8 (32)		6 (54.5)	
Positive	17 (68)		5 (45.5)	
Grading		**0.040**		0.490
G2	12 (33)		6 (54.5)	
G3	6 (86)		3 (27.3)	
G4	1 (100)		0	
Gx	5 (20.8)		2 (18.2)	
Number of liver metastasis		0.370		0.862
Solitary	18 (72)		8 (24)	
Multiple	7 (28)		3 (18)	
Time of diagnosis of liver metastases		**0.037**		**0.048**
Metachronous	5 (20)		10 (90)	
Synchronous	20 (80)		1 (10)	
Maximal diameter of the largest metastasis		0.747		0.913
<5 cm	19 (76)		8 (73)	
≥5 cm	6 (24)		3 (28)	
Growth pattern		0.668		0.725
Desmoplastic	0 (0)		0 (0)	
Pushing	7 (46.7)		4 (57)	
Replacement	2 (13.3)		1 (14)	
Mixed	6 (40.0)		2 (29)	

Surgical margin*		0.759		0.763
R1	10 (42)		6 (55)	
R0	14 (58)		5 (45)	
Surgical margin stratified in mm		0.560		0.546
0 mm	5 (22)		3 (30)	
0.1 – 1 mm	9 (39)		2 (20)	
> 1mm	9 (39)		5 (50)	
CRS		0.084*		0.162
0	0 (0)		0 (0)	
1	8 (32)		5 (45.5)	
2	6 (24)		1 (9.1)	
3	8 (32)		4 (36.4)	
4	3 (12)		1 (9.1)	
5	0 (0)		0 (0)	
KRAS		0.418		0.123
Wild type	10 (62.5)		2 (40)	
Mutated	6 (37.5)		3 (60)	
CEA		0.384		0.475
< 200 ng/ml	21 (84)		8 (73)	
≥ 200 ng/ml	4 (16)		3 (27)	
CT neo-adjuvant		0.239		0.163
No	18 (72)		9 (82)	
Yes	7 (28)		2 (18)	
CT adjuvant		0.239		0.977
No	14 (56)		7 (64)	
Yes	11 (44)		4 (34)	
Postoperative Complications**		0.082*		0.314
0	7 (28)		2 (18.2)	
I	10 (40)		3 (27.3)	
II	3 (12)		2 (18.2)	
IIIa	4 (16)		3 (27.3)	
IIIb	1 (4)		1 (9)	
IVa	0 (0)		0 (0)	

Abbreviation: CRS Clinical Risk Score (Fong et al.[33])
Note: *according to Pawlik[25]; **Dindo Clavien classification[64].

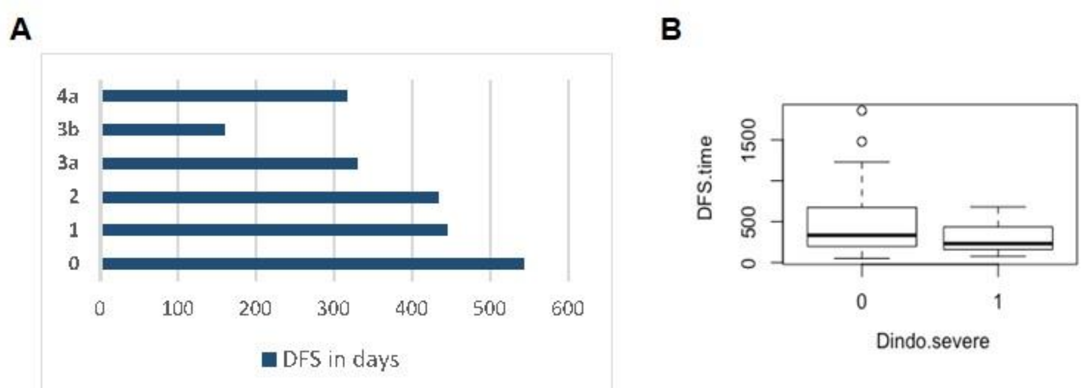


Figure 11. Distribution of mean DFS in days stratified by postoperative complication according to Dindo-Clavien Classification (**A**) and boxplot comparing group of patients with Dindo-Clavien I-II and with Dindo-Clavien III-IV (**B**).

