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**Ph.D. Thesis**


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# Inflammatory Markers, Hepatic Resection Efficacy, and Liver Transplantation Role in patients with Colorectal Liver Metastases: A Comprehensive Analysis


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**ABSTRACT:**

**Background**: Hepatic resection is considered an effective treatment for colorectal cancer liver metastases (CRLM) and colorectal cancer (CRC). This study aimed to evaluate the efficacy of hepatic resection, as well as the impact of demographic, clinical, and inflammatory factors on patient outcomes. Additionally, we describe the liver transplantation program at IRCCS-ISMETT-UPMC and its role in treating oncological diseases.

**Methods**: Fifty patients with CRLM and CRC who underwent surgical treatment at IRCCS-ISMETT-UPMC were included in this retrospective and prospective analysis. Demographics, clinical features, inflammatory markers, and outcomes were collected and analyzed. A case study of a patient undergoing liver transplantation for CRLM through the COlorectal Liver Metastases Transplantation (COLT) protocol is also presented.

**Results**: Hepatic resection was found to be a safe and effective treatment option, with improved overall and disease-free survival rates. The study found no significant impact of demographic and clinical variables, inflammatory indices, and scoring systems on patient outcomes, except for a positive correlation between diarrhea and procalcitonin levels (p-value=0.004). The liver transplantation program at IRCCS-ISMETT-UPMCI provided transplants for oncological diseases in 591/1595 (37%) of cases between 1999 and 2023, predominantly for hepatocellular carcinoma. One patient underwent liver transplantation for CRC.

**Conclusions**: This study provides valuable information on the demographic and clinical characteristics of patients with CRLM and CRC and their outcomes following hepatic resection, supporting its safety and efficacy. Additionally, it highlights the potential of liver transplantation as a treatment option for selected patients with CRLM through the COLT protocol and the importance of a multidisciplinary approach to patient management. Further research is needed to better understand the relationships between various factors and to identify potential prognostic or predictive markers in this patient population.

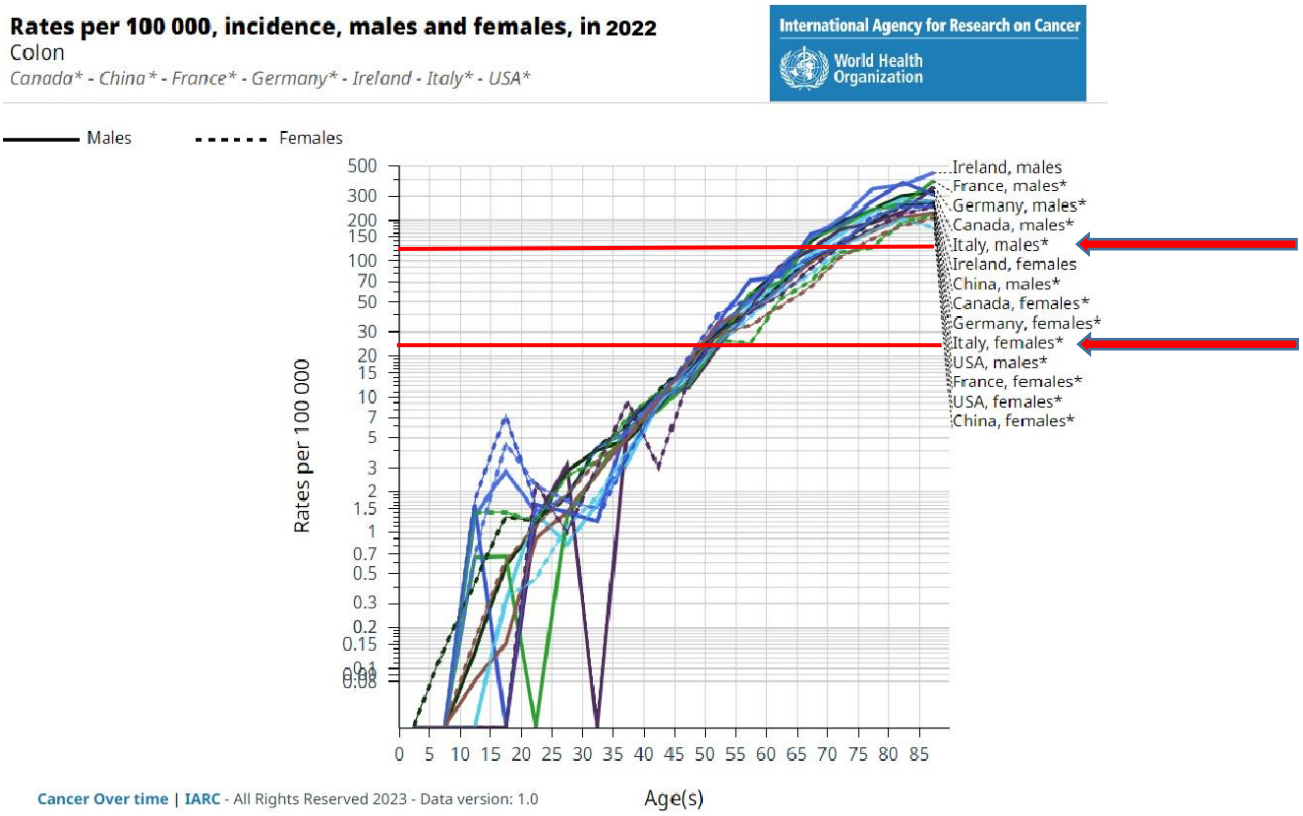
## Contents

## Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths in the world. World health organization estimated a number of 1.9 million new cases and about 880,000 deaths worldwide in 2022 (1).
The epidemiology of CRC has many variables including gender, risk factors, racial groups, age, geographical distribution, and exposure to potential mutagenic agents. Therefore, wide variability, determine different curves of occurrence all around the world, and this significantly influences prognosis and response to clinical treatment. (2).
On a global scale, the incidence of CRC represents 9.7% of all cancers and is more common in men than women. In industrialized countries, CRC is more frequent: Australia and New Zealand are the countries with the highest incidence (44. 8% and 32. 2% per 100,000 inhabitants, respectively). In the United States, there are 145000 patients affected by CRC and 15950 (11%)

are newly diagnosed (3).

*Table 1 - WHO CRC incidence for 100.000 inhabitants.*



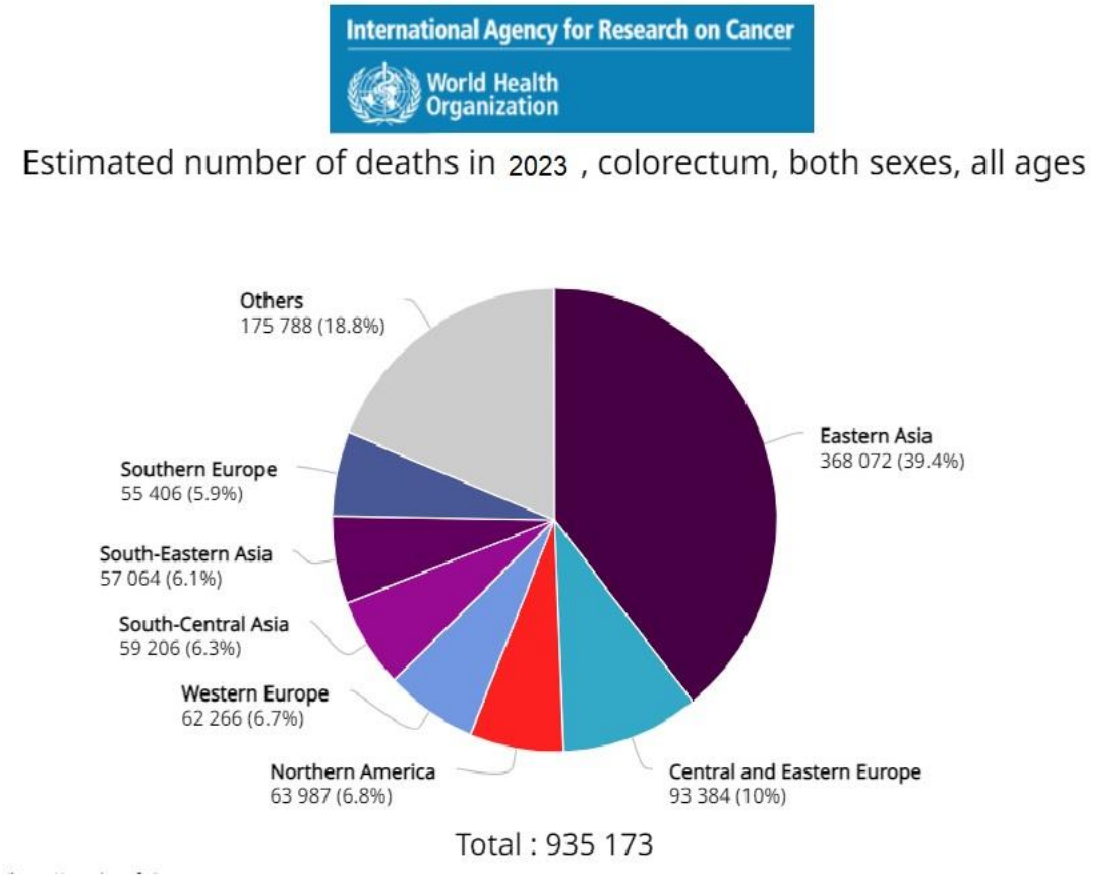

In the UK, 12.1% CRC is cause of death-related, in 74% of patients with an average age of 51 years (4).

The age-related CRC mortality rate in industrialized countries, is higher in men than women (11.6% /100,000 population); while in developing countries (6.6% /100,000 population). From 1992 to 2013 the incidence of mortality was strongly influenced by the increased attention to colorectal screening programs providing the opportunity for early diagnosis and treatment. Hence, a global increase of 57% was documented, but areas such as Europe, North America, and Asia showed a marked decrease in the rate. (5).

About 1.7 million new CRC diagnoses are expected in 2023, accounting for about 1/10 cancer cases and deaths (6) (7).

In the last two decades, there was a significant improvement of survival in CRC and patients affected by colorectal liver metastasis (CRLM), with an overall survival increased to 35-40% in the 2010s (8).

*Table 2 - WHO 2023 mortality prevision*




In the past two decades, many advances in research and awareness campaigns for colorectal cancer screening has given the possibility of early diagnosis and surgical treatment with significantly better clinical outcomes (9).

## Liver metastasis from colorectal cancer:

Liver is the most common organ of spread, with an incidence of 15–25% in patients affected by CRC at the time of primary diagnosis. In 18–25%, patients will develop metastases within 5 years from the first diagnosis of CRC (10).
The main cause of mortality in patients affected by colorectal cancer is due to lymphatic and blood dissemination to the liver. The literature has shown that surgery represents the best treatment for CRLM, with a 30%-58% of survival rate at 5-years. (11).
Despite clinical and therapeutic advances in chemotherapy treatments, 37-68% of CRC patients develop recurrent liver metastases after the first resection, with an average time to relapse of 15(6/24) months. (12) (13).

R1 resection is often characterized by progression of micrometastatic cancer recurrence from occult lesions LLRsed after the first hepatectomy (14). Experience of hepatobiliopancreatic center, carried out that 27%–38% patients can be eligible for multiple hepatectomy as usefule clinical treatment for recurrence of CRLM after initial resection (15) (16).
After appropriate clinical cases selection and multidisciplinary evaluation, a large number of patients were treated with multiple surgical procedure for oncological hepatectomy. Survival curves (SC) of this cohort of patients were comparable to SC of the first hepatic resection we (17) (18).

## Colorectal cancer in Italy: Italian statics

In Italy, the CRC screening program involves residents aged 50-70 years old, which are invited every 2 years to perform a fecal occult blood test (FOBT), without any dietary restriction (19). People with a negative FOBT are recommended to repeat screening every 2 years, while patients with a positive FOBT are referred to a gastroenterologic center.
When a colorectal lesion is discovered, a biopsy is taken for histologic study and they are enrolled for a clinical surgical program.
The National Screening Observatory (ONS) conducts an annual survey of the results of CRC screening program in Italy (20).
The significance of the national screening is determined by population adherence to the clinical trials. In 2020, nearly 6 million Italians aged 50-70 years were invited for CRC screening. Overall involvement was 75% of the annual target population, with varying regional adherence to the screening program: in the North (91%) and the Center (95%), and in the South and Islands (43%) (21). In 2019 85% of patients with diagnosis of CRC underwent to surgical procedure, while in 15% of cases only an endoscopic resection was performed.
Adenomas and pT1 stage carcinoma were treated with endoscopic procedure, with a low rate of complications (3.4%) and with a low rate of perforation (1.2%) (22).

