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PROGNOSTIC FACTORS IN HEPATIC SURGERY FOR COLORECTAL METASTASIS

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BACKGROUND

❖ Liver metastasis and surgical resection

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer death in the world (1, 2). Approximately 20% of patients with CRC already have metastases at diagnosis, and nearly 35% of patients with colorectal cancer will develop advanced metastatic disease (3). Metastatic colorectal cancer has historically been associated with poor survival and, without treatment, median survival is less than 12 months and 5 years survival is less than 10% (4). Over the last 20 years the treatment of metastatic CRC has changed in terms of closer follow-up after primary tumor resection with clinical presentation of metastatic disease at earlier stage, improvements in the efficacy of systemic therapies, increased number of patients candidate for surgical resection and multidisciplinary approach with integration of multiple specialists. This changes have led to median overall survival of almost 30 months and 50% at 5 years in recent series, more than double that 20 years ago (3-5).

Oligometastatic disease may be defined as the localization of the disease to a few sites and lesions. The liver is the most common site of metastasis from CRC (6); this is thought to be due to the venous drainage of the colon and rectum. In patients with metastatic CRC, the liver is the sole organ with metastases in approximately one-third of patients. Depending on the resectability of the metastases, patients with liver metastases from CRC have different prognosis. The lungs are the second most common site of distant metastases from CRC. Previous studies have shown that 10%-15% of patients with CRC develop lung metastases during the course of the disease (7). Compared to colon cancer, patients with rectal cancer are at a higher risk of synchronous and metachronous lung metastases, probably due to direct spread of rectal cancer into systemic circulation through the hemorrhoidal veins (6).

Even in the absence of randomised controlled trials comparing surgical with non-surgical disease management, surgery has become the standard treatment approach for patients with resectable oligometastatic disease (3).

Clinical presentation of colorectal liver metastasis is widely heterogeneous with single lesion, multiple lobar lesions or multiple bilobar lesions. Surgery for CRLM has become the standard of care, as it provides the best chance for durable cure and should be directed towards complete (R0) resection whenever possible. The role of hepatic resection as a potentially curative therapy for appropriately selected patients with metastatic colorectal cancer has been established with an actual 10- year cure rate documented in at least 1 in 6 patients. Several large single- and multi-institutional experiences have shown 5-year overall survival rates of 35% to 60% after hepatectomy (5, 8). Unfortunately approximately 20% of patients with hepatic metastases present with resectable disease at diagnosis. The definition of resectability has undergone several revisions since Ekberg et al. initially proposed in 1986 that resection of CRLM was only indicated with the presence of less than four liver tumors, no evidence of extrahepatic disease, and the possibility of obtaining resection margins ≥ 10mm (9). Though these recommendations have evolved over the past three decades, there remains variability in the definition of "resectable CRLM" among studies and even among hepatobiliary surgeons. Patients with CRLM who undergo hepatic resection demonstrate significantly improved 5-year overall survival (OS) compared to patients treated with chemotherapy and non-surgical modalities (10, 11). Thus determination of resectability has significant prognostic implications. Therefore, defining which patients are candidates for surgery, as well as employing efforts at safely expanding the indications for resection, are critical for extending the benefits of surgery.

As outlined in a 2012 HPB Expert Consensus Statement, the determination of CRLM resectability should include two considerations: oncologic and technical (12). The current consensus proposes that disease should be considered technically resectable as long as complete macroscopic resection is feasible, while maintaining at least a 30% future liver remnant. Despite improved operative strategies to clear all detectable sites of metastases, recurrence is observed in as many as three-fourths of patients. Risk of recurrence and disease-specific death after liver resection can be stratified by validated prognostic scoring systems that incorporate clinical factors serving as surrogate indicators of tumor biology (13). Despite improved ability to predict outcomes with clinical factors, it has been difficult to define scenarios that preclude long-term survival after resection for colorectal metastases.

Tomlinson et al. led a study with the aim of defining cure after resection of CRLM, they analyzed the CRS and found that the lower scores of 0, 1, and 2 seem to predict similarly better survival when compared with the higher scores of 3, 4, and 5. Both groups contained 10-year survivors, showing that having a high CRS diminishes but does not preclude the possibility of long-term survival and cure and they were not able to find any preoperative factors that were sufficiently discriminatory to negate the potential for attaining a cure after resection, while a positive margin negated the potential for long-term survival (14). Recently Creasy et al. demonstrated that microscopic positive resection margin does not preclude 10-year survival or cure proposing that a microscopic positive margin may be an indicator of aggressive tumor biology as opposed to surgical technique. Furthermore, this factor is not easily predictable preoperatively and has limited utility in patient selection. They observed cure rate for a positive margin was 8.3%. Although low, this number represents a real possibility of cure in a group with aggressive tumor biology (15).