Patients with a resection margin of ≥1 mm presented shorter DFS compared with those with margin < 1 mm, with median survival of 13 months and 16 months, respectively. However, there was no statistically significant difference between the R0 and R1 groups and even between the stratification of surgical margin size in relation to the DFS and early recurrence. Indeed, patients with wider-margin groups showed similar trend of recurrence in comparison with the narrow-margin group. This is confirmed by the overlapping Kaplan–Meier curves demonstrated in Figure 12 A and B.

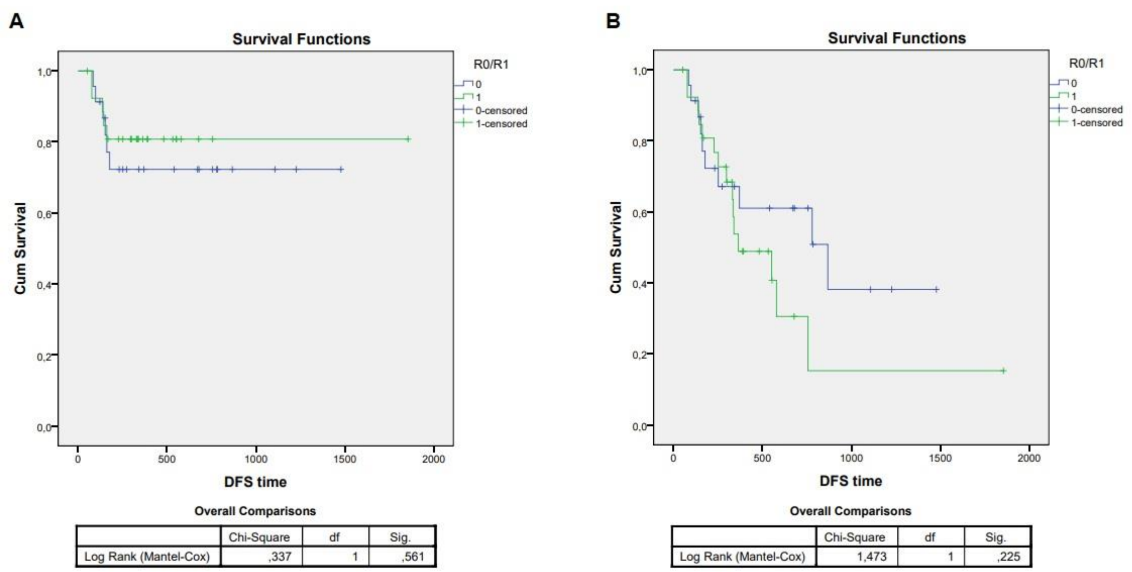


Figure 12. Kaplan-Meier curve comparing early recurrence (**A**) and DFS (**B**) after resection of colorectal liver metastases in patients with resection margin status R0 versus R1.

2.4 DISCUSSION

Liver resection, combined with modern chemotherapy, is considered the standard treatment for patients with resectable CRLM. Along with the advances in perioperative care, resectability and the overall survival of the patients with colorectal liver metastasis have shown remarkable improvements. However, the recurrence of hepatic metastasis after liver resection remains a concern worldwide.

An increasing number of complex resections are performed in which the extent of hepatic involvement frequently mandates close resection margins. Nevertheless, the prognostic significance of margin status still remains unclear, mainly in the relationship with the risk of early recurrence. Therefore, the optimal margin width represents a challenging issue in hepatic surgery.

In this study, we presented data from a single-center experience on hepatic resection of colorectal metastases with a minimum follow up of 6 months and an average 23 months.

Early recurrence rates were reported at about 21% in a previous large-scale study[50] and our cohort of patients showed similar early recurrence rates (22%). Conversely, other reports described excellent outcomes, as in Jung's study in which early recurrence occurred in 10,8% patients[34] or in the LiverMetSurvey in the 10,6%[43]. Anyway, recurrence after resection remains a common event after liver resection. In fact, recently Imai found that in patients who received preoperative chemotherapy, early recurrence (within 8 months) reached the 45% and age, number of preoperative chemotherapy lines, response to last-line chemotherapy, number of tumors, and CA19-9 at hepatectomy were identified as independent predictive factors for early recurrence[44].

These different results in recurrence rate may be due to the clinical and methodological heterogeneity of the published studies, in term of single institution enrollment, small sample size, exclusion/inclusion of patients with extrahepatic disease and different span time of follow up. Moreover, the cutoff value used to define early recurrence varied in different series, ranging from 4 months to 18 months[40, 42, 44]. However, in the present study early recurrence was defined as a relapsed disease within 6 months, which is the most commonly adopted definition [56, 57].