*Table 3 - Italian cancer incidence / mortality*

Oncologia Medica, Comprehensive Cancer Centre, AUSL-IRCCS di Reggio Emilia – pinto.carmine@ausl.re.it

| COLON-RETTO | | | | |
|---|---|---|---|---|
| **Incidenza** | Nel 2022, sono state stimate circa 48.100 nuove diagnosi (uomini = 26.000; donne = 22.100) | | | |
| **Mortalità** | Nel 2021, sono stimati 21.700 decessi (uomini = 11.500; donne = 10.200). Le stime per il 2022 non sono disponibili | | | |
| | UOMINI | | DONNE | |
| Tipo/sede di tumore maligno | Numero morti 01-06/2020 | Differenza % 01-06/ 2015-19 | Numero morti 01-06/2020 | Differenza % 01-06/ 2015-19 |
| Tutti i tumori maligni | 48.449 | -2,6 | 39.290 | -1,0 |
| Labbra, cavità orale e faringe | 993 | -4,1 | 488 | -4,6 |
| Esofago | 661 | -2,0 | 274 | +8,3 |
| Stomaco | 2.491 | -8,1 | 1.749 | -8,7 |
| Colon, retto e ano | 5.064 | -3,1 | 4.249 | -2,9 |
| Fegato e dotti biliari intraepatici | 2.884 | -5,9 | 1.337 | -15,8 |
| Pancreas | 3.144 | +8,3 | 3.284 | +6,3 |
| Laringe | 628 | -7,6 | 85 | -15,8 |
| Trachea, bronchi e polmoni | 10.962 | -8,8 | 5.031 | +2,0 |
| Melanomi della cute | 637 | +4,7 | 395 | -2,8 |
| Mammella | | | 6.460 | +0,9 |
| Cervice uterina | | | 259 | +9,9 |
| Utero | | | 1.307 | 0,0 |
| Ovaio | | | 1.620 | -1,1 |
| Prostata | 3.902 | +3,1 | | |
| Rene | 1.171 | +1,4 | 620 | +0,2 |
| Vescica | 2.388 | +1,7 | 667 | +0,1 |
| Cervello e sistema nervoso centrale | 1.220 | +3,3 | 896 | -3,2 |
| Tiroide | 121 | +15,9 | 148 | -6,7 |
| Linfomi | 1.462 | -1,4 | 1.163 | -1,2 |
| Leucemie | 1.746 | +0,9 | 1.323 | -1,2 |
| Altri tumori maligni | 5.380 | -2,6 | 4.820 | -4,3 |


## Colorectal cancer and liver metastasis during covid, what's changed?

The global spread of SARS-CoV-2 infection determined a wasting effect in terms of mortality for pneumonia infection and for delay of clinical follow up. Covid worldwide diffusion with a pressing necessity for hospitalization of infected patients, meant that many wards had to be converted in covid areas. This has caused a significant delay of the diagnosis and treatment for a great number of patients affected by CRC (23). The growing number of infections in Italy determined a significant decline of attitude to all cancer screenings with a decrease of 30% in CRC diagnoses and subsequent late surgical treatment observed between March 2020 and May 2021.
Italy was hard hit by the pandemic COVID-19 which led the government to impose severe restrictive containment measures, such as the lockdown that began on March 9, 2020. The pandemic spread of SARS-COV-2 caused a marked reduction of oncological screening. Compared to 2019, there was a significant reduction in screening tests for colorectal cancer at the national level, with a decrease of 45.5%, and a corresponding decrease in participation rates by

20%. This reduction resulted in an estimated 1299 undiagnosed lesions of colorectal cancers and 7474 colorectal advanced adenomas. As of May 2021, screening invitations and tests have returned to pre-pandemic levels, albeit not yet in all regions (24).

*Table 4 - Characteristics of the Sample, Overall and by Period of Surgery in Italy*

| Variable | Overall sample (N = 17 938) | Prepandemic period (January 2018 to February 2020) (n = 10 142) | Pandemic period (March 2020 to December 2021) (n = 7796) | Difference between prepandemic and pandemic periods (95% CI) | *P* value[a] |
|---|---|---|---|---|---|
| Age, mean (SD), y | 70.6 (12.2) | 70.5 (12.0) | 70.7 (14.0) | −0.2 (−0.5 to 0.2) | .40 |
| Age class, No. (%) | | | | | .048[b] |
| <60 y | 3437 (19.2) | 1950 (19.2) | 1487 (19.1) | 0.1 (−1.0 to 1.3) | .80 |
| 60-69 y | 3969 (22.1) | 2286 (22.5) | 1683 (21.6) | 0.9 (0.3 to 2.2) | .13 |
| 70-79 y | 5766 (32.1) | 3296 (32.5) | 2470 (31.7) | 0.8 (−0.6 to 2.2) | .25 |
| ≥80 y | 4766 (26.6) | 2610 (25.7) | 2156 (27.7) | −1.9 (−3.2 to −0.6) | .004 |
| Sex, No. (%) | 18284 | 10142 | 7796 | - 12,83% | |
| Men | 10 007 (55.8) | 5724 (56.4) | 4283 (54.9) | −1.5 (−3.0 to 0.0) | .045 |
| Women | 7931 (44.2) | 4418 (43.6) | 3513 (45.1) | | |
| Asymptomatic disease, No. (%) | 3153 (17.6) | 1941 (19.1) | 1212 (15.6) | 3.6 (2.5 to 4.7) | <.001 |
| Positive fecal occult blood test screening result, No./total No. (%) | 4529/17 174 (26.4) | 2583/9694 (26.6) | 1946/7480 (26.0) | 0.6 (−0.7 to 2.0) | .35 |
| Location, No. (%) | | | | | |
| Right or transverse colon | 7750 (43.2) | 4387 (43.3) | 3363 (43.1) | 0.1 (−1.3 to 1.6) | .87 |
| Left colon | 5253 (29.3) | 2932 (28.9) | 2321 (29.8) | −0.9 (−2.2 to 0.5) | .21 |
| Rectum | 4935 (27.5) | 2823 (27.8) | 2112 (27.1) | 0.7 (−0.6 to 2.1) | .27 |
| Tumor histologic type | | | | | |
| Adenocarcinoma | 17 626 (98.3) | 9992 (98.5) | 7634 (97.9) | 0.6 (0.2 to 1.0) | .002 |
| Squamous cell carcinoma | 145 (0.8) | 76 (0.8) | 69 (0.9) | −0.1 (−0.4 to 0.1) | .31 |
| No histology (palliative surgery) | 167 (0.9) | 74 (0.7) | 93 (1.2) | −0.5 (−0.7 to −0.2) | .001 |

Colorectal Cancer Stage at Diagnosis Before vs During the COVID-19 Pandemic in Italy. Matteo Rottoli, Alice Gori, Gianluca Pellino, Maria Elena Flacco, Cecilia Martellucci, Antonino Spinelli, Gilberto Poggioli. JAMA Netw Open. 2022 Nov; 5(11): e2243119.

## Biology of CRLM:

The liver is the most common site for metastatic disease to occur in colorectal cancer (CRC). When cancer cells from the primary sites in the colon escape into the bloodstream, the liver is the most likely location for lodgment. Kelly et al. suggested that micrometastasis occurs when cancer cells from the primary CRC site escape into the portal circulation. Cancer cells from gastrointestinal malignancies, especially from CRC, hematogenously spread via the portal circulation, often resulting in the liver being the first site of metastasis. Furthermore, when hepatic metastases grow beyond 2 mm, the derivation of additional blood supply becomes crucial for cancer cells to survive. These metastatic tumors secrete angiogenic factors to induce neovascularization and derive blood supply from the hepatic artery, while normal hepatocytes are mostly perfused from the portal circulation. (25) (26).

Recently, the concept of the liver metastasis microenvironment (LME) has emerged as we gain a better understanding of the interactions between cancer cells and the microenvironment in the liver parenchyma. The engraftment of metastatic colon cancer cells in the liver microenvironment and subsequent growth and proliferation within the liver parenchyma involve intricate communication between the cancer cells, inflammatory and immune cells in the liver, as well as the hepatocytes and non-parenchymal cells in the liver (27) (28).
Strategies that harness the engagement of the immune system to target both cells and molecules within the liver metastasis microenvironment (LME) have shown to be successful approaches, yielding highly effective and durable therapeutic modalities. Colorectal liver metastasis (CRLM) can be classified into two specific niches: premetastatic niche formation and post-tumor invasion niche. The latter consists of four distinct phases of the tumor metastasis process, namely the microvascular phase, preangiogenic phase, angiogenic phase, and growth phase. During the premetastatic niche, primary tumor cells secrete factors that recruit nonparenchymal cells, including Kupffer cells (KC), hepatic stellate cells (HepSC), myeloid-derived suppressor cells (MDSC), and neutrophils, to aid their invasions. Recent evidence supporting this postulation has demonstrated that tumor-derived factors can activate the cells at the LME to render them perLLRsive to metastatic outgrowth in advance of tumor cell entry (29) (30).
Once cancer cells enter the liver microvasculature during the microvascular phase, they must evade local immune cell elimination, including Kupffer cells (KC) and hepatic natural killer (NK) cells. To evade destruction by proinflammatory cells, cancer cells may bind to cytokine-induced endothelial cell adhesion molecules (CAMs) and transmigrate into the space of Disse if they express the appropriate counter receptors. (31)
After successfully evading proinflammatory cytokines, tumour cells infiltrate and expand within the liver parenchyma, facilitated by quiescent hepatic stem cells (HepSCs) during the proangiogenic phase. HepSCs deposit collagen and fibronectin, which provide a scaffold for endothelial migration, angiogenesis, and the establishment of extravascular micrometastases. This process is mainly driven by TNFαβ and TGFβ. This sets the stage for the angiogenic phase, during which metastatic cancer cells within the liver parenchyma start co-opting surrounding vessels to draw blood supply to prepare for their growth.
Classically, vascular endothelial growth factors (VEGF) and basic fibroblast growth factor (bFGF) are the factors that trigger the angiogenic process. Many cells in the liver microenvironment secrete

these factors in response to cytokine release, including Kupffer cells (KCs), newly recruited polarized tumour-associated macrophages (TAM) to M2 phenotype, tumour-associated neutrophils (TAN), and HepSCs (32).

Once tumour cells have gained access to the bloodstream, they proliferate and expand during the growth phase. However, this is not a "free-for-all" situation for the cancer cells. The T-cell mediated response, including CD4+ T helper cells and CD8+ cytotoxic T lymphocytes (CTLs), within the liver can curtail metastatic expansion by activating different cytolytic mechanisms. The tumour cells have been shown to evade the cytolytic process via co-inhibitory molecules such as programmed cell death protein 1 (PD-1) that binds to ligands PD-L1 or PD-L2 on the cancer cell, and the CTL-associated protein 4 (CTLA-4), resulting in inhibition of T effector cell functions. In the transforming growth factor beta (TGFβ)-rich tumour microenvironment (TME), tumour-associated macrophages (TAMs) and tumour-associated neutrophils (TANs) can acquire immunosuppressive M2 and N2 phenotypes, respectively. Immune tolerance by cancer cells is further enhanced by recruitment of immunosuppressive lymphoid and myeloid subsets, including myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs). Other pro-tumorigenic growth factors in this liver microenvironment (LME) include type I insulin-like growth factors, epidermal growth factor (EGF), hepatocyte growth factor (HGF) produced by hepatocytes, and M2 TAMs and HepSCs, respectively (33) (34).

Understanding the tumor microenvironment (TME) is of paramount importance in identifying suitable targets for preventing and treating metastatic colorectal liver metastasis (CRLM). Cancer cells rely on the TME for their survival and growth, and within this microenvironment, cells exhibit genetic stability and predictable properties and responses. Targeting the microenvironment may prove beneficial across various tumor types, particularly those that metastasize to common secondary sites such as the liver (35) (36).

## Biological markers for CRLM

Based on the current standard of care, the mutations in KRAS and BRAF are among the most extensively studied in the context of colorectal cancer (CRC). The presence of a KRAS mutation has been linked to a reduced likelihood of resectable colorectal liver metastasis (CRLM), as well as a higher risk of extrahepatic disease and an unfavorable response to targeted anti-EGFR therapy, oxaliplatin, or irinotecan-based peri-operative chemotherapy. Furthermore, patients with RAS

mutations have been found to have lower survival rates after undergoing CRLM metastasectomy. Hence, determining the RAS mutation status is crucial in guiding treatment decisions, particularly in cases where aggressive surgical approaches such as two-stage liver resections or liver resections after second-line chemotherapy are being considered. Similarly, BRAF mutation in CRC has been linked to poorer survival outcomes and reduced response to biological therapies (37) (38). The outcomes of patients with BRAF mutation status who underwent metastasectomy for colorectal liver metastases (CRLM) have been demonstrated to be poor. Along with KRAS and BRAF mutations, caudal-type homeobox transcription factor 2 (CDX2), a critical regulator of intestinal development and oncogenesis, has been identified as a useful marker for prognostication in colorectal cancer (CRC). Recently, CDX2 expression has been found to correlate well with the behavior of CRLM. Patients with metastatic colorectal disease who have CDX2-negative status were found to have poorer overall survival (OS). CDX2 negativity was also correlated with a higher likelihood of right-sided primary tumors, poorly differentiated cancers, distant lymphatic metastasis, and being female (39) (40).

In a systematic review conducted by (CRLM), it was revealed that a majority of studies reported differences in molecular marker expression between CRLM and their respective primary tumours in both the synchronous and metachronous groups. Furthermore, investigations on genetic aberrations showed that the majority of changes identified in the primary tumours were retained in the CRLM. Additionally, the study found conflicting results indicating that CRLM in the synchronous and metachronous groups exhibit some differences, suggesting a more aggressive tumour subtype in the synchronous group. For instance, p27 marker expression was found to be correlated with advanced stages of CRC, with reduced expression observed in liver metastasis in the metachronous group, possibly due to post-translational degradation of the protein in the liver metastases (41) (42) (43) (44)

In synchronous colorectal liver metastases (CRLM), the expression of cyclin-E was also found to be decreased, although its significance and role remain uncertain at present. Pantaleo et al. reported an elevation in the expression of the cyclooxygenase-2 (COX-2) gene in synchronous CRLM, while contrasting results were observed in the expression of epidermal growth factor receptor (EGFR) in metachronous CRLM. Some studies reported overexpression of EGFR, while others found no difference in EGFR expression between synchronous and metachronous CRLM. Stratifying the immune environment and responses has led to the development of immunescoring,

which has proven to be a superior prognostic tool for patients with colorectal cancer (CRC) than microsatellite instability (MSI), which is currently used to predict the response of these patients to anti-programmed cell death protein 1 (PD-1) therapy. Further extension of this concept has led to the use of liquid biopsy to identify specific expressed genomic materials, which can guide prognostication and therapeutic decision-making in cancer treatment. Efforts have been made to rationalize and establish instrumental guidelines for personalized therapies (45) (46). Blank et al. have proposed a dynamic model of the "cancer immunogram," which necessitates the evaluation of a combination of biomarkers to aid in individualizing treatment options for cancer patients. Initially, a framework comprising of seven parameters has been established: tumor foreignness, general immune status, immune cell infiltration, absence of checkpoints, absence of soluble inhibitors, absence of inhibitory tumor metabolism, and tumor sensitivity to immune effectors. The assessment of these factors can be achieved by utilizing a combination of tumour genomics, immunoscore assay, immunohistocheLLRtry, standard blood assays, and immune gene signature, both pre and post-therapy. This approach could be instrumental in identifying the most effective therapeutic intervention for individual patients. The use of liquid biopsy is anticipated to become the standard diagnostic modality in the near future (47) (48).