The oncologic evaluation of resectability emphasizes the selection of patients most likely to benefit from major liver resection based on the criteria used in numerous retrospective evaluations and in the FONG score and should take into account the burden of liver metastases, the presence of extrahepatic disease, and the response to neoadjuvant therapy, when administered (13). For some patients neoadjuvant chemotherapy demonstrated to be a better option than upfront surgery. The use and timing of perioperative chemotherapy in patients with resectable CRLM remains somewhat controversial. A landmark randomized controlled trial (EORTC Intergroup trial 40983) investigated the role of perioperative FOLFOX (folinic acid, 5-floururacil, oxaliplatin) and surgery versus surgery alone in patients with initially resectable CRLM. In this trial, 364 patients with resectable CRLM were randomized to receive either 12 cycles of perioperative chemotherapy (6 cycles before resection of liver metastases and 6 cycles after resection) or to undergo surgery alone. Trial eligibility was limited to patients with 4 or fewer metastatic lesions and no evidence of extrahepatic disease, and patients in whom the primary tumor had either previously been completely resected (R0) or was felt to be completely resectable in the case of synchronous disease. The primary trial endpoint was progression free survival (PFS). Interval trial results were reported with a median follow-up of 3.9 years. Among patients for whom complete resection was achieved the HR for PFS with the addition of perioperative FOLFOX4 was 0.73 (95% CI 0.55-0.97, p=0.025), which equated to a 9.2% absolute increase in 3-year PFS from 33.2% in surgery alone compared to 42.4% when pre and post-operative chemotherapy was added to the treatment regimen. Similar to the previously reported response rates to chemotherapy with FOLFOX, about 40% of patients had complete or partial response in their liver following preoperative chemotherapy. Additionally, operative mortality was only 1% in both groups, suggesting that pretreatment with FOLFOX did not increase the mortality associated with major liver resection. While perioperative morbidity was higher in the group who had received chemotherapy, the morbidity rates were not beyond the expected range for all patients undergoing major liver resection. Overall, these results from an adjusted early endpoint demonstrated a modest but statistically significant benefit to perioperative chemotherapy with FOLFOX without significant added morbidity or mortality associated with dual modality therapy administered in this design. Follow-up long-term results of this

EORTC trial were published five years later, with a focus on their overall survival data. At a median follow-up of 8.5 years there was no statistically significant difference in OS (16).

One consideration in the use of perioperative chemotherapy in patients with resectable CRLM is the risk that their disease will progress through the best chemotherapeutic agents available and become unresectable or require a more aggressive surgical approach. In large clinical trials, however, this rate has remained low, at 5-7%. Progression of disease burden during neoadjuvant therapy has been associated with decreased survival and may be a relative contraindication to surgical intervention (17, 18).

A subset of patients who receive pre-operative chemotherapy for any indication will have a complete radiographic response. The incidence of disappearing liver metastases ranges from 5-38%, depending on the completeness and quality of pre-operative imaging, the response to therapy, and the pre-treatment size of the metastasis. One question is whether this imaging response correlates with pathologic response and whether the responses are durable. One question is whether this imaging response correlates with pathologic response and whether the responses are durable. A systematic review found that 25-45% of disappearing liver metastases contained residual macroscopic disease at the time of resection. Nevertheless, whether resection of disappearing liver metastases results in an improvement in OS is unknown. In the absence of better evidence, current recommendations are to resect all disappearing liver metastases when feasible (19, 20).

KRAS mutational status has been found to be a predictor of response to chemotherapy and to have an association with survival. Nevertheless KRAS mutational status alone cannot be recommended as grounds for excluding patients from surgery, but the finding of wild-type KRAS may encourage the use of more aggressive treatment in patients with borderline resectable disease (21-23).

In practice, the evaluation of clinical risk factors should involve a multidisciplinary team consisting of hepatobiliary surgeons, radiologists, hepatologists, and pathologists, to evaluate the liver anatomy, histology, and behavior (23).

❖ Principles of anatomy and technique of hepatic resection

Precise knowledge and mastery of the surgical anatomy of the liver, blood vessels, and biliary channels is essential for performing partial hepatectomy. The liver is divided into sectors that comprise liver segments, each supplied by branches of the portal triads and drained by hepatic veins. Partial hepatectomy involves removal of one or more segments by isolation of the relevant portal pedicle, severance of the relevant hepatic veins and biliary drainage channels, and removal of the associated liver tissue.

The anatomic division between the right and left liver is not at the falciform ligament, but rather follows a line projected through a plane—the principal plane or Cantlie's line—running from the medial margin of the gallbladder bed to the left of the IVC posteriorly (Fig.1). Each of these major right and left portions of the liver is divided into sectors and segments.

The Brisbane terminology dictates that the hepatic veins form the boundaries between the various sectors of the liver (Strasberg et al, 2000). Specifically, the medial margin of the right posterior sector is the right hepatic vein and comprises segments VI and VII. The right anterior sector is bordered by the right hepatic vein and middle hepatic vein, coursing along the principal plane, and it comprises segments V and VIII. Based on the Brisbane terminology, the area of liver that comprises segments IVa, IVb, and III forms the left medial sector; segment II forms the left lateral sector, because the left hepatic vein actually divides segment II from III. From a clinical perspective, resections of segments III, IVa, and IVb are rarely performed; furthermore, segment IVa/b is often referred to as the *left medial sector,* or the *left medial section* in Brisbane terminology, and it is bordered by the middle hepatic vein and umbilical fissure. The left lateral sector, or section, is comprised of segments II and III and represents the portion of liver to the left of the ligamentum teres and falciform ligament; thus in essence, the left liver is divided into a medial and lateral sector along the line of insertion of the ligamentum teres and the falciform ligament. The portal venous and hepatic arterial branches conform to the segmental organization and run within the segments, and the draining hepatic veins converge posteriorly toward the inferior vena cava and mark the main scissurae of the liver, within which they run (Couinaud, 1954, 1957).

Practically speaking, five types of major anatomic resections are practiced (Fig. 2; see also Fig. 1). The nomenclature of these operations is based on the anatomic descriptions of Couinaud (1954, 1957) and of Bismuth (1982). This classification emphasizes the importance of the scissurae of the liver and the umbilical fissure. The five different resections depicted in Figure 2 can also be referred to as 1) right hepatectomy, 2) left hepatectomy, 3) extended right hepatectomy, 4) left lateral sectorectomy, and 5) extended left hepatectomy.

The portal vein and hepatic artery divide into major right and left branches outside the liver substance below the hilus (see Fig. 1). Here, when the overlying peritoneum is incised, it is possible to dissect each major branch beyond its bifurcation. The confluence of the right and left hepatic ducts also occurs outside the liver. At the hilum of the portal vein, the right branch is short, and its first branch often arises posteroinferiorly, close to the bifurcation, where it is easily damaged during dissection. By contrast, the left branch of the portal vein and the left hepatic duct pursue a longer, more horizontal extrahepatic course beneath segment IV and are more easily dissected free along their length.