In the present study, several clinical, pathological, and surgical factors have been tested for correlation with early recurrence and DFS in univariate analyses with a specific focus on the impact of resection margin depth.

Time of diagnosis of liver metastases was the only significant factor related to early recurrence, whereas only two variables showed significant relevance in the occurrence of DFS. In details, patients with poorly differentiate tumor and synchronous metastasis tended to have disease recurrence compared to patients with G1-2 or metachronous lesions. These results were in accordance with previous report[50], suggesting that the difference in prognosis was not merely related to the time of detection in the disease progress, but synchronous metastasis might represent a more disseminated disease, compared to metachronous metastasis. This tendency to spread, leading to earlier recurrence and worse prognosis, could encourage to give more intense follow-up and adjuvant chemotherapy after liver resection in the synchronous group of patients[66].

Furthermore, there was no significant difference in recurrence disease according to the three different histological patterns of the tumour-liver interface of CRC liver metastases, termed pushing, replacement and desmoplastic growth pattern. This feature was in contrast with previous studies [58-60] but probably the lack of consistency was due to the high prevalence in our sample of the pushing and mixed growth pattern.

The present study examined also the impact of postoperative morbidity, establishing that patients who experienced a complication had an increased risk of recurrence. Mainly, the severity of the complication correlated with outcome as patients with more severe complications (grade III and IV) had the worse DFS.

The overall morbidity rate in the present study was not consistent with other previous series, in which complication rate is lower, about 22%[67] or 30%[68]. The high rate of complications was probably due to the peculiar phenotype of enrolled patients, characterized by older adults with a median age 70.5 years and with several comorbidities and associated polypharmacy (with a mean number of drugs of 4). Interestingly, the median age of the present study was almost ten years higher than the current reports in the field of colorectal liver metastasis surgery.

Anyway, even though the elevated overall postoperative morbidity, our series reported a median CCI of 12.2, describing complications of very modest severity. In other term, they corresponded to two complications of grade I, which were probably related to organ dysfunction secondary to patient's premorbid conditions.

Differently from Dindo-Clavien Classification, in the present study CCI positive correlated with the length of stay. In fact, while Dindo-Clavien grading is based only on the most severe forms of complications and ignores other minor complications, the key feature of the CCI is the mathematical summation of all complications, displaying a continuous figure from 0 (no complications) to 100 (death)[65], that measured the overall magnitude of all complications. In line of these considerations, the continuous monitoring of the CCI can mirror surgical performance and provide feedback to the surgeon.

Few previous studies examined the association between the severity of complications and short-term and long-term outcomes, rarely focusing on DFS and reporting conflicting results. The current study supported the notion of reduced DFS in patient who had severe postoperative complications. It has been hypothesized that major abdominal surgery initiates a systemic inflammatory response characterized by raised levels of inflammatory cytokines such as interleukin. Complications may further perpetuate an inflammatory response, thereby maintaining a state of immunosuppression, that promote cancer growth and may be responsible for such poor prognosis.[67]. In particular, severe infectious complications like septicemia lead to an extended period of immunosuppression, which allows residual tumor cells to further proliferate and survive in the host[69]. Indeed, patients who experience postoperative complications might be unable to undergo postoperative chemotherapy.

In line with that a preoperative optimization, meticulous surgical technique and careful management in the postoperative period became a key issue in CRLM surgery, able to reduce the incidence of complications and influencing long-term outcomes.

As regard the main objective of this study, no significant differences were found in the early recurrence rates and disease-free survival in R1 versus R0 patients. Indeed, no significant difference was found between coincidental margins (0 mm) or wider margins with regard to DFS and to early recurrence (Table 5). So, the study supports the concept that the width of cancer-free resection margin is not important in modern liver resection practice, showing that 1-mm margin is sufficient for cure of patients with resectable CRLM.

About twenty years ago, important studies overwhelmed the historical concept that 1.0-cm margin was not an absolute requirement for a curative approach in the treatment of patients with colorectal cancer liver metastases. In the early 2000s both Kokudo et al. and Pawlik et al. found that even 2-5 mm and 1-4 mm is enough to improve survival[24, 25]. In 2008 Haas et al. were one of the first to publish a follow-up study including nearly 500 CRLM resected patients and suggested that the survival of patients who had R1 resection was similar to those who underwent R0 resection, despite a higher recurrence rate[29]. Whereas several authors agree that R1 resection is associated with a higher local recurrence risk[29, 70, 71], other studies stated that R1 margin status was not associated with survival after controlling for competing risk factors[72]. Bodingbauer et al. found that the sub-centimeter surgical margins were not an independent risk factor for recurrence[73].