## Inflammatory markers as a useful tool for early diagnosis in colorectal cancer

Reactive oxygen species (ROS) are produced through biochemical redox reactions that occur during normal cellular metabolism. However, if ROS are present in high quantities and/or not adequately eliminated, they can lead to oxidative stress (OS), resulting in severe metabolic dysfunctions and cellular damage. Elevated levels of ROS can interact with biomolecules, such as lipids, nucleic acids, and proteins, ultimately impairing their function. It is well-established that OS and inflammation play critical roles in the pathogenesis of chronic diseases, including cancer, and particularly colorectal cancer (CRC). Conversely, increased cellular proliferation within an inflammatory cytokine-rich microenvironment fosters cancer development. This process is dependent on ROS and has been implicated in the initiation and progression of CRC (49) (50). Within the genome, guanine (G) is highly susceptible to oxidative stress (OS) due to its relatively lower redox potential. Oxidative stress results in the formation of various lesions, one of which is 8-oxo-7,8-dihydro-20-deoxyguanosine (8-oxodG), a mutagenic base. If not repaired efficiently, 8-oxodG can pair with adenine (A) to cause GC > TA transversion mutations. This makes 8-oxodG one of the primary forms of free radical-induced oxidative DNA damage and a pivotal marker for

the initiation and promotion of carcinogenesis in humans.
Under physiological conditions, antioxidant and pro-oxidant systems coexist in equilibrium. Protective antioxidant mechanisms involve catalase (CAT) and the glutathione system. Physiologically, CAT plays a fundamental role in the detoxification of hydrogen peroxide generated by certain peroxisomal enzymes such as amino-oxidase. In cells, glutathione exists primarily in a reduced state (GSH) and, to a lesser extent, in an oxidized state (GSSG). This redox state is maintained by glutathione reductase, which reduces GSSG back to GSH. This enzyme is constitutively active and can be induced during oxidative stress (51) (52).
Inflammatory factors have emerged as valuable prognostic markers in colorectal cancer (CRC), aiding in the development of treatment plans and guiding therapeutic interventions. The role of cancer-related inflammation in promoting tumor proliferation, angiogenesis, metastasis, and chemotherapy resistance is well established. Various serum inflammatory markers have been identified as prognostic biomarkers in different cancer types, including CRC. Neutrophils, lymphocytes, monocytes, platelets, C-reactive protein (CRP), and albumin, alone or in combination, have been associated with CRC survival. These markers can be classified into cellular and protein components.
CRP, an acute-phase protein, is regulated by pro-inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1, and interleukin-6.
Albumin, a nutritional status parameter, is associated with chronic inflammation. The Glasgow Prognostic Score (GPS) and the modified Glasgow Prognostic Score (mGPS) are classic scoring systems that utilize these two protein markers.
Both GPS and mGPS have been reported as independent prognostic factors for CRC. By incorporating inflammatory markers, these scores provide a more comprehensive evaluation of the patient's overall inflammatory and nutritional status, which is critical in predicting outcomes and guiding therapeutic interventions (53) (54) (55).
Ishizuka et al. reported a statistically significant increase in overall survival among the low pre-treatment Cancer-Associated Ratio (CAR) subgroup relative to the high pre-treatment CAR subgroup (HR 2.596, $P < 0.001$) in their analysis of 627 patients with colorectal cancer who had undergone elective surgery. Conversely, Zhou et al. found that the dynamic change in CAR from pre- to post-surgery strongly correlated with overall survival in patients with colorectal cancer who had undergone surgery. However, when using only pre-operative CAR data, there was no

significant impact on overall survival (HR 1.59, 95% CIs 0.86–2.91) (56).
In the CLUE II medical records, which were linked with the Washington County and Maryland State cancer registries, the research team at Johns Hopkins University identified 172 individuals who were diagnosed with colon or rectal cancer subsequent to their initial blood draw date until December 2000. Specifically, 131 had colon cancer and 41 had rectal cancer. For each of these cases, the team compared their medical records with those of up to two healthy individuals who had enrolled in the study at the same time, with the healthy group serving as a control. At baseline, the median level of C-reactive protein (CRP) was higher among individuals who later developed colon cancer (2.69 mg/L) than in those who did not develop the disease (1.97 mg/L). Furthermore, the study demonstrated a progressive increase in the likelihood of developing colorectal cancer with higher levels of CRP. Individuals in the highest quartile of CRP had a twofold greater risk of developing colorectal cancer overall, and a 2.5-fold higher risk of developing colon cancer, than those in the lowest quartile. The findings were consistent among non-smokers as well, with those in the highest quartile of CRP being 2.5 times more likely to develop colorectal cancer and 3.5 times more likely to develop colon cancer than those in the lowest quartile. Moreover, the study showed that individuals who had taken aspirin or nonsteroidal anti-inflammatory drugs within 48 hours prior to blood draw had a lower risk of developing colorectal cancer. Finally, the study revealed that the association between inflammation and colon cancer was not related to diabetes, contradicting the belief that diabetes acts as a mediator between inflammation and cancer risk (57).
Some authors have reported a higher inflammatory index in right colon cancer (RCC) compared to other segments of the colorectal region. This has been shown to impact the prognosis of RCC due to its aggressive oncological behavior and worse survival rates when compared to left-sided colon cancers (LCC). The lymphatic system in the right-sided colon is believed to be more complex, which can potentially facilitate a cancer-related inflammatory response in RCC. Several studies have reported a more intense inflammatory response in the growth and development of RCC, as evidenced by histopathological analysis of colorectal tumor tissue samples, when compared to LCC (58).
The aim of this study is to examine possible correlations between oxidative stress (OS) markers and the presence of tumors, as well as laboratory and inflammatory markers that are currently utilized in clinical practice. It is hypothesized that pro-oxidant markers would be increased and

antioxidant markers would be decreased in colorectal cancer (CRC) patients.

## Definition of synchronous and metachronous liver metastasis

There are varied definitions of synchronous and metachronous colorectal liver metastases (CRLM) reported in the literature. While most definitions of synchronous CRLM include liver metastasis detected at or before diagnosis or surgery of the primary tumor, there are others that include metastases detected up to 3-6 months following diagnosis.
To address this issue and review the recommendations for the management of CRLM, the Expert Group on Onco-Surgery management of Liver Metastases (EGOSLIM) convened to debate on this matter (59) (60). The results of the meeting yielded the international consensus statements as follows:

- Synchronous colorectal liver metastases (CRLM) are associated with less favorable cancer biology and lower expected survival compared to metachronous metastases, particularly late metachronous metastases.

- Synchronous CRLM should be defined as "synchronously detected liver metastases," which refers to liver metastases detected at or before the diagnosis of the primary tumor.

- Early metachronous metastases are those detected within 12 months after the diagnosis or surgery of the primary tumor.

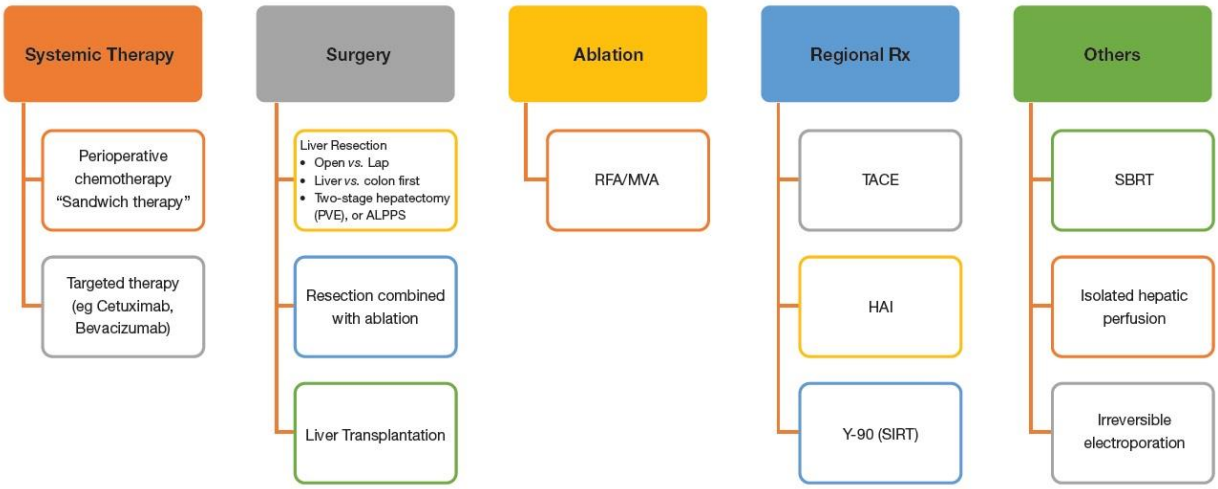
- Late metachronous metastases are those detected more than 12 months after the diagnosis or surgery of the primary tumor.

Clear definitions of these conditions are essential, as the tumor biology of synchronous and metachronous colorectal liver metastases (CRLM) are now understood to be distinct, and the natural history of the disease as well as response to treatment can vary.

## Treatment of CRLM

Two decades ago, treatment options for metastatic colorectal cancer were limited. Today, a variety of treatment modalities have emerged that provide reasonably good long-term survival rates, as mentioned above. However, the key to successful treatment of CRC with liver metastases and other extrahepatic metastases is a multidisciplinary approach involving medical oncologists, radiation oncologists, colorectal surgeons, hepatobiliary surgeons, and other specialists.

*Table 5 - Current treatment options for colorectal liver metastasis*




### Resection of CRLM

In past patients with metastatic colorectal cancer had limited treatment options and were often relegated to palliative care, with a median life expectancy of around 9 months and a 5-year survival rate of only 3%. However, the landscape of treatment options has significantly improved with the development of effective systemic therapies such as chemotherapy and biologic agents. As a result, surgical resection of colorectal liver metastases (CRLM) has emerged as a potentially curative treatment with good long-term survival rates (61) (62).
The combination of systemic chemotherapy with resection of colorectal liver metastases (CRLM) has demonstrated a 5-year survival rate of 50%, according to findings reported by Norlinger et al. in the EORTC 40983 trial. Despite the relatively high incidence of colorectal cancer (CRC) recurrence, which can occur in up to 70% of cases, this treatment approach represents a substantial

improvement compared to historical standards. Continued research and advancements in this area are expected to yield valuable insights into the most effective treatment strategies for CRLM in the future (63).

Identifying which patients will benefit from liver resection for colorectal liver metastases (CRLM) has proven to be a difficult undertaking.

In 1999, Fong et al. developed the Clinical Risk Score, an algorithm that included variables such as a positive surgical margin, presence of extrahepatic disease, node-positive primary tumor, disease-free interval from primary to metastases, the number of hepatic metastases (>1), the largest hepatic lesion (>5 cm), and a carcinoembryonic antigen (CEA) level >200 ng/mL. Based on the prognostic scoring system, low risk patients demonstrated a 5-year survival of 47% as compared to high risk patients with only 24% of 5-year survival (64).

Making the decision for surgery in patients with CRLM is a complex task that requires consideration of various factors. These include the timing of systemic chemotherapy administration, with or without anti-EGFR agents, before or after liver resection, as well as how to assess response before proceeding with liver resection to ensure an adequate future remnant liver (FRL). Additionally, the optimal sequence of liver surgery, such as whether colon resection or liver resection should be performed first, or if combined simultaneous surgery is the best option, is also a matter of debate. With the advent of liquid biopsy, precision surgery guided by the identification of specific genetic mutations and biomarkers may soon become a reality. This approach could help to accurately identify patients with CRLM who would benefit from surgery and improve survival outcomes (65) (66).

Nonetheless, before we reach that final destination, there are currently some recommendations by the international consensus from the EGOSLIM (Expert Group on OncoSurgery management of Liver Metastases) group with regard to the timing and roles of liver resection in the context of synchronous and metachronous CRLM.

In general, potentially curative treatments are goals for patients with one site of surgically resectable metastatic disease, such as in CRLM, especially in metachronous setting. For those with more than one site of metastatic disease, the general goal is cancer control.

To summarise the clinical approach to synchronous and metachronous CRLM as follows (67):

**I) Synchronous Colorectal Liver Metastasis (CRLM) in Patients with Resectable CRLM and**

**Asymptomatic Colorectal Cancer (CRC)**

The management of synchronous CRLM in patients with resectable CRLM and asymptomatic CRC involves the following considerations:

- Preoperative chemotherapy should be administered unless early surgery of the primary and LM is being considered.
- Preoperative radiotherapy is a standard of care for rectal tumors, except for high rectal tumors or T2 tumors, and one-stage surgery should not be performed.
- One-stage surgery for colonic primary tumors is not recommended for tumors requiring complex surgery, in high-risk patients, or when hepatectomy would be major.
- A total of 6 months of chemotherapy is recommended, regardless of whether it is given preoperatively or postoperatively.
- Postoperative chemotherapy may differ from preoperative chemotherapy and may be less intense.