The ligamentum teres (round ligament) runs sharply into the umbilical fissure of the liver, at the base of which the main vascular and biliary pedicle branches to the segments of the left liver (II, III, IVa, IVb). After entering the umbilical fissure, the left branch of the portal vein curves caudally and gives branches not only to the left lateral sector, segments II and III, but together with branches of the left hepatic artery, it gives rise to feedback vessels to the left medial sector—segment IVa and IVb of the left liver, also known as the *quadrate lobe* (see Fig. 1).

Outside of the liver substance, there is not a distinct sheath around the portal triad structures, and they must be dissected independently. The structures of the portal triad—the portal vein, hepatic artery, and bile duct—are covered with the Glisson capsule as they enter the liver parenchyma such that within the liver, they are contained in well-formed branching fibrous sheaths often referred to as *pedicles.* Thus, dissection outside of the liver substance mandates individual isolation of each portal triad structure, where there is considerable variation in anatomy. Pedicles are strong structures that contain the constituents of the portal triad, and intrahepatic dissection of these pedicles enables isolation and control of vascular and biliary elements without the need to individually expose each structure (Launois & Jamieson, 1992).

The liver straddles the IVC immediately below the diaphragm, and the hepatic veins have a short extrahepatic course to empty into the vena cava (see Fig. 1). This superior portion of the vena cava with the draining hepatic veins is masked behind a fold of peritoneum that extends from the cephalad aspect of the falciform ligament to the right and left triangular ligaments. The right hepatic vein emerges from the right scissura and usually enters the vena cava separately. By contrast, the left hepatic vein, which runs in the left scissura between segments II and III, is often joined by the middle hepatic vein, which occupies the principal scissura, before entering the vena cava. Several smaller veins from the posterior surface of the liver and the caudate lobe drain directly into the IVC.

An additional but important hepatic vein, the umbilical vein, runs beneath the falciform ligament and empties into the left hepatic vein. This vein is important in resections that remove segment IVa, because it provides drainage of segment IVb in the presence of ligation of the middle hepatic vein (24).

After meeting criteria for resectability, the technical aspects of liver resection for CRLM are similar to the management of primary hepatic malignancies. One notable difference is the emphasis on parenchymal-sparing approaches for CRLM, often achieved via non-anatomic resections, which allow for preservation of liver volume and function and have been associated with improved outcomes. Compared to major hepatectomy, parenchymal-sparing hepatectomy has been associated with lower rates of overall complications (34% vs. 25%), lower risk of liver failure (7% vs. 2%), and less utilization of ICU resources (25-27). Furthermore, patients who are managed with Parenchymal-sparing hepatectomy are more likely to be candidates for repeat resection in the event of intra-hepatic recurrence. Parenchymal-sparing techniques should be considered the first-line surgical approach for CRLM unless the anatomy or the extent of disease preclude such an approach.

❖ Two-Stage Resection with Portal Vein Embolization

Patients with extensive bilobar liver metastases represent a unique challenge. Use of neoadjuvant chemotherapy to decrease tumor burden combined with portal vein embolization (PVE) and two-stage resection can afford prolonged survival similar to initially resectable patients, with 5-year OS of 40-50% reported (28-29). Dropout due to tumor progression after the first stage occurs in approximately 20% of cases and is associated with worse OS (30-31). On the other hand, tumor progression after PVE that does not preclude second stage resection did not affect overall survival, although this was associated with earlier tumor recurrence. A borderline response to neoadjuvant chemotherapy may predict tumor progression after PVE (32). PVE is the primary FLR augmentation strategy and has been shown to permit resection in 63% of patients who initially had an inadequate sized FLR (33). It may also serve as a preoperative test of hepatic function by evaluating the regenerative capacity of the FLR in response to PVE. PVE should be performed in an ipsilateral transhepatic approach (in order to avoid injury to the FLR) and the degree of hypertrophy (DH) is optimized when PVE is performed using microspheres and coils. Measured 4-6 weeks following PVE, a DH of the FLR by 5% has been associated with reduced rates of PHI (34). In addition, the kinetic growth rate (KGR), calculated as the DH divided by the number of weeks since PVE, has been shown to be one of the strongest indicators of post-hepatectomy outcomes (35). In a large single institution series of patients undergoing PVE prior to extended hepatectomy, the best predictor of outcome was a KGR of >2%, with none of these patients experiencing PHI or mortality, compared to 21% PHI and 8% mortality in those patients with KGR < 2% (36). Extension of the PVE to segment 4 can help achieve an improved hypertrophic response when extended right hepatectomy is anticipated (37-38). Identification of strategies to maximize the DH and KGR after PVE will potentially improve outcomes in patients undergoing extended and two-stage resections.