These controversies regarding the optimal width of surgical margins indicate that other biological factors could be involved in the physiopathology of recurrence. The development of recurrence and life expectancy after liver resection depend on the complex interaction between the tumor biology of the primary colorectal cancer, treatments' plan and patient response. Cucchetti et al. observed a significant relationship between doubling time in the primary tumor and CRLM growth rate. Mainly, the fast-growing tumors, that showed a peak for recurrence within the first year after surgery up to 7%, represented a form of aggressive colorectal cancers that may have already seeded in the liver and other organs. Of outmost importance, this aggressiveness is maintained after hepatectomy and might account for high rates of early recurrence[54].

Indeed, if an R1 margin was simply due to surgical failure, the risk for recurrence should be high early after surgery and then decrease over time. Instead, it remained consistently above that for R0 margins, suggesting that an R1 margin reflects a more advanced tumor burden with higher metastatic potential over the entire postoperative time period[54].

Similarly, in the present study, the lack of association between R1 status and DFS or early recurrence disease suggested that R1 margin status may be a surrogate indicator of advanced and/or more extensive disease. Even exploratory in nature, the present study demonstrated that tumor biology (in term of grading and synchronous metastasis) rather than R1 resection was associated recurrence disease. As such, the negative impact of R1 status on DFS may not derive from the leaving of microscopic tumor cells at the surgical margin, but, rather, from the more aggressive biological phenotype that makes extirpation of the tumor with negative surgical margins more difficult.

Surgical resection of colorectal liver metastases should nowadays be focused on the recurrence-free survival time rather than the overall survival time, as it is known that in the era of efficient chemotherapy the long-term outcome benefit conferred by R0 resection disappeared. Up to date, the risk of an R1 resection should not be considered a contraindication to surgery with curative intent, as neoadjuvant chemotherapy may destroy peripheral micrometastases before liver resection, minimizing consequently the residual micro-metastatic disease[74]. In line with that, Ayez and colleagues supported that the correlation between the width of the surgical margin and survival was only applicable in patients who did not receive preoperative chemotherapy[30].

Even exploratory in nature, the strengths of the present study are its prospective nature, the choice of a short-term oncological outcome, mainly the early recurrence disease, which has been scarcely investigated in the field of colorectal liver surgery and the effort to analyze numerous factors potentially related to DFS. Another strength of this study is the analysis of a “real-world” population, characterized by an advanced age compared with previous study and affected by a multimorbidity. This complex biological phenotype is not found in clinical trials where highly selected populations are generally enrolled. Moreover, in these series, all patients received surgery for both primary colorectal cancer and for liver resection in our center.

Interestingly, the mean resection margin in our cohort of patients was 1.4 mm ± 1.5 mm, and the majority of parenchymal sparing are ≤ 1 mm. These features reflected an extreme parenchyma-sparing operative approach, if compared with the contemporary literature, and suggested that the possibility of achieving a minimum size of the surgical margin strictly depend on the experience of the surgeon and the applied resection technique. It is noteworthy that diverse transection techniques may create a margin of different character and it has been repeatedly reported that certain transection technique, as in the case of CUSA (Cavitron Ultrasound Surgical Aspirator), may distort the margin edge by aspirating or ablating a few mm of surrounding hepatic tissue. Consequently, pathologic assessment may tend to underestimate margin width and overestimate the frequency of R1 resections in such cases. In a recent Cochrane meta-analysis, assessing the benefits and risks of the different techniques of parenchymal transection during liver resections, clamp-crush technique is advocated as the method of choice in liver parenchymal transection in comparisons with CUSA or with radiofrequency dissecting sealer (RFDS)[75]. Unfortunately, in our study Kelly clamp liver transection technique was used in all the series, not allowing any possible comparison.