**II) Synchronous CRLM in Patients with Non-resectable CRLM and Asymptomatic CRC**

The management of synchronous CRLM in patients with non-resectable CRLM and asymptomatic CRC involves the following considerations:

- Chemotherapy should be administered initially with the aim of achieving resectability of CRLM metastatectomy.
- If the CRLM become resectable, a reverse strategy should be advocated.
- For rectal cancer, radiotherapy may be given before chemotherapy or after resection of the CRLM.

**III) Synchronous CRLM in Patients with Resectable CRLM and Symptomatic CRC**

The management of synchronous CRLM in patients with resectable CRLM and symptomatic CRC involves the following considerations:

- For bleeding CRC, following transfusions, preoperative chemotherapy should be advocated.

- For perforations, resection of the primary to remove the tumor (right colon) or suture or creating a stoma (left colon) is advocated.

- For proven occlusion with distended evidence of obstruction, resection of the primary should be performed first.

- For occlusions, stents are an option, but the results have been poor.

- Liver resection will be done after the crisis for the primary colon tumor is taken care of.

**IV) Synchronous CRLM in Patients with Non-resectable CRLM and Symptomatic CRC**

The management of synchronous CRLM in patients with non-resectable CRLM and symptomatic CRC involves the following considerations:

- The aim is to make the CRLM resectable, and chemotherapy should be administered initially with the aim of achieving resectability of CRLM metastatectomy to have a safe liver resection.

- Liver surgeons are often asked during the multidisciplinary tumor board to review the scans of patients with CRC with liver lesions to determine whether those metastatic lesions are resectable or not.

- Resectability of the CRLM is determined by many factors, such as the size and number of nodules, the relationship of the lesion(s) with major hepatic vessels, and the segmental localization of the lesions in the liver, response after neoadjuvant chemotherapy, non-

tumoral liver quality-cirrhotic or not-mandatory to check hep b/c before chemo, NASH or CASH liver, and adequate remnant liver volume after resection (68) (69).

## Recurrence pattern according to the NCCN and AJCC guidelines

After reviewing the guidelines from the National Comprehensive Cancer Network (NCCN) and the American Joint Committee on Cancer (AJCC), we have observed a correlation between the incidence of metastatic liver lesions and the location of colorectal tumors. Rectal cancers located ≤12 cm from the anal verge showed a higher rate of liver metastasis (8.3%) compared to colon cancers (P=0.0631, P=0.0117). In rectal cancer patients treated with surgical monotherapy, the liver recurrence (LR) rate was 8.5% in those located ≤12 cm from the anal verge, which was significantly higher than that in colon cancer patients located less than 12 cm from the anal verge (P=0.0467).

These findings suggest that rectal cancer patients with tumors located ≤12 cm from the anal verge may be at a higher risk of developing liver metastasis and LR compared to colon cancer patients. Therefore, more aggressive surveillance and treatment strategies may be necessary for these patients to improve outcomes (70) (71).

*Table 6 - Recurrence pattern according to National Comprehensive Cancer Network and American Joint Committee on Cancer guidelines.*

| | Liver (%) | | | Lung (%) | | | Local (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Metastasis | 〃 | *P* value | Metastasis | 〃 | *P* value | Metastasis | 〃 | *P* value |
| Colon cancer | 77 (12.6) | 530 (87.4) | | 33 (5.4) | 574 (94.6) | | 21 (3.4) | 586 (96.6) | |
| > 12 cm | 6 (11.5) | 46 (88.5) | | 2 (3.8) | 50 (96.2) | | 4 (8.3) | 48 (91.7) | |
| ≤ 12 cm | 25 (8.3) | 274 (91.4) | 0.0631 | 29 (10.7) | 270 (89.3) | 0.0117 | 7 (8.5) | 75 (91.5) | 0.0467 |
| Total | | 958 | | | 958 | | | 740 | |

Miyakita H, Kamei Y, Chan LF, Okada K, Kayano H, Yamamoto S. Classification of rectal cancer according to recurrence types-comparison of Japanese guidelines and Western guidelines. World

## Oncologically appropriateness

While previously thought that the greater the number and size of the lesions, the worse prognosis of the CRLM. However, if a complete resection of CRLM can be achieved with negative margins (R0), then the survival rate is not affected by the number of lesions. The major challenge lies in identifying patients who are suitable candidates for liver resection.
Several criteria have been proposed to aid in the selection of patients for CRLM liver resection to maximize survival benefits.
The Clinical Risk Score by Fong et al., which was published in 1999, was the first scoring system to provide guidance on the selection of appropriate candidates for liver resection. Since then, additional prognostic scoring systems have been developed, many of which have shown good correlation with long-term survival. However, these scoring systems are still considered a crude model for selecting patients who will benefit from resection of CRLM.
As numerous systemic and potentially immunotherapeutic options become available, the future of CRLM liver metastasectomy case selection will likely be based on serum biomarkers and genomic profiling of tumors (72) (73) (74) (64).

## Resection margins

The adequacy of resection margins in colorectal liver metastases (CRLM) liver resection has been a subject of long-standing debate. The "1 cm margin rule" has been questioned as some studies have shown that resection margins less than 1 mm in CRLM metastasectomy do not impact prognosis, provided that the patient receives timely and effective systemic therapy. Although the "1 cm margin rule" is no longer the standard for resectability, some studies suggest that wider margins may be associated with a better prognosis. However, other studies have demonstrated that narrower margins (<1mm) do not lead to inferior outcomes.
To address this issue, the Expert Group on OncoSurgery management of Liver Metastases (EGOSLIM) convened a meeting in 2015. The outcome of this meeting emphasized that safe resection margins are still a therapeutic goal, and a minimal surgical clearance margin of 1 mm has been suggested as sufficient. However, the optimal surgical margin for CRLM remains a matter of debate (75) (76) (77).

Recently, Margonis et al. conducted a systematic review and meta-analysis of 34 studies comprising of 11,147 hepatic resections. They found that a wider resection margin (>1 cm versus <1 cm) was significantly associated with improved overall survival (OS) at 3, 5, and 10 years. Additionally, disease-free survival (DFS) was also positively associated with >1 cm resection margin at 3, 5, and 10 years. Their meta-regression analyses did not reveal any significant modifying role of the study features under investigation, such as the administration of neoadjuvant/adjuvant therapy. Therefore, they concluded that while a >1 mm margin is associated with better prognosis than a submillimeter margin, achieving a margin >1 cm may result in even better oncologic outcomes and should be considered if possible (78) (79).
Assuring adequate future liver remnant (FLR) volume and liver parenchyma quality is crucial for the liver surgeon to assess liver scans to determine the location and size of the lesion in relation to critical surrounding structures, such as bile duct, portal vein, hepatic artery, and hepatic veins. The relationship of the lesion(s) to these structures significantly influences surgical planning.

Peripherally located tumors can be easily resected if the quality of the liver parenchyma allows it. In most cases, the liver parenchyma of patients with CRLM can withstand liver resection, provided that it is not exposed to excessive systemic chemotherapy, which may cause chemotherapy-associated liver injury (CALI), as discussed above. Small wedge resection is generally safe in most patients. However, if tumors are located deep within the liver parenchyma and near major hepatic veins, portal veins, or biliary pedicles, major liver resection may be necessary to achieve R0 resection. In this case, careful consideration must be given to the size of the FLR and the adequacy of liver function post-resection. In most cases, up to 70-75% of non-cirrhotic liver can be resected, as long as the remnant liver volume contributes to 25-30% of the total liver volume. The safety margin increases significantly in these patients with non-cirrhotic liver if a smaller resection is required (80) (81).
Further evaluation of hepatocyte quality and function can be achieved by performing the indocyanine green (ICG) clearance test. This dye is exclusively cleared by hepatocytes and excreted into the biliary system, and the amount of ICG retained in the blood at a certain duration after injection can be used to stratify the risk of major liver resection. Imamura et al. proposed the use of the Makuuchi decision algorithm, which is based on ICG retention at 15 minutes, as follows: <10% at 15 min for trisectionectomy or bisectorectomy of the liver; 10% to 19% for hemihepatectomy, right-sided sectorectomy; 20% to 29% for segmentectomy; 30% to 39% for

limited resection (e.g., wedge resection); and >40% for enucleation. Hepatobiliary surgeons may occasionally face challenging situations where liver resection is technically feasible and oncologically sound, but the remnant liver volume is deemed inadequate (i.e., <25% of the total liver volume). In such situations, methods to increase the future liver remnant (FLR) may need to be considered. Options to grow the FLR can be divided into portal vein embolization (PVE) and staged hepatectomy, portal vein ligation (PVL) and staged hepatectomy, and the association of liver partition with portal vein ligation for staged hepatectomy (ALPPS) (82) (83) (84).

To leverage the regenerative potential of the liver and promote the growth of the future liver remnant (FLR), the technique of portal vein ligation (PVL) was first introduced by Honjo et al. in 1975. However, the concept of inducing liver hypertrophy by manipulating portal blood flow was initially proposed by Cantlie in 1897 and later by Rous in 1920. PVL is commonly employed in two-stage procedures, where FLR cleansing from tumors may be carried out simultaneously with PVL. Subsequently, after achieving adequate FLR hypertrophy, the diseased portion of the liver is excised during a second stage (85) (86) (87).

Patients with bilateral colorectal liver metastasis (CRLM) and a small estimated tumor-free future liver remnant (FLR) pose a treatment challenge. Two-stage hepatectomy (TSH) may be necessary for these patients, with portal venous ligation (PVL) or portal venous embolization (PVE) included in the first stage to stimulate FLR hypertrophy before final resection. This approach results in a 27% to 39% increase in FLR volume within 4 to 8 weeks, although longer periods may be required. However, this method carries inherent risks, such as tumor progression during the waiting period and insufficient hypertrophy, which can make resection impossible in 25% to 38% of patients preparing for TSH (88).

Kinoshita et al. and Makuuchi et al., in the late 1980s, introduced the techniques of portal vein embolization (PVE) by injecting embolizing agents into one of the portal branches. In recent decades, PVE has gained wide acceptance in the field of liver surgery. Direct comparisons between PVE and portal vein ligation (PVL) regarding the hypertrophy of the future liver remnant (FLR) have been reported, but the results remain controversial. Despite their popularity, these techniques are associated with a high drop-out rate. The drop-out rate has been reported to be as high as 35% of patients due to insufficient liver hypertrophy of the FLR or tumour progression. The high drop-out rate associated with these techniques, was

particularly due to insufficient liver hypertrophy of the FLR or tumour progression. (89).

In 2011, a new liver resection concept, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), was introduced. The first clinical series of ALPPS was conducted in 2012. This method appears to increase liver growth rate and volume, rendering more patients resectable in a shorter amount of time. However, the initial study reported complications in 68% of the patients and a surgical mortality rate of 12%. Since the first description of ALPPS, there has been significant interest in this treatment, but criticism of the approach has been raised mainly regarding surgical morbidity and mortality (90) (91).
The international ALPPS registry (www.ALPPS.org) was initiated, and the first report from the registry included 202 patients. The feasibility of ALPPS was found to be 98%, and complications of Clavien–Dindo grade ≥3a were observed in 36% of patients with colorectal liver metastasis (CRLM). The 90-day mortality rate for the CRLM patients who underwent ALPPS was 8%, which is comparable to that of CRLM patients who underwent two-stage hepatectomy (TSH) (92). This analysis published results also indicate that ALPPS leads to rapid and increased hypertrophy of the future liver remnant (FLR) compared with the effects of TSH.
However, to establish the role of ALPPS in the treatment of patients with advanced CRLM, a larger proportion of patients must achieve tumor freedom in the liver without an increased frequency of severe complications or perioperative mortality. Given the reported safety profile of ALPPS in treating CRLM, this method should be compared with traditional TSH in a randomized setting with resection rates (RRs) as the primary endpoint (93).
The use of ALPPS for patients with CRLM resulted in a higher RR without a higher 90-day mortality rate or a higher rate of severe complications or a lower rate of negative surgical margins in the liver. Therefore, ALPPS is applicable when no other treatment option is available. Nonetheless, long-term outcomes remain to be elucidated, and the role of ALPPS regarding oncological outcome remains uncertain (94).

### Technical feasibility

When feasible, laparoscopic liver resection (LLR) may be a viable option for the treatment of colorectal liver metastases (CRLM). LLR may be considered a gold standard technique for CRLM

in hepatobiliary centers, as evidence suggests that patients undergoing LLR and open liver resection (OLR) have comparable oncological outcomes.
A meta-analysis by Schiffman et al. included 610 patients with metastatic colorectal cancer and compared LLR to OLR. The LLR group had lower estimated blood loss, blood transfusion rate, length of stay, and overall complication rate compared to the OLR group. There was no significant difference in operative time, margin positivity, liver-specific complications, or 30-day mortality. Moreover, there was no significant difference in 5-year disease-free survival or overall survival (OS) between the groups (95) (96) (97).
Subsequently, the Oslo-CoMet study conducted in Norway reported that laparoscopic surgery for parenchymal-sparing liver resection in patients with colorectal metastases was associated with significantly fewer postoperative complications compared to open surgery. LLR was also cost-effective compared to OLR with a 67% probability. The rate of free resection margins was the same in both groups (98) (99).
The feasibility of LLR for liver resection depends on the location of the lesions and their relationship with major structures such as the portal vein, hepatic artery, bile ducts, and hepatic veins. In some cases, the lesions may be present in multiple locations, and laparoscopic HPB surgeons need to tailor their strategy to individual patients to achieve R0 resection for all lesions, while leaving behind sufficient future liver remnant (FLR) for post-operative survival. Advances in surgical instruments have made it possible to perform laparoscopic surgery even for lesions located in difficult areas such as the caudate lobe in segment I of the liver or segment VII, with a high success rate (100) (101).