❖ Associating Liver Partitioning and Portal Vein Occlusion for Staged Hepatectomy (ALPPS)

A novel accelerated two-stage technique using in situ portal vein ligation (PVL), ALPPS was first performed in 2007 and then reported in 2012 (39). The first stage of ALPPS involves clearing tumor from the FLR, splitting the liver along a planned transection line, and performing contralateral PVL. This results in rapid hypertrophy of the FLR, which permits completion hemihepatectomy at a second stage operation 7 to 14 days later (40). This technique has generated significant interest and controversy, as initial data reported a high rate of morbidity (28% major complication rate) and mortality (12% 90-day mortality) (41). Technical causes surrounding adaptation of a new procedure and poor patient selection may have initially accounted for these poor outcomes; more recent series reported improved, albeit still elevated 90-day mortality rates of 8.8%, with the predominant cause being liver failure in 75% of these patients (42). The consensus remains mixed regarding the benefits of ALPPS as compared to a two-stage approach. In a meta-analysis comparison of ALPPS to the planned two-stage approach, ALPPS was associated with more rapid and greater increase in the size of the FLR, and a greater proportion of patients made it to the second stage of resection than with the two-stage approach (40). These benefits of the ALPPS were offset, however, by increased morbidity and mortality (up to 73% and 12%, respectively). One study found similar gain in FLR volume (47% vs. 41%) but found increased rates of major complications after the second stage of ALPPS (41.7% vs. 17.6% in the two- stage group) (43). Overall survival was decreased in the ALPPS group (42% vs. 77% OS at 2 years) and recurrence rates within the liver were higher in the ALPPS group, with fewer patients able to be salvaged by repeat hepatectomy (44). As with any new procedure, it remains critical to define the optimal selection criteria for this procedure, with special scrutiny for patients that are candidates for other curative-intent treatments.

AIM OF THE STUDY

The purpose of this study is to identify more effective and reliable predictive factors for overall survival and disease-free survival after liver resection for colorectal cancer metastasis, with special focus on clinical-pathological features of the primary colon cancer (TNM stage, grading, tumor budding, lymphovascular invasion, perineural invasion, lymphocyte infiltration). In patients with stage II and III, molecular characterization is not currently performed routinely, although it may provide some useful information on the patients' prognosis. For this reason we excluded data on mutational analyses from our study, because colorectal cancer mutational status is generally carried out on all patients at the time of diagnosis of CRLM, not at the time of diagnosis of primary CRC. Secondary endpoint was to confirm the actual prognostic criteria considered when evaluating patients for surgery; so we also collected data on clinical-pathological features of the liver disease that constitute Fong criteria in clinical risk score (margins of liver resection, disease-free interval, number and size of liver nodules, CEA levels) and histopathological features of CRLM (glissonian infiltration, lymphovascular invasion of the liver).

In conclusion, the study investigates new prognostic criteria in liver surgery for colorectal liver metastases in order to improve the preoperative patient risk stratification.

METHODS

The medical records of patients with diagnosis of colorectal liver metastasis (CRLM) who underwent hepatic resection between August 2005 and March 2017 at Clinica Chirurgica Generale of Parma Hospital, were retrospectively reviewed. A database of patients with a histological diagnosis of colorectal liver metastasis was created. All patients who underwent primary hepatic resection or two-stage hepatectomy with curative intent were included in the analysis. Patients underwent hepatic resection if they had an adequate future liver remnant at the diagnosis or after staged hepatectomy, appropriate medical fitness for surgery and no evidence of disseminated disease. Exclusion criteria were: hepatic resection for recurrent CRLM, extra-hepatic disease.

Preoperative radiological staging consisted of contrast-enhanced computed tomography of the chest, abdomen and pelvis. Positron emission tomography, magnetic resonance imaging or transabdominal ultrasound were used at the discretion of the treating physician. Intraoperative hepatic ultrasound was performed routinely to confirm preoperative diagnosis and to guide surgical plan. Prior to any treatment, patients were discussed at a specialist multidisciplinary meeting that included hepatobiliary surgeons, oncologists, pathologists and radiologists. Collected data included information on patient demographics, clinical data and laboratory analysis (age, gender, body mass index, Child-Pugh score, Meld score, pre-hepatectomy CEA levels, synchronous vs metachronous presentation of liver metastases, portal vein embolization, chemotherapy treatment scheme), type of surgical resection of liver metastasis (type of procedure, number of hepatic segments resected, anatomical vs non-anatomical resection, estimated blood loss, pedicle clamping time), histopathology of the primary colorectal cancer and liver metastasis. Histopathological data for the primary colorectal tumor were obtained by a detailed review of cancer specimens and data extracted included site of the primary disease, grade, pathologic staging according to the American Joint Committee on

Cancer (AJCC) 7th edition (45), number of examined lymph nodes, number of positive lymph nodes, lymphocytic infiltration, perineural invasion (PNI), lymphovascular invasion (LVI) and tumor budding. LVI was defined as single tumor cell or cluster of cells within a lymphatic or small blood vessel and was scored as being present or absent (46). PNI was defined tumor cells within any layer of the nerve sheath or tumor in the perineural space and was scored as being present or absent (47). Tumor budding was defined as the presence of single tumor cells or small clusters of up to 5 cells in the tumor stroma (48).

The pathology report of the resected liver specimens consisted of number of metastasis, size of the largest tumor, resection margin, biliary invasion and lymphovascular invasion. Biliary invasion was defined by the presence of adenocarcinoma cells infiltrating through part of or completely replacing the bile duct epithelium of large, medium-sized or small bile ducts (49). A negative margin (R0) was defined within 1 mm of the margin. All patients were stratified following the clinical risk score for predicting recurrence after hepatic resection for CRLM developed by Fong et al.(13). We determined the disease free interval (DFI), defined as the time from presentation of the primary colorectal tumor to the time of presentation of colorectal liver metastasis and the disease free survival (DFS), the interval between hepatic resection and disease recurrence. Follow-up and overall survival were calculated from the date of liver resection to the date of last clinical examination or to the date of death.