The main limitations of our study include, in the first place, its small size and “single-centre" nature, that poses the risk of a bias selection. Moreover, during the study period that spanned over 5 years, starting from 2014, the center acquired a progressive specialization in the field of hepatobilary surgery. The centralization of complex surgical procedures has been proposed to optimize short- and long-term outcomes of liver surgical procedures and it is strictly correlated with hospital volume. Viganò et al. demonstrated that patients managed by HPB referral centers at the first moment of the diagnosis have several benefits compared with those initially managed in non-HPB referral hospitals: shorter chemotherapy, better disease control, fewer surgical procedures, and, most importantly, longer survival[76].

Finally, the present study enrolled a cohort of patients treated with different neoadjuvant or adjuvant chemotherapy plans and the response data for preoperative chemotherapy were not routinely recorded at our institution. For this heterogeneity, an analysis regarding the effect of chemotherapy in relation to recurrence disease has not been performed and it will be investigated in future researches.

2.5 CONCLUSION AND FUTURE DIRECTIONS

Due to the broadening indication of CRLM resection, the preferred surgical technique should be a parenchymal-sparing non-anatomic resection using modern surgical devices to keep as much liver parenchyma as possible. Many studies have attempted to define factors predicting survival and non-recurrence after hepatic resection in patients with colorectal liver metastases, but there is still debate over which groups of patients benefit from surgery. As surgery remains the only curative treatment, a careful patient selection and a judicious use of adjuvant therapies prior to and after surgery are crucial to continue offering patients with CLM a real chance of a cure. The identification of those patients at risk of early recurrence development, failing to benefit from surgery, may help select patients to undergo further detailed pre-operative radiological staging of the disease.

Future study will need to consider the tumor margin microenvironment as well as other indicators of underlying tumor biology, or stratifying patients according to gene mutation status. These kinds of researches might shed light on the creation of new scores overwhelming the current models proposed by Fong and colleagues[33] and leading to a better selection of patients who could truly benefit from surgery.

Concluding, since surgery represents only one of the most decisive step of the treatment of this complex oncologic disease, a multidisciplinary team becomes a key feature in its managing. Each professional figure (oncologist, surgeon, radiologist and pathologist) should demonstrate high expertise and competence in liver metastasis management, as the only effective strategy able to guarantee short term and long term oncological and survival outcomes.

3. APPENDIX

Appendix A. Clinicopathologic characteristics of the 24 patients with recurrence.

ID patient	Gender	Age	LN*	Onset**	Number of metastasis	GP	FU status	OS	Site recurrence	DFS
1	F	82	+	S	1	NA	Death	423	Liver, lung	140
2	F	65	+	S	1	NA	Death	366	Lung; lymph node	340
3	F	70	+	S	1	NA	Death	1056	Peritoneal	370
4	M	59	+	S	1	NA	Death	1581	Liver; pelvis	868
5	M	58	-	M	1	NA	Recurrence	1781	Liver	298
6	M	59	+	S	2	Pushing	Death	1581	Liver; other	780
7	M	58	-	M	2	Mixed	Recurrence	1781	Liver	162
8	M	86	-	M	1	Pushing	Death	268	Liver	252
9	F	75	-	S	1	Pushing	Death	218	Liver	162
10	F	74	+	M	1	Mixed	Recurrence	1468	Liver	331
11	F	68	+	S	1	Mixed	Death	660	Liver	335
12	F	38	-	S	1	NA	Death	879	Lung; brain	153
13	M	77	+	S	1	NA	Recurrence	435	Lymph node	252
14	M	74	+	S	1	Pushing	Recurrence	249	Liver; lung; bones	98
15	M	76	+	S	1	NA	Recurrence	1060	Lung	177
16	F	76	-	S	1	NA	Recurrence	1067	Liver	137
17	M	86	+	M	1	Mixed	Recurrence	783	Liver	228
18	F	43	+	S	4	NA	Recurrence	706	Anastomosis	364
19	M	79	+	M	3	Replacement	Death	670	Liver	278
20	F	55	+	S	1	Mixed	Recurrence	691	Liver; peritoneal	579
21	M	74	-	S	3	Mixed	Recurrence	680	Liver	144
22	M	53	+	S	1	Pushing	Recurrence	598	Lung	77
23	M	65	-	S	1	Pushing	Recurrence	598	Liver; peritoneal	85
24	M	55	+	S	14	Replacement	Death	743	Liver; peritoneal	77

Abbreviations: *onset: Synchronous or Metachronous; GP: Growth pattern; **LN: lymph node metastasis of the primary tumor; NA: not available.

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