## Repeated liver resection for liver metastasis

Resection of liver metastases from colorectal cancer (CRLM) has been demonstrated to provide a reasonably high 5-year survival rate of 47% to 60% (10-12). However, despite hepatectomy, approximately 50% to 70% of patients ultimately develop recurrence, with around one-third of these patients experiencing isolated liver recurrence (102) (103).
Vaillant et al. have demonstrated that repeated hepatectomies in selected patients with recurrent CRLM may yield an overall 5-year survival of 30%. Following this report, several other publications have shown that repeated liver resection of CRLM may result in favorable survival outcomes in patients who would otherwise be considered palliative candidates.

In a meta-analysis conducted by Wang et al., which pooled data from 3,039 patients across 34 studies, the overall survival (OS) of repeat hepatectomy for recurrent CRLM was 42%. While the median overall morbidity was reported to be 23% in this cohort, the median mortality rate was 0% (range, 0% to 6%). The study also identified negative prognostic factors related to repeat hepatectomy, including high primary tumor stage (T3/T4), multiple tumors, largest tumor size ≥5 cm, and positive surgical margin at initial hepatectomy.
In the context of repeat hepatectomy, high serum CEA levels, short disease-free interval of ≤12 months, multiple tumors and bilobar disease at recurrence, largest liver lesion ≥5 cm, positive resection margins at repeat hepatectomy, and presence of extrahepatic metastases were significantly associated with poorer OS (104) (105) (106).
Repeat hepatectomy presents a considerable challenge due to several factors.
The exposure required for a repeat hepatectomy may be impeded by post-operative adhesions resulting from previous liver resection. Additionally, hypertrophy of the residual liver and changes to the hepatic anatomy from prior hepatectomy can significantly complicate vascular and biliary ductal access (107) (108). These challenges may increase the risk of morbidity and mortality in repeat hepatectomy. However, the majority of studies suggest that performing repeat hepatectomy in colorectal liver metastases (CRLM) is feasible with reasonably low morbidity and mortality rates (109) (110).
Achieving a fine balance between parenchymal preservation and anatomical resection of liver metastatic lesions is crucial. The most important consideration should be the ability to achieve R0 resection. Sparing more liver parenchyma is critical in preparing for a potential future need for another liver resection. In the event that repeat liver resection is no longer possible due to limitations in liver vascular and biliary anatomy or inadequate future liver remnant (FLR), could there be a role for liver transplantation? At this juncture, there is very little evidence to support this strategy, but the body of evidence is growing (see below on liver transplant in CRLM).
In an attempt to achieve curative treatment in CRLM, the role of systemic chemotherapy in combination with surgery is pivotal (111).

### Ablation of CRLM [radiofrequency ablation (RFA) or microwave ablation (MWA)]:

Ablation of liver lesions identified in colorectal cancers (CRCs) is a viable option considered as part of liver-targeted therapy. However, selecting patients for ablative therapy versus offering liver

resection poses a challenge, as ablation of the lesion may not confer similar survival benefits as compared to resection. Nevertheless, in cases where the tumor has recurred after previous liver resection, and re-resection is not possible, ablation of the tumor may be a feasible option to palliate the growth of the tumor, particularly when patients are fatigued from prolonged systemic chemotherapy (112) (113).

Although the long-term results of hepatic resection for colorectal liver metastases (CRLM) are established, the evidence regarding the benefits of radiofrequency ablation (RFA) as a treatment for CRLM is limited at present. Unlike hepatic resection, where long-term efficacy is relatively established, evidence regarding the benefit of RFA for the treatment of hepatic colorectal metastases is limited.

A 2009 Clinical Evidence Review by the American Society of Clinical Oncology on RFA of CRLM reported that the quality of evidence is limited. It emphasized the need for more good quality clinical trials to determine the efficacy and utility of RFA for these patients (114). Depending on the location and number of lesions, RFA can be performed percutaneously under radiological guidance (either ultrasound-guided or CT scan-guided), laparoscopically or via an open procedure. The use of laparoscopic and open surgical procedures to guide therapy allows for better evaluation of previously undetected intrahepatic disease with intraoperative ultrasound (IOUS). Additionally, IOUS permits better localization of lesions and a method to monitor ablation progress. The reported operative morbidity and mortality rates at 30 days are low (3.9% and 0.4%, respectively). Patients with poorer long-term prognoses include those with more than three lesions (median survival, 17 months) and a pre-RFA carcinoembryonic antigen (CEA) level greater than 200 ng/mL (median survival, 16 months versus 26 months for those with CEA less than or equal to 200 ng/mL).

Tumor size and location are the most significant factors associated with local recurrence following RFA. Tumors 3 cm or less and those not immediately adjacent to major vascular structures have considerably less risk of local recurrence in long-term follow-up. While some literature has reported a high local recurrence rate after RFA (40% to 50%) for CRLM lesions, some studies have reported a five-year survival of up to 40% (115).

The alternative approach for ablating colorectal liver metastases (CRLM) lesions is microwave ablation (MWA). MWA utilizes an electromagnetic field to generate direct heat destruction of tumors. The microwave field is capable of heating a larger volume of tissue more rapidly, with

less regional heat sink effect from adjacent vessels. This feature can allow for more predictable and larger tissue destruction, at a greater speed (116) (117). However, reports regarding the efficacy of MWA remain limited. Two decades ago, a small randomized study demonstrated that 30 patients treated with either resection or MWA for tumors exhibited similar survival rates, as well as similar complication rates. The median survival rates were also comparable between the two treatment modalities (median survival rates for MWA: 27 months versus resection: 25 months). A more recent series involving 50 patients with CRLM who underwent MWA for tumors up to 6 cm in size (median, 3 cm) and one to 12 tumors treated per patient, reported a median overall survival of 36 months, with a disease-free survival of 12 months post-treatment (118) (119) (120).

### Combining resection and ablation:

In patients with colorectal liver metastases (CRLM) involving both lobes of the liver, some medical centers may consider these cases as unresectable. However, innovative methods for growing the future liver remnant (FLR), such as Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) and portal vein embolization (PVE), have demonstrated efficacy in facilitating liver resection in patients previously considered unresectable.

The ultimate goal of liver resection is to achieve a state of "no evidence of disease" (NED) (121) (122). However, in some cases, a small lesion in the FLR may pose a challenge for resection. Combining microwave ablation (MWA) for small FLR lesions with resection of the part of the liver containing the majority of lesions can increase the likelihood of successful liver resection while minimizing damage to the FLR parenchyma (123) (124).

The initial experience with the combined treatment strategy for colorectal liver metastases (CRLM) was demonstrated to have inferior survival outcomes compared to liver resection alone in a study conducted by Abdalla et al. Specifically, their series showed that the overall survival (OS) rate was highest after resection (58% at 5 years), while the 4-year survival after resection, microwave ablation (MWA) and resection, and MWA alone were 65%, 36%, and 22%, respectively ($P<0.0001$). Notably, survival for "unresectable" patients treated with MWA and resection or MWA only was significantly greater than those treated with chemotherapy only ($P=0.0017$) (125) (126).

However, recent studies have demonstrated that this combination strategy can yield similar survival benefits as major liver resection for CRLM. Imai et al. reported that the combination of hepatectomy and radiofrequency ablation (RFA) can achieve outcomes comparable to hepatectomy alone. Specifically, they compared 553 patients who underwent hepatectomy combined with RFA (37 patients) with those who underwent hepatectomy alone (516 patients). In this matched cohort, overall and disease-free survival in the hepatectomy and RFA group were similar to those among patients who had hepatectomy alone (5-year OS rate 57 versus 61 per cent, P=0.649; 5-year disease-free survival rate 19 versus 17 per cent, P=0.865) (127) (128) (129).

## Liver transplantation in CRL liver metastasis

Although hepatocellular carcinoma (HCC) has emerged as the conventional indication for liver transplantation over recent decades, there is mounting evidence over the past few years that liver transplantation can confer acceptable survival benefits in cases of unresectable colorectal liver metastases (CRLM). This was demonstrated in the SECA I trial conducted by the Norwegian group in Oslo (130) (131) (132).

The main considerations when using liver transplantation as a treatment for colorectal liver metastases (CRLM) are as follows:

- Oncologically sound: survival outcomes that are comparable to other standard indications for liver transplantation.
- Interaction between immunosuppressants, systemic chemotherapy, and tumor recurrence: the use of immunosuppressants may affect the efficacy of systemic chemotherapy and the incidence of tumor recurrence.
- Availability of organs for liver transplantation: competition with other indications, such as hepatocellular carcinoma (HCC) and non-malignant cases.
- Technically sound: the choice between living-donor liver transplantation (LDLT) and deceased-donor liver transplantation (DDLT) should be made based on the individual patient's needs and the availability of organs.

These considerations are crucial in determining the suitability of liver transplantation as a treatment for CRLM (133).

One of the earliest reported experiences of using liver transplantation (LT) for patients with unresectable colorectal liver metastases (CRLM) came from the Medical University of Vienna. They published the initial experience of 25 patients who underwent LT from 1982 to 1994. The initial 3- and 5-year survival rates were 32% and 12%, respectively, but the 30-day mortality rate was high at 30%. From this study, they learned that patients with negative lymph nodes for metastasis had better long-term survival. This finding triggered a follow-up study that showed 15 of 21 patients initially classified as lymph node negative actually had micrometastases. The median survival of patients without lymph node micrometastases who underwent LT was significantly better at 118 months, compared to 28 months in patients with lymph node micrometastases (P=0.01) (134) (135).

These findings suggest that the presence of micrometastases in lymph nodes may negatively impact long-term survival outcomes in patients undergoing LT for CRLM. Therefore, careful patient selection is crucial when considering LT as a treatment option for unresectable CRLM (136) (137).

Similarly, data from the European Liver Transplant Registry, involving 58 cases of liver transplantation (LT) for non-resectable colorectal liver metastases (NRCLM) performed between 1977 and 1995, showed poor survival outcomes with a 5-year survival rate of only 18%. The reported 1, 3, and 5-year survival rates were 73%, 36%, and 18%, respectively (138) (139). The initial enthusiasm for LT in patients with unresectable CRLM waned rapidly due to unsatisfactory initial results. The key reasons were attributed to poor patient selection without a standardized protocol, the learning curve of surgical expertise in LT, and the absence of standardized immunosuppression protocols (140).

Indeed, in many initial experiences, the postoperative mortality after LT was high. Furthermore, the systemic options for chemotherapy for colorectal cancer (CRC) towards the end of the last century were not associated with good outcomes. As a result, the liver transplant community accepted that unresectable CRLM should not be treated with liver transplantation due to poor 5-year survival (<20%) and a high recurrence rate (141).

However, the results of the SECA I trial conducted by the group from Oslo University Hospital, Norway, demonstrated excellent results for patients with unresectable CRLM treated with liver transplantation. In this study, 21 out of the 25 recruited patients underwent deceased donor liver transplantation. Four patients dropped out because they developed extrahepatic disease. The median follow-up time was 27 [8–60] months, and the 1-, 3-, and 5-year overall survival (OS) rates were 95%, 68%, and 60%, respectively. Recurrence occurred in 19 (90%) patients, and 6 (29%) patients died of disseminated CRC after a median of 26 [6–41] months (142). The strict selection criteria in the SECA I trial were the main reason how this result was achievable. The inclusion criteria for this trial were R0 primary colorectal resection; at least 6 weeks of one or more chemotherapy agents received for metastatic disease; non-resectable liver metastases; no extrahepatic disease; and Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. All patients who qualified underwent an intraoperative staging laparotomy to examine the hepatic ligament lymph nodes before the transplant. If there was no disease in the frozen sections, then the transplant was performed (143) (144).

When comparing the results of the SECA I trial with systemic chemotherapy alone treatment in patients from the NORDIC VII trial retrospectively, it was demonstrated that the 5-year survival rate of the SECA I cohort was 56%, while the 5-year survival rate of the 21 patients with the longest survival in the NORDIC VII trial cohort was 19% (P=0.01). The NORDIC VII trial was a multicenter randomized 3-arm trial to assess overall survival (OS) between fluorouracil/folinic acid and oxaliplatin (FLOX) when administered in bolus (Nordic FLOX) and FLOX combined with cetuximab and intermittent FLOX associated with cetuximab in patients with advanced colorectal cancer. The 47 patients with liver-only metastases who did not undergo liver resection in the NORDIC VII trial (and therefore were treated with chemotherapy only) were compared to the 21 patients who underwent liver transplantation (LT) in the SECA trial (145) (146). The two groups were comparable, except for the CEA levels (the SECA trial cohort had a median of 15 μg/L compared with 42 μg/L in the NORDIC VI trial). All patients in the NORDIC VII trial received first-line chemotherapy, while 57% of patients in the SECA trial received second and third lines of chemotherapy. Given that there are no randomized controlled trials comparing LT to standard chemotherapy in patients with liver-only non-resectable colorectal liver metastases (NRCLM), this is the best available evidence comparing LT with standard of care chemotherapy. However, the evidence of this cohort study is still weak with several biases, and further

comparisons are needed (147) (148).