Statistical Analysis

A descriptive analysis of the parameters thus collected was first performed: the continuous characters were described by expression of the mean +/- standard deviation (DS), while the discrete variables were described by expression of the percentage value. In order to exclude associations between the variables that could preclude a subsequent multivariate analysis, the association of the collected variables was first evaluated, as described above, with the primary site, dichotomized in colic vs. rectal. The univariate analysis was conducted with Student's t test for continuous variables (preferred to the Mann Whitney test for greater reliability in case of high variance heterogeneity), and with Pearson's square Chi test with Yates correction for reduced sample size. As no parameter was associated with $p < 0.05$ with a specific primary site, all the collected parameters were analyzed, with a similar univariate analysis mode (ie Student's t test for continuous variables, Chi Square test for discrete ones), with respect to the status of "post-hepatectomy recurrence". Finally, the association of the aforementioned variables with the DFI parameter was evaluated, again with the aforementioned methods. The variables that were associated with $p < 0.250$ to the DFI equal to or greater than 12 were therefore included in a multivariate model of binary logistic regression, and estimate of the degree of association with determination of the Odds Ratio (OR) values with corresponding intervals of confidence at 95% (95% CI).

The variables that were associated with recurrence, both positively (ie greater frequency of the parameter found), and negatively (ie lower frequency of the parameter), with $p < 0.250$ were included in two statistical models of multivariate analysis, realized by regression according to Cox and consequent determination of the Hazard Ratio (HR) value with the corresponding 95% confidence intervals with respect to the two main outcomes: recurrence and death.

RESULTS

❖ Clinical and pathological findings

A total of 115 patients underwent hepatic resection for CRLM between August 2005 and March 2017, while 21 patients were excluded because they were undergoing hepatectomy for recurrent CRLM and 6 patients were excluded because of disease progression after the first stage of the two-stage hepatectomy. Further 27 patients have been excluded because the specimens of the primary tumour were no long retrievable.

Therefore, the study group consisted of 61 patients, of whom 42 were male (68.9%). The mean age at diagnosis of primary colorectal cancer was 66.7 years (range: 50-83). The majority of patients had a primary tumour of the colon (85.2%). Our specimens presented a poor degree of differentiation for 63.9% of cases and 68.9% were found with nodal involvement. LVI, PNI and tumour budding resulted in 46 (75.4%), 18 (29.5%) and 36 (59%) cases respectively.

Liver metastasis were metachronous for 28 patients (45.9%) and 6 patients had liver recurrence within 12 months of colorectal resection (range:4-46). The majority of patients had small liver metastasis (<5cm) (80.3%) and 64% of the group had multiple tumors (>1). We accepted a positive margin <1 mm (R1) for 7 patients when we were forced to dissect the tumor off the vessels. We stratified patients according to Clinical Risk Score and we found 17 patients in the high risk group (CRS 3-5).

We evaluated the presence of tumor budding, lymphocytic reaction and PNI but we didn't demonstrate an association between these pathological features of the primary colorectal tumor and histopathology of the CRLM.

The degree of nodal involvement was found to be 79% for patients with LVI-positive tumors versus 46% for patients with LVI-negative tumors (p 0.06).

❖ **Survival analysis**

Median follow-up was 29 months. Mean overall survival was 30.9 months (CI 95% 23.9 - 37.9) with a predicted 5-years overall survival rate of 42%.

The median disease free survival after hepatectomy was 22 months and the recurrence rate was 50.8%.

Survival analysis showed that pathologic features of primary CRC didn't affect overall survival. Univariate analysis identified 5 factors associated with poor prognosis after hepatectomy, two of this related to the primary colorectal cancer (grading p 0.216 and perineural invasion p 0.06). Other characteristics were positive margins (p 0.119), the number of hepatic lesions >3 (p 0.137) and high CRS (p 0.102). Multivariate analysis associated PNI with a likelihood of recurrence after hepatectomy (p 0.078 HR 2.08 95%CI 0.92-4.69) and R1 margins with a worse survival (p 0.008 HR 7.7 95%CI 1.68-35.29).

Considering recurrence within 1 year as a dicothomic variable, PNI of the primary colorectal cancer was found to be associated with a 44% recurrence rate after hepatectomy, versus a 11.6% recurrence rate in PNI-negative tumors. (p 0.03).

DISCUSSION

In our study group the favorable 5-years survival rate of 42% reflects the results observed in numerous case series that show long-term survival or even cure in 20-50% of patients who undergo complete R0 resection of CRLM. Even the recurrence rate after hepatectomy is similar to what reported in literature, where 50.8% of patients experience recurrence of CRLM. Surgery has proven to be the only approach able to achieve long-term survival, however outcome after hepatectomy is extremely heterogeneous and many patients still do poorly even if advances in surgical techniques and chemotherapy regimens have extended the criteria for resectability allowing a careful selection of patients.

The use of easily measurable clinical factors to predict long-term outcome has been rigorously studied. Several scoring systems have been developed using retrospectively collected data on large patient cohorts. The Fong Clinical Risk Score (CRS) is widely used to stratify patients into high-risk and low-risk groups for overall survival, and assigns a single point for each of the following variables: node-positive primary tumor, disease-free interval from primary to metastases, carcinoembryonic antigen level, size and number of CRLM (46). The use of scoring systems as clinically relevant models has been challenged, as they appear to function relatively well in predicting survival outcomes but have not been validated for guiding treatment or surveillance decisions. An analysis led by Tomlinson et al. on the basis of actual 10-year survivors, demonstrated that no single preoperative risk factor precluded the possibility of long-term survival and they didn't find any preoperative factor that was sufficiently discriminatory to negate the potential for cure after resection, showing that having a high CRS reduces but doesn't prevent long-term survival and possibility of cure (14).

Therefore novel prognostic predictors are necessary to help clinicians in selecting patients with potentially resectable CRLM and to establish adequate surveillance protocol after surgery.

Histopathological factors (vascular or perineural invasion and response to chemotherapy), as described for primary tumors have been investigated in CRLM. Only few studies have hypothesized that primary colorectal tumor's histology may help to discern the biological behavior of resected CRLM (50). Therefore the aim of our study was to identify which pathological features of the primary colorectal cancer can significantly predict the oncologic outcomes of patients treated with a curative surgery for CRLM.