There is more data showing that well-selected patients with colorectal liver metastases (CRLM) may have good survival benefits with LT. A European consortium published a series of 12 patients who underwent LT for unresectable CRLM, showing that the OS of the cohort was 83%, 62%, and 50% at 1, 3, and 5-year, respectively. While 6 patients had recurrence, mainly in the lungs, 4 patients were alive without cancer recurrence after 48 months. These patients underwent LT after a median of 41 months following primary CRC resection, and 11 patients received chemotherapy before LT, with irinotecan and oxaliplatin being the most common protocols. While this study was a retrospective study with a very small sample size, it showed that long-term cure can be achieved with LT in these patients, and therefore, the results are very encouraging (149) (150).

The significant improvement of the 5-year survival rate of patients with unresectable CRLM treated with LT to around 50% could be attributed to better selection criteria, coupled with the discovery of effective systemic chemotherapy and improvements in perioperative care for LT recipients. However, we must acknowledge that this treatment strategy remains controversial as the cancer recurrence rate remains high (151) (152).

The Oslo group reported in a follow-up study from the SECA I trial that the median time to recurrence in their study cohort was 6 months. All the patients who were followed up for longer than 11 months experienced recurrence, with lung metastasis being the most common site. With aggressive surgical therapy, including resection of the lung lesions, they were able to achieve a 5-year survival rate of 72% after recurrence was diagnosed in patients with pulmonary first-site metastases. Multiple metastatic disease sites can be resected, and adjuvant chemotherapy can control tumor progression. While tumor recurrence certainly has an impact on patient survival, many consider metastatic CRC a chronic disease, just like metastatic breast cancer, due to effective systemic chemotherapy (153) (154).

Several studies have demonstrated the potential benefits of liver transplantation (LT) in selected patients with unresectable colorectal liver metastases (CRLM). However, one of the main challenges in LT for CRLM is the limited availability of liver grafts for transplantation, particularly in countries with a short supply of liver organs. At present, it may be difficult to justify using deceased donor liver grafts for this indication in such countries.

Fortunately, Norway enjoys a favorable donor situation, with more donors than potential recipients, and a median waiting time for LT of less than one month. As a result, the SECA I trial

was conducted successfully, paving the way for this new innovation to demonstrate the benefits of LT in unresectable CRLM (155).

Several other studies are currently underway to evaluate the efficacy of LT for CRLM. The SECA-II study, a phase 3 trial, compares deceased donor LT with liver resection in selected patients with six or more liver-only metastases from colorectal cancer (CRC) deemed technically resectable. The results of the SECA-II trial will be published soon, and we are eagerly anticipating its findings (156).

Another innovative method, which combines the concepts of ALPPS and living donor liver transplantation to left liver resection (LLR), is the RAPID concept. The Norwegian group introduced the availability of liver grafts through RAPID (Resection And Partial Liver Segment 2/3 Transplantation With Delayed Total Hepatectomy). This procedure involves the use of the ALPPS procedure, followed by living donor LT of segments 2 and 3 (left lateral section of the liver graft from the living donor) and total hepatectomy (157) (158).

It is challenging for surgical oncologists to accept the RAPID concept, as it involves resection of the left lateral section of the liver with CRLM, and concurrently implanting a segment II/III graft in the form of LDLT, with the concern that the new graft may be at risk of tumor metastasis during the growth period of the graft while the patient is on immunosuppressants. Although the diseased liver will eventually be removed with a delayed total hepatectomy, the possibility of tumor metastasis to the new graft remains a concern (159) (160).

The COLT trial is an investigator-driven, multicenter, non-randomized, open-label, controlled, prospective parallel trial aimed at assessing the efficacy (in terms of overall survival (OS)) of liver transplantation (LT) in patients with liver-only metastatic colorectal cancer (CRC), compared to a matched cohort of patients with similar tumor characteristics who were included in the phase III TRIPLETE trial investigating modified FOLFOXIRI plus panitumumab versus FOLFOX plus panitumumab (161).

The primary endpoint of the COLT trial is to compare the 3- and 5-year OS of patients enrolled in the trial with the COLT-eligible subpopulation of patients enrolled in the parallel TRIPLETE trial conducted over the same period of time. The secondary endpoints are to compare the 5-year disease-free survival and the pattern of recurrence/progression of transplanted patients enrolled in the COLT trial with the OS in the liver-limited population enrolled in the ongoing TRIPLETE trial converted to potentially curative surgical resection. The safety of LT will also be assessed using

the Dindo-Clavien Classification and the Comprehensive Complication Index, integrated with a specific list of complications possibly related to LT (162). Translational genomics, transcriptomics, and proteomics analyses on blood, plasma, peripheral blood mononuclear cell samples, and fresh-frozen tumor tissue samples will be retrospectively and prospectively collected in order to identify early tumor relapse and monitor tumor recurrence.

The main inclusion criteria for patients' enrollment are as follows:

- Age ≥ 18 and ≤ 69 years.
- Adenocarcinoma of the colon or the upper rectum, pT1-3, pN0 or pN1 (metastases in < 4 regional lymph nodes, a minimum of 12 lymph nodes should be examined), absence of peritoneal tumor deposits, absence of mucinous component >50%, confirmed R0 resection with adequate tumor-free margin.
- RAS wild-type, BRAF wild-type, and MSS molecular status
- Absence of extra-hepatic metastatic disease or local recurrence according to CT scan + MRI + PET/CT scans.
- Liver metastases not eligible for curative liver resection.
- Objective response according to RECIST 1.1 to first-line treatment, with sustained response for at least 4 months, OR disease control during second-line treatment for at least 4 months.
- A maximum of 2 prior chemotherapy treatment lines
- Performance status, ECOG 0
- CEA <50 ng/ml

- Absence of hereditary syndromes including familial adenomatous polyposis and Lynch syndrome.

- No prior extra-hepatic metastatic disease or primary tumor local relapse.

The results from this trial will shed light on the safety and efficacy of LT as a curative treatment option for a hyperselected group of patients with unresectable liver-only CRLM. The findings from this study, combined with the results of other ongoing trials on LT for CRLM, will help establish whether LT for unresectable CRLM can be offered to a specific subgroup of patients (163) (164) (165).

A number of ongoing clinical trials are currently investigating the efficacy of liver transplantation (LT) compared to different regimens of palliative chemotherapy in unresectable patients with colorectal liver metastases (CRLM). These trials include a randomized clinical trial (Transmet, NCT02597348) and two parallel studies (COLT, NCT03803436, and MELODIC, NCT04870879), with overall survival as their primary endpoint rather than recurrence-free survival. These trials are expected to yield results within the next 2-3 years. Liver transplantation represents an intriguing therapeutic option for patients with unresectable CRLM, and may also be considered for selected resectable patients. Although current evidence in this field is limited, ongoing trials are likely to substantially expand our knowledge of outcomes, selection criteria, and prognostic factors over the next decade as experience grows (166).

## Systemic therapy for treatment of CRLM

Advancements in systemic chemotherapy and biologic agents have significantly improved the overall survival (OS) of patients with colorectal liver metastases (CRLM) and other metastatic diseases in colorectal cancer (CRC) treatment (167).

Based on current evidence, possible first-line chemotherapy options for treating CRC with CRLM include fluorouracil, leucovorin, and oxaliplatin (FOLFOX), fluorouracil, leucovorin, irinotecan (FOLFIRI), capecitabine plus oxaliplatin (XELOX), and fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXFIRI). They can also be complemented with biological agents such as bevacizumab or cetuximab during treatment (168).

The RAS and BRAF mutation status are crucial in determining whether these biologic agents will

be useful in treatment strategies as discussed above. Fakih summarized the recommendations based on the RAS and BRAF mutation status. FOLFOXFIRI with or without bevacizumab, FOLFOX, or FOLFIRI with anti-EGFR are favored for downstaging for resection. However, bevacizumab must be avoided in patients at high risk of bowel perforation or thrombotic events. These regimens have been shown to have a good response rate of over 50% with an improvement in OS by approximately 30 months (169).

In the event that a response is not observed after administration of first-line therapy, there is still hope to use second-line therapy for CRLM with FOLFIRI and panitumumab to elicit some treatment response. By this time, the chance of resection of the CRLM will have significantly decreased, although it may still be possible in selected cases as shown by Adam et al. and Brouquet et al. Bearing in mind the potential toxicity of perioperative chemotherapy on the liver, which may result in chemotherapy-associated liver injury (CALI), careful discussion at the multidisciplinary tumor board will help to select appropriate patients for CRLM resection (170). Chemotherapy associated liver injury (CALI) typically presents as one of three histological patterns: steatosis, steatohepatitis, and sinusoidal obstruction syndrome (SOS) (171). Oxaliplatin is commonly associated with the development of SOS, characterized by a "blue liver," while steatohepatitis is primarily caused by irinotecan.

Studies have shown that two factors - the duration of systemic chemotherapy cessation and the total number of cycles of chemotherapy received - are significantly associated with increased post-operative complications following colorectal liver metastasis (CRLM) metastatectomy (172). Welsh et al. have reported an inverse correlation between the complication rate post-hepatectomy and the duration of time between chemotherapy cessation and surgery (173). Furthermore, Kishi et al. have reported that the administration of more than nine cycles of systemic chemotherapy may increase the likelihood of sinusoidal injury and hepatic insufficiency, without substantial improvement in pathological response rates (174).

It is evident that a combined therapeutic approach encompassing systemic chemotherapy with or without biologic agents, in addition to colorectal liver metastasis (CRLM) resection, would enhance survival outcomes for patients previously relegated to palliative care owing to their stage IV disease status. Nonetheless, judicious patient selection remains pivotal.

To ensure successful CRLM resection, it is imperative to restrict preoperative chemotherapy to no

more than six cycles, and to verify the adequacy of future liver remnant (FLR) volume and function prior to surgery (175) (176).

## Other therapeutic options for non rectable CRL liver metastasis

### Transarterial chemoembolisation (TACE)

Although transarterial chemoembolization (TACE) has been established as a therapy for hepatocellular carcinoma (HCC), its effectiveness in treating colorectal liver metastases (CRLM) is limited. The challenges of using TACE as a treatment for CRLM are twofold. Firstly, CRLM lesions are typically hypovascular due to their blood supply coming from the portal vein, rather than the arterial blood supply seen in HCC. Therefore, the uptake of the embolic material is less effective. Secondly, the chemotherapeutic agents used in TACE can be quite variable, with doxorubicin, cisplatin, and mitomycin C being the most commonly used agents for the treatment of CRLM (177) (178).

It is important to note that these agents are distinct from the mainstream systemic chemotherapeutic agents used to treat CRLM. These drugs have been combined with various microspheres and embolic agents, used alone or in combination, such as lipiodol oil, collagen particles, polyvinyl alcohol particles, or trisacryl gelatin microspheres, in order to occlude tumor vasculature (179) (180).

Most of the available data on the use of TACE in CRLM comes from prospective studies, with reported two-year survival rates as high as 66% and complete responses of 10%. An older study with 40 patients showed a median survival of 10 months with a median duration of response of 7 months, while a small phase II trial with 30 patients reported a median survival of 8.6 months. Regarding patient selection, it has been suggested that those with large tumor burdens (occupying 75% of the liver volume) may not benefit from this procedure (181).

### Yttrium-90 (Y-90) for liver metastasis

The utilization of Y-90 as a selective internal radiation therapy (SIRT) has demonstrated comparable survival outcomes to palliative systemic therapy with Sorafenib in the treatment of hepatocellular carcinoma (HCC). However, the roles of Y-90 in the treatment of colorectal liver

metastases (CRLM) have only recently been explored (182).
This modality involves the selective delivery of microspheres incorporated with radioactive Y-90 to the affected regions of the liver, similar to transarterial chemoembolization (TACE). Currently, there are two commercially available vehicles for Y-90 delivery: resin microspheres (SirSpheres, SIRTEX Medical Ltd., Sydney, New South Wales, Australia) and glass microspheres (TheraSpheres, MDS Nordion, Inc., Kanata, Ontario, Canada), each with distinct performance and delivery characteristics (183).
Limited results have been published regarding the treatment of CRLM, with initial studies conducted in highly selected patients.
In these studies, the use of SIR-Spheres in combination with hepatic arterial infusion (HAI) resulted in an improvement in time-to-progression. In a second small study, Kennedy et al. reported improved survival in patients who responded to 90-Y therapy compared to those who failed to respond (184).
Currently, the data on the efficacy of 90-Y radiotherapy are limited and its use should be approached with caution outside of a clinical trial (185).

### Stereotactic body radiotherapy (SBRT)

The use of external-beam radiotherapy for the treatment of colorectal liver metastases (CRLM) is infrequent due to concerns about the risk of radiation-induced hepatitis. The available data on its efficacy and survival benefits are limited, and it has previously been used as a palliative option in advanced metastatic liver disease.
Recently, the development of stereotactic radiation techniques has allowed for more precise and targeted delivery of radiation to the metastatic deposits, making it a viable treatment option for unresectable CRLM (186).
Therefore, stereotactic radiation may be considered in patients with symptomatic metastatic liver lesions. In a systematic review by Petrelli et al., 18 studies involving 656 patients were analyzed to evaluate the role of stereotactic body radiation therapy (SBRT) in the treatment of liver oligometastases. The pooled one- and two-year overall survival rates were 67.18% and 56.5%, respectively.
The median progression-free survival and overall survival were 11.5 and 31.5 months, respectively. The incidence of mild-moderate and severe liver toxicity was 30.7% and 8.7%, respectively. The authors concluded that SBRT is an effective option for patients with advanced

colorectal cancer, with encouraging local control and survival rates. However, further validation through large randomized studies is required due to the retrospective or non-randomized nature of the included studies and the heterogeneity in doses and treatment schedules (187) (188).

## Hepatic artery infusion (HAI)

The technique of hepatic arterial infusion (HAI) for the selective delivery of chemotherapy to intrahepatic tumors has been under investigation for more than three decades. The approach has been evaluated in both adjuvant and palliative settings, but the outcomes have been mixed. The objective of HAI is to achieve a high concentration of therapeutic agents directly in the liver tumor by delivering them through the hepatic artery. Technical challenges with catheter placement have limited its routine use in clinical practice (189) (190).
HAI is more commonly employed in the palliative setting, where colorectal liver metastases (CRLM) are unresectable. A combination of HAI with intravenous (IV) irinotecan/5-FU/oxaliplatin or oxaliplatin/irinotecan (HAI-FUDR) has been shown to increase tumor response rates up to 80% (191). In selected patients, these combinations have led to response rates of 80% as first-line therapy and 50% as second-line therapy. In the United States, the combination of FUDR-irinotecan with HAI-oxaliplatin has shown a 90% response rate and a 50% secondary resection rate.
While these data demonstrate promising results in the palliative treatment of unresectable CRLM, with some even successfully converted to a resectable state, the role of HAI in the adjuvant setting following resection remains controversial (192).
The initial controlled trial by Lorenz et al. comparing HAI and systemic chemotherapy was terminated early due to a low probability of detecting a significant survival benefit when used in combination with resection.
The reported median survival was almost six months shorter than the control group (34.5 versus 40.8 months). On the other hand, other studies have shown improved overall survival (OS) at two years for patients who receive HAI after resection combined with systemic chemotherapy compared to systemic chemotherapy alone.
Despite the potential benefits of HAI, its complexity of drug infusion, high incidence of complications, including biliary sclerosis, and limited generalizability to more than selected

centers have dampened enthusiasm for this approach (193).

### Isolated hepatic perfusion (IHP)

IHP, or isolated hepatic perfusion, is a medical technique that involves the infusion of therapeutic agents through the hepatic artery and the aspiration of chemo-saturated blood from the inferior vena cava. Typically performed during open surgery, this technique can also be achieved percutaneously through interventional radiology.

The percutaneous method involves the placement of catheters in the hepatic artery to perform the perfusion, as well as in the IVC to aspirate the chemo-saturated blood, which is then filtered and returned to the patient. Due to the requirement for invasive vascular access and treatment near critical blood vessels, this procedure must be performed with haemodynamic monitoring and support (194).

The originally described treatment agents used in IHP were tumor necrosis factor and melphalan, which demonstrated an overall objective radiographic response rate of 60-76% (195). Recently, oxaliplatin has also been trialled as the agent for IHP. However, this treatment modality for CRLM remains experimental due to the complexity of the procedure and the unclear efficacy based on current evidence (196).

### Irreversible electroporation (IRE)

In the field of liver metastasis ablation, irreversible electroporation (IRE) has emerged as an alternative technique. In cases where lesions are located in proximity to vital structures, conventional ablation techniques are often contraindicated. IRE employs electrical pulses to cause cell death and results in non-thermal tissue ablation (197).

The technique can be performed via open surgery or percutaneously, and the heat sink effect is less of a concern than with other conventional ablative methods (198).

The ability of IRE to successfully ablate colorectal liver metastases (CRLM) in humans has been demonstrated in patients with resectable CRLM in the COLDFIRE-1 ablate and resect trial. In this trial, CRLM lesions were ablated using IRE, and the resection of the lesions was performed one hour later. The resected specimens showed cell death within 1 hour of the IRE, but no significant damage to vascular structures located in the ablated zone (199).

While there have been a mixture of case reports, retrospective studies, and prospective studies in the literature, the evidence supporting IRE as a treatment for CRLM is still weak at present (200).

## Patients and methods – The ISMETT – UPMC series

The primary objectives in managing patients with colorectal liver metastases (CRLM) are to optimize their quality of life and achieve maximal survival rates. At present, surgical resection of the associated metastases constitutes the cornerstone of treatment, leading to favorable life expectancies and minimal mortality rates. Therefore, an early and personalized therapeutic approach, grounded in a thorough evaluation of the diagnosis, tumor staging, and prognosis, is highly recommended.

The aim of hepatectomy is to obtain a negative surgical margin while simultaneously preserving as much non-tumorous liver parenchyma as feasible. Nonetheless, numerous patients continue to undergo anatomic resection (AR), which is defined as the resection of one or more anatomic liver segments for CRLM, accompanied by the removal of normal hepatic parenchyma during surgery.

To determine the size, location within the liver parenchyma, and presence of vascular invasion, all patients underwent computed tomography (CT) imaging.

Patients with resectable CRLM lesions and insufficient.

Patients with resectable CRLM lesions and insufficient future liver remnant (FLR) of less than 30% were managed with portal vein embolization (PVE). This procedure was employed to induce hypertrophy of the FLR, enabling liver resection (LR) in patients with inadequate FLR prior to LR.

Liver transplantation is considered a potential curative option for patients with end-stage liver disease or those with liver cancer where curative resection is not feasible due to inadequate liver remnant or tumor margins.

Between 1999 and 2023, a total of 2796 patients underwent surgical procedures at IRCCS- IRCCS-ISMETT-UPMC-ITALY-Italy.

Prior to surgery, each patient underwent a comprehensive review by a multidisciplinary tumor board to evaluate resectability and develop an optimal resection strategy.

A total of 1201 therapeutic hepatectomies were conducted at the Department of Hepatobiliary and

Transplantation Surgery within IRCCS- ISMETT-UPMC-ITALY, as illustrated in Figure 1.

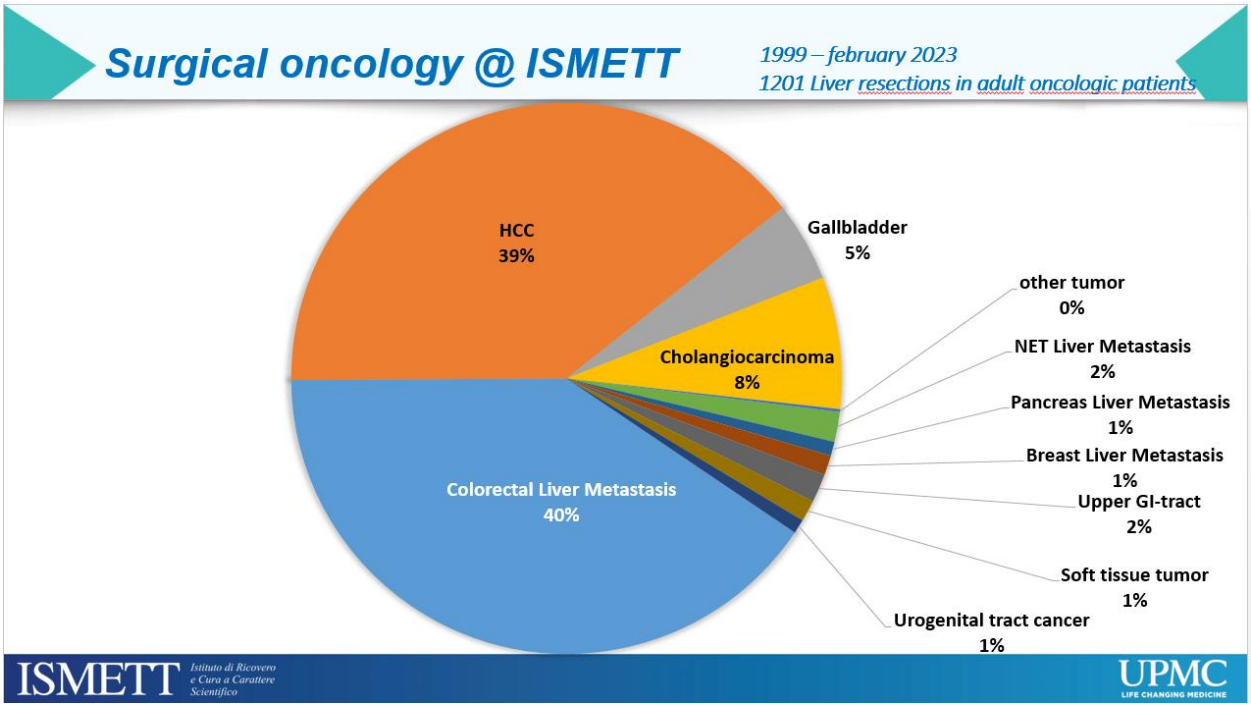



*Figure 1 - Liver resections IRCCS - ISMETT - UPMC Italy*

The retrospective analysis of this cohort demonstrated that out of 1,200 patients, 468 (39%) presented with hepatocellular carcinoma in cirrhotic livers; 480 (40%) exhibited colorectal liver metastases; 96 (8%) were diagnosed with cholangiocarcinoma; 24 (2%) had neuroendocrine tumor (NET) liver metastases; 12 (1%) displayed pancreatic liver metastases; 12 (1%) were affected by breast liver metastasis; 24 (2%) presented with upper gastrointestinal (GI) liver metastases; 12 (1%) were affected by soft tissue metastases; and the remaining 12 (1%) had liver metastases originating from urogenital tract malignancies.

## Liver resection for colorectal liver metastases IRCCS-ISMETT-UPMC-Italy series.

Between 1999 and 2023, a cohort of 486 patients underwent hepatic resection for colorectal liver metastases (CRLM). Of these patients, 428 (88%) underwent open hepatic resection, while 58 (11.9%) underwent laparoscopic liver resection (LLR). The cohort can be stratified into two groups: those who underwent major hepatectomy, defined as resection of three or more liver segments; and those who underwent minor hepatectomy, involving resection of fewer than three segments.

In the major hepatectomy group, 85 (17.4%) patients underwent right hepatectomy, with one case

performed via LLR; 21 patients (4.32%) underwent left hepatectomy; and 3 patients underwent other types of hepatectomies. In the minor hepatectomy group, 30/486 (6.17%) patients underwent left lobectomy, with 5/30 (16.6%) performed laparoscopically; 23/486 (4.73%) patients underwent bisegmentectomy, with 1/23 (4.54%) performed using LLR; 34/486 (6.99%) patients underwent segmentectomy, with 3/34 (9.67%) performed using LLR; 66/486 (13.5%) patients underwent more than 3 wedge resections, with 8/66 (13.7%) performed using LLR; 66 (13.5%) patients underwent fewer than 3 wedge resections, with 6/66 (10%) performed using LLR; and lastly, single wedge resection was performed in 160 (32.9%) patients, with 34/160 (21.2%) performed using LLR.