LVI has been shown to be a predictor of poor outcome in patients with primary non-metastatic colorectal cancer and other primary malignancies (i.e., cholangiocarcinoma, breast, and melanoma). Cardona et al. demonstrated that the presence of LVI in the primary colorectal tumor was a poor prognostic indicator for outcome after hepatic resection for CRLM (46).

In our study we identified a possible association between poor differentiation, PNI, positive margins, number of hepatic lesions > 3, high CRC and recurrence after hepatectomy at univariate analysis. The multivariate analysis confirmed these parameters, except grading, as possible independent factors. LVI was correlated with a shorter disease free interval (DFI) after resection of primary tumor, but it failed to predict prognosis in terms of overall survival after hepatectomy.

PNI has been recognized in many series as a prevalent pathology feature of colorectal cancer and is reported in up to 33% of these tumors at the time of resection (47). Several studies have demonstrated a significant association between the presence of PNI in colorectal cancers and higher rates of metastatic disease, recurrences ad reduced survival, therefore it has been increasingly recognized as an important independent prognostic factor in colorectal cancer. In a study of 563 rectal and rectosigmoid cancers, the presence of PNI was associated with a 27% cancer-specific 5-year survival rate versus a 78% 5-year survival rate in PNI-negative tumors (51). Similar results were reported by Krasna et al. in their review of 77 patients with colorectal carcinoma. In that series, not only survival was lower in PNI-positive patients, but those patients were almost 3 times more likely to have metastatic disease at the time of diagnosis.

Our results show that PNI is correlated with an increased recurrence rate, expecially within 1 year after hepatectomy in 44% of patients, versus a 11% recurrence rate in patients with PNI-negative tumors. Although the small number of patients didn't allow any conclusion, higher recurrence rates suggest that PNI indicates a more aggressive tumor phenotype.

The prognostic significance of PNI become relevant in lymph node negative disease, particularly stage II CRC, in which it has been demonstrated that chemotherapy has no survival benefit.

It has been demonstrated that patients with node-negative disease without perineural invasion had 5-year disease-free survival rate of 56% versus 29% for patients with node-negative, perineural invasion-positive tumors (51).

Therefore, PNI status may be useful in selecting a subgroup of high-risk patients, such as lymph node negative stage II patients, who could benefit from taylored treatment regimens or different surveillance regimens because they still have the potential for long-term survival. Furthermore, since underreporting of PNI remains an obstacle to gain an adequate understanding of its true prognostic significance, it is conceivable that nerve-specific staining of specimens may become a routine part of the pathologic evaluation of malignancies in which PNI status could affect treatments.

In the current study population a positive R1 surgical margin was associated with a reduced DFS after hepatectomy. Different parenchymal transection technique could modify the impact of R1 margins (i.e. ultrasonic dissector). However R1 resection could be expression of more advanced disease, hence the impact of positive margins on OS or DFS may be related to more aggressive tumor. Increasingly efficient chemotherapy may have changed the long-term outcome after R1 resection. Recent studies comparing R0 vs R1 resection in patients submitted to neoadjuvant chemotherapy showed that there were no differences in survival rates (52).

As an observational retrospective study, this analysis has inherent selection limitations and we did not confirm the generalisation of these results. In addition the relatively limited number of patients analysed, did not allow specific conclusion. Despite adjustment in a multivariable model, any study that spans a long period is exposed to temporal bias; however, an additional limitation of our study was that patients were submitted to different postoperative chemotherapy among different hospitals with predictable differences in outcome. However preoperative chemotherapy was not routinely administered at our institution with no influence of systemic therapy on the interval between primary cancer resection and hepatic surgery.

Further studies are needed to determine whether adjuvant treatment strategies should be based on these adverse prognostic histological factors and if these should drive the preoperative management and the timing of perioperative chemotherapy. Furthermore the retrospective nature of the present study exposes to selection bias. A study from prospectively collected database in which we include analysis of KRAS mutational status in the primary CRC could be methodologically preferable and will allow to consider even biomarkers as predictive factors at the time of diagnosis of primary CRC.

	No., %	**Mean ± SD**
Age		66.7 ± 9.9
Age ≥ 60	42, 68.9%	
Male	42, 68.9%	
Primary tumor		
Colon	52, 85.2%	
Rectum	9, 14.8%	
Primary tumor characteristics		
T		
T1 + T2	5, 8.2%	
T3 + T4	56, 91.8%	
N (+)	42, 68.9%	
Grading		
G2	22, 36.1%	
G3	39, 63.9%	
LVI (+)	46, 75.4%	
Budding (+)	36, 59.0%	
PNI (+)	18, 29.5%	
Lymphocytic reaction (+)	21, 34.4%	
CRLM characteristics		
Size > 5 cm	12, 19.7%	
Margin < 1 mm	7, 11.5%	
Glissonian infiltration	12, 19.7%	
LVI (+)	32, 52.5%	
Synchronous	33, 54.1%	
Recurrence	31, 50.8%	
Status (death)	14, 23.0%	
Fong Criteria		
N+	42, 68.9%	

DFI < 12 m	36, 59.0%	
Number > 3	23, 37.7%	
Size > 5 cm	11, 18.0%	
CEA > 200	8, 13.1%	
CRs > 2	17, 27.9%	
DFS		8.9 ± 12.0
FU Time		32.3 ± 24.2

	Primary Colon (No./52, %)	**Primary Rectum** (No./9, %)	Chi squared test (p value)
Age ≥ 60	36, 69.2%	6, 66.7%	1.000
Male	36, 69.2%	6, 66.7%	1.000
T3 / T4	48, 92.3%	8, 88.9%	1.000
N+	36, 69.2%	6, 66.7%	1.000
G3	31, 59.6%	8, 88.9%	0.189
LVI +	39, 75.0%	7, 77.8%	1.000
Budding +	30, 57.7%	6, 66.7%	0.890
PNI +	15, 28.8%	3, 33.3%	1.000
Lymphocytic reaction	17, 32.7%	4, 44.4%	0.760
Size > 5 cm	12, 23.1%	0, -	0.249
Margin < 1 mm	5, 9.6%	2, 22.2%	0.597
Glissonian infiltration	10, 19.2%	2, 22.2%	1.000
LVI-MTS +	27, 51.9%	5, 55.6%	1.000
Synchronous	29, 55.8%	4, 44.4%	0.789
Recurrence	27, 51.9%	4, 44.4%	0.958
Status (death)	14, 26.9%	0, -	0.179
Fong Criteria			
N+	36, 69.2%	6, 66.7%	1.000
DFI < 12	31, 59.6%	5, 55.6%	1.000
Number > 3	20, 38.5%	3, 33.3%	1.000
Size > 5 cm	11, 21.2%	0, -	0.292
CEA > 200	7, 13.5%	1, 11.1%	1.000
CRS > 2	15, 28.8%	2, 22.2%	0.995
DFS (m)	8.8 ± 12.3	9.6 ± 10.7	0.853
FU time (m)	32.0 ± 28.2	33.8 ± 40.3	0.870

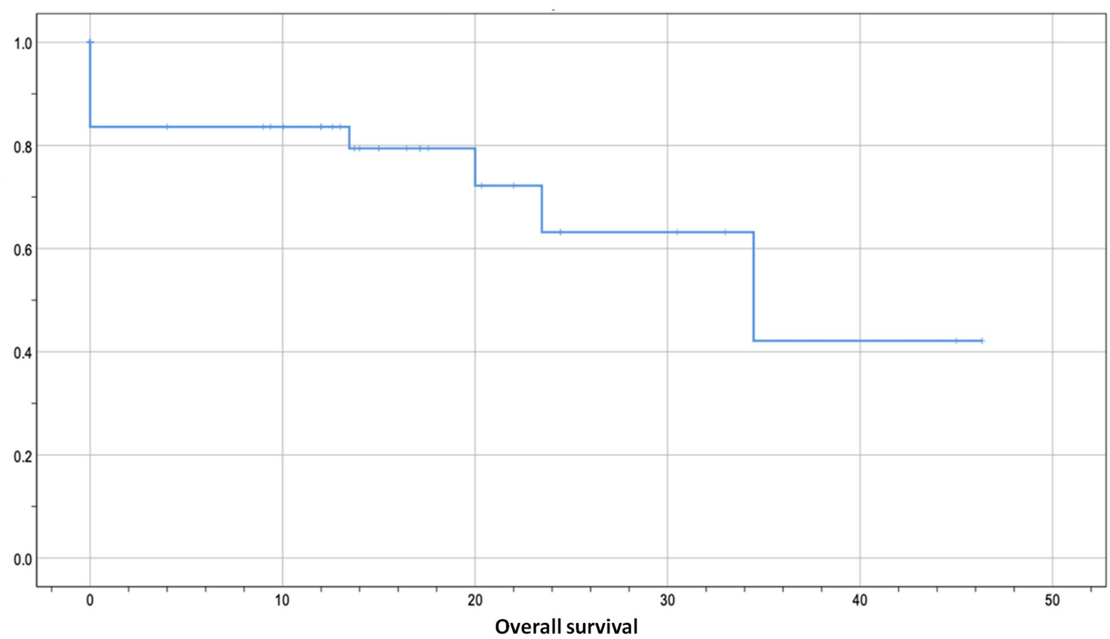
	Rec post-hepatectomiy (No./31, %)	**No rec post-hepatectomy** (No./30, %)	Chi squared test (p value)
Age ≥ 60	21, 70.0%	21, 67.7%	1.000
Male	**17, 54.8%**	**25, 83.3%**	**0.034**
Primary Colon	27, 87.1%	25, 83.3%	0.958
T3 / T4	27, 87.1%	29, 96.7%	0.371
N+	23, 74.2%	19, 63.3%	0.523
G3	**17, 54.8%**	**22, 73.3%**	**0.216**
LVI +	25, 80.6%	21, 70.0%	0.504
Budding +	17, 54.8%	19, 63.3%	0.679
PNI +	**13, 41.9%**	**5, 16.7%**	**0.060**
Lymphocytic reaction	9, 29.0%	12, 40.0%	0.528
Size > 5 cm	5, 16.1%	7, 23.3%	0.700
Margin < 1 mm	**6, 19.4%**	**1, 3.3%**	**0.119**
Glissonian infiltration	5, 16.1%	7, 23.3%	0.700
LVI-MTS +	19, 61.3%	13, 43.3%	0.251
Synchronous	20, 64.5%	13, 43.4%	0.261
Status (death)	10, 32.3%	4, 13.4%	0.146
Fong Criteria			
N+	23, 74.2%	19, 63.3%	0.523
DFI < 12	20, 64.5%	16, 53.3%	0.530
Number > 3	**15, 48.4%**	**8, 26.7%**	**0.137**
Size > 5 cm	4, 12.9%	7, 23.3%	0.468
CEA > 200	5, 16.1%	3, 10.0%	0.742
CRS > 2	**12, 38.7%**	**5, 16.7%**	**0.102**
DFS (m)	8.1 ± 12.5	9.8 ± 11.6	0.593
FU time (m)	34.0 ± 25.9	30.5 ± 33.8	0.656

DFS	p value	Hazard Ratio	95%CI
G3	0.546	0.773	0.342; 1.747
PNI	0.078	2.080	0.921; 4.695
R1 (<1 mm)	0.134	2.176	0.787; 6.018
Number > 3	0.104	2.449	0.832; 7.204
CRS > 2	0.198	2.101	0.679; 6.505

OS	p value	Hazard Ratio	95%CI
G3	0.848	0.885	0.255; 3.076
PNI	0.336	2.257	0.429; 11.869
R1 (<1 mm)	0.008	7.716	1.687; 35.291
Number > 3	0.203	2.702	0.585; 12.489
CRS > 2	0.602	1.528	0.311; 7.510

	DFI ≥ 12 m No./25, %	DFI < 12 m No./36, %	P value
Age ≥ 60	19, 76.0%	23, 63.9%	0.469
Male	18, 72.0%	24, 66.7%	0.872
Primary tumor of colon	21, 84.0%	31, 86.1%	1.000
T3/T4	23, 92.0%	33, 91.7%	1.000
N+	14, 56.0%	28, 77.8%	**0.127**
G3	14, 56.0%	25, 69.4%	0.421
LVI +	16, 64.0%	30, 83.3%	**0.155**
Budding +	12, 48.0%	24, 66.7%	**0.233**
PNI +	7, 28.0%	11, 30.6%	1.000
Lymphocytic reaction	10, 40.0%	11, 30.6%	0.624

	OR	95%CI
N+	0.473	0.055; 4.075
LVI +	1.728	0.134; 22.261
Budding +	0.738	0.079; 6.888


1.0
0.8
0.6
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0.2
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0
10
20
30
40
50
Overall survival

Fig. 1 A, Enlarged view to show the sectors (separated by the major hepatic veins) and the segmental structure of the liver. Each segment is supplied by a portal triad; the left portal pedicle traverses beneath segment IV to the umbilical fissure; the umbilical portion of the pedicle curves ventrally and caudally in the umbilical fissure. The blood supply to segment IV is recurrent as feedback vessels. **B,** Inferior surface of the liver; segment VIII is not seen because it lies superiorly. The anatomic division into right and left lobes by the umbilical fissure and into a right and left liver in the principal plane, along the principal scissura, is evident. IVC, inferior vena cava.

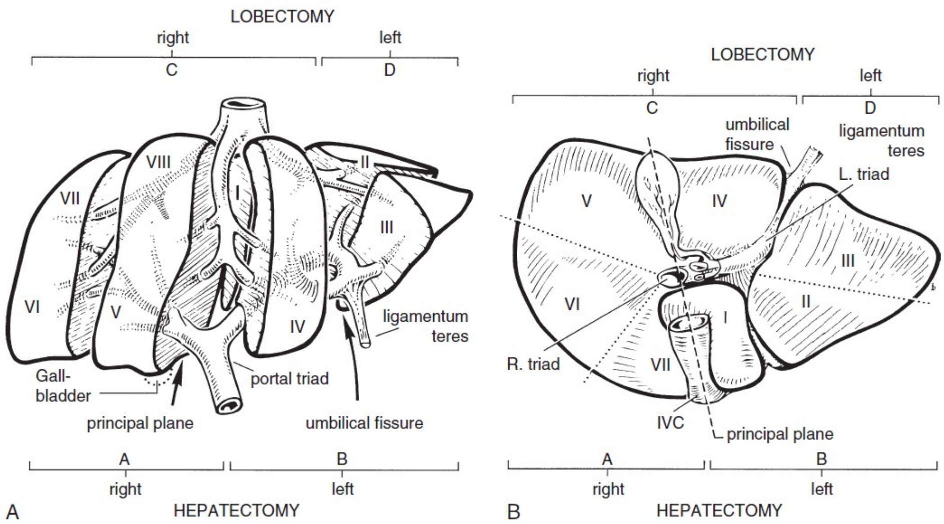
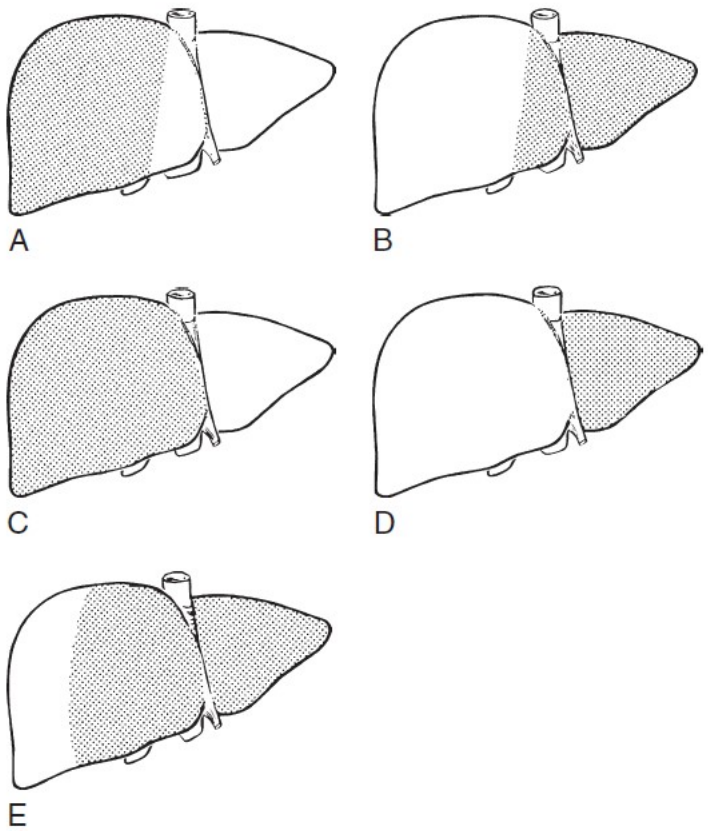


Fig. 2 Commonly performed major hepatic resections are indicated by shaded areas. **A,** Right hepatectomy. **B,** Left hepatectomy. **C,** Right lobectomy. **D,** Left lobectomy. **E,** Extended left hepatectomy.



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