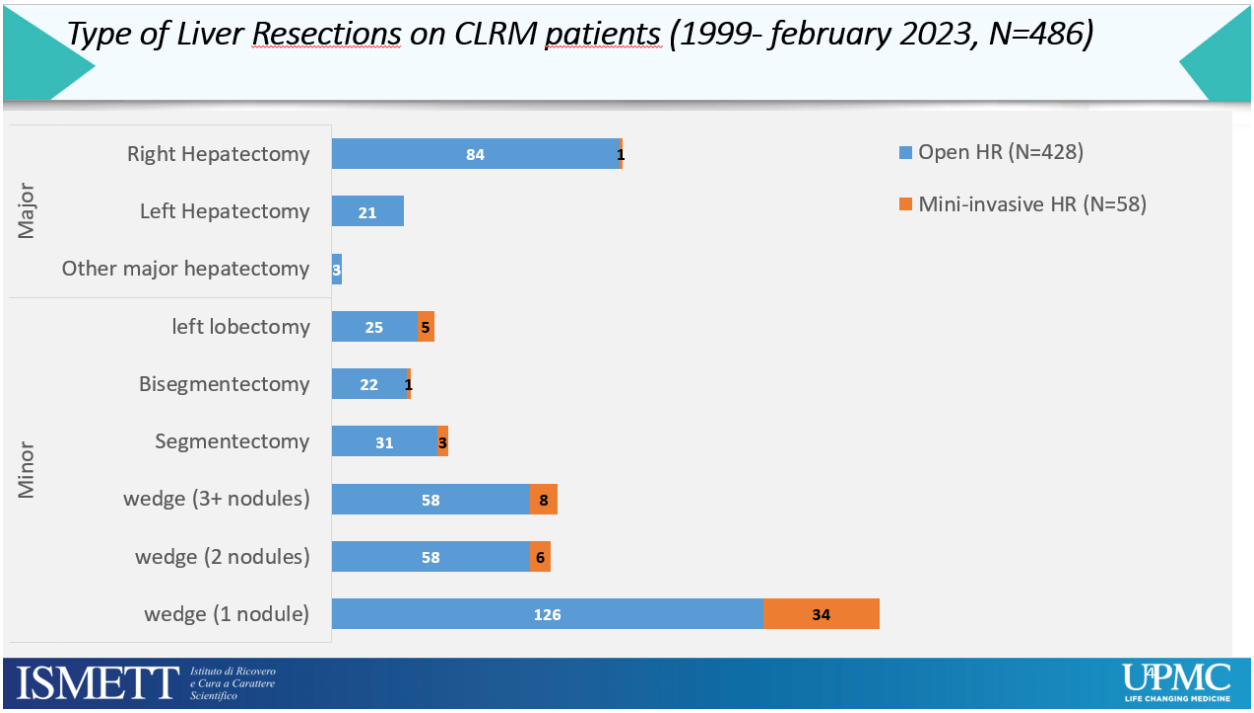



*Figure 2 -CRLM resections – IRCCS –ISMETT-UPMC-Italy series.*

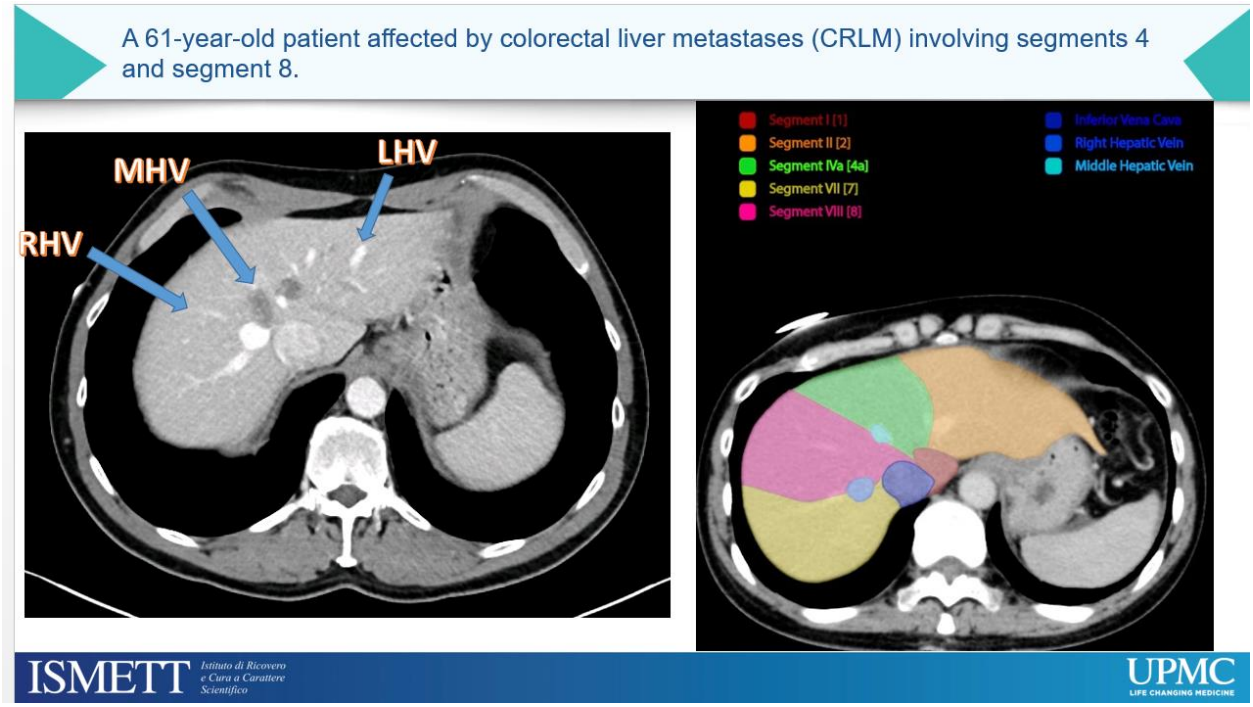



*Figure 3 - Case of patient affected by colorectal liver metastasis*

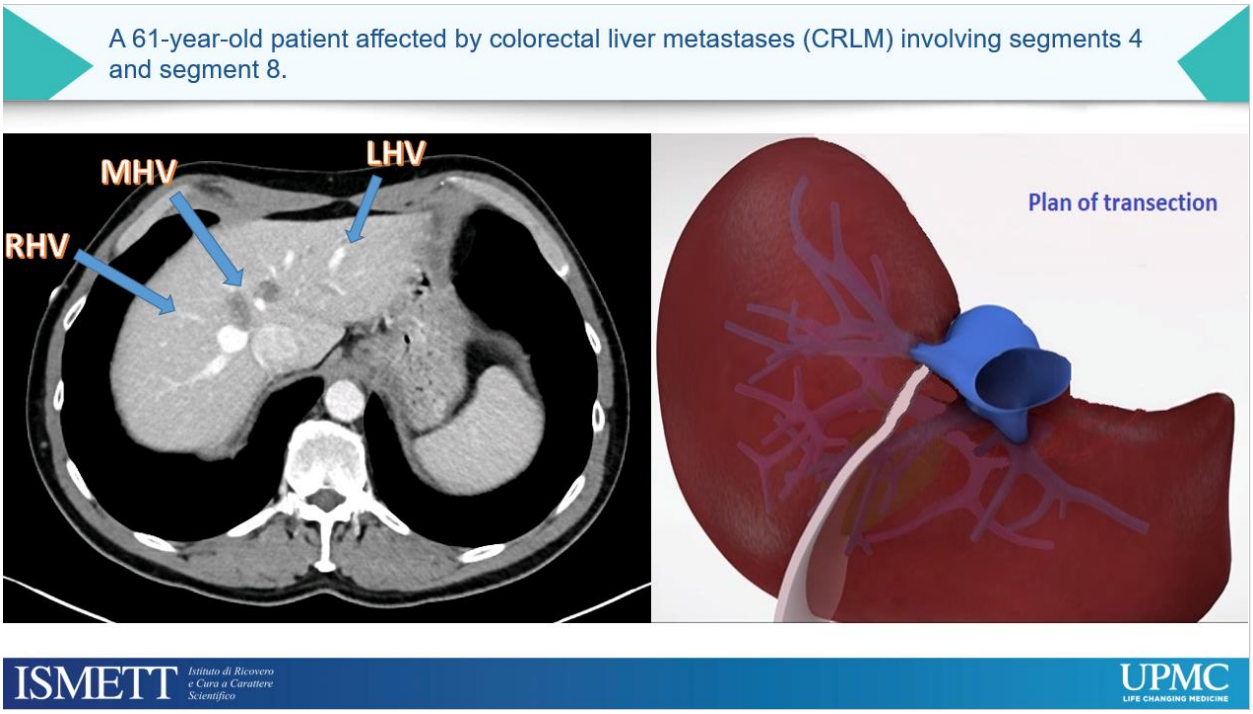



*Figure 4 - Plan of liver transection for left hepatectomy*

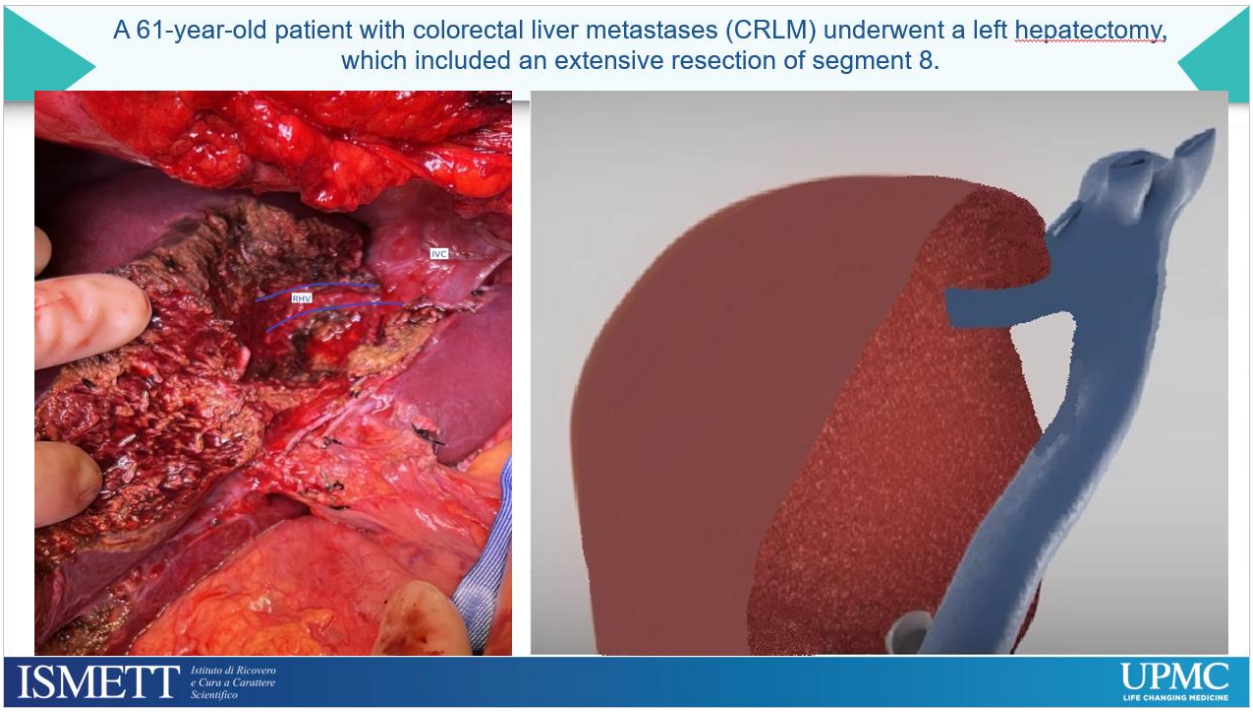



*Figure 5 - A 61-year-old patient with colorectal liver metastases (CRLM) underwent a left hepatectomy, which included an extensive resection of segment 8.*

## Colorectal liver metastasis treatment - IRCCS-ISMETT-UPMC-Italy series

A retrospective analysis was conducted on 226 patients diagnosed with colorectal cancer liver metastases (CRLM) from 2016 to 2023, who underwent procedures at our institution. Of this group, 213/226 (94.2%) underwent hepatic resection, with 172/213 (80.7%) undergoing open resection and 26/172 (15.1%) receiving a combined procedure of hepatic resection and microwave ablation.

A total of 41/213 (19.2%) patients underwent laparoscopic liver resection, with 5/41 (12.1%) receiving combined hepatic resection and microwave thermoablation. Additionally, 12/226 (5.3%)

patients underwent microwave thermoablation of CRLM exclusively during surgery, with 2/12(16.6%) performed laparoscopically.

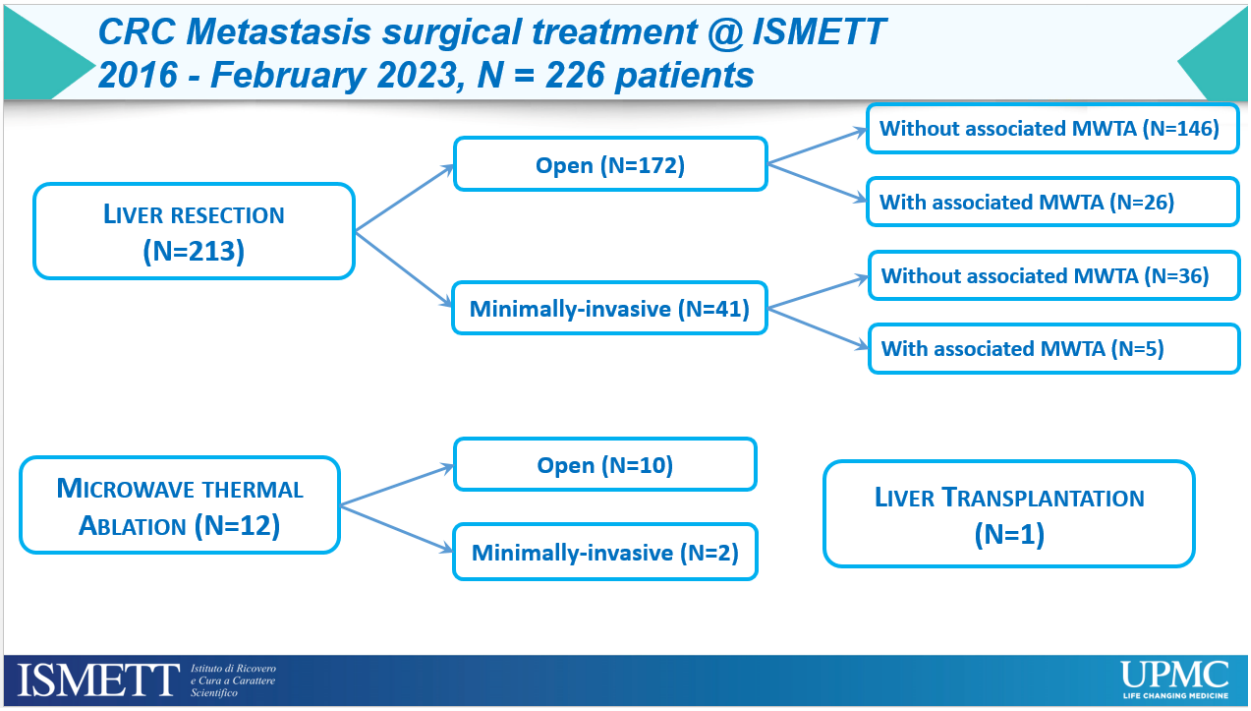



*Figure 6 - Colorectal liver metastasis treatment - IRCCS-ISMETT-UPMC-Italy series*

## Orthotopic liver transplantation – IRCCS-ISMETT-UPMC-Italy

From 1999 to 2023, a total of 1595 patients underwent liver transplantation at our institution. Of these patients, 591/1595 (37%) received transplants for oncological diseases, while the remaining patients were transplanted due to cirrhosis with end-stage organ failure. Among the oncological cases, 568/591 (96%) underwent transplantation for hepatocellular carcinoma, and 24/591 (4%) were transplanted for other tumor types.
Of the patients with other tumor types, 6/24 (25%) had cholangiocarcinoma; 5/24 (21%) had hepatic metastases from neuroendocrine tumors (NET); 5/24 (21%) had hepatic hemangioendothelioma; 1/24 (4%) had other primary hepatic malignancies; 1/24 (4%) had other

secondary hepatic malignancies; and 1 patient (4%) underwent liver transplantation for colorectal cancer. Lastly, 4/24 (17%) of the patients had benign liver tumor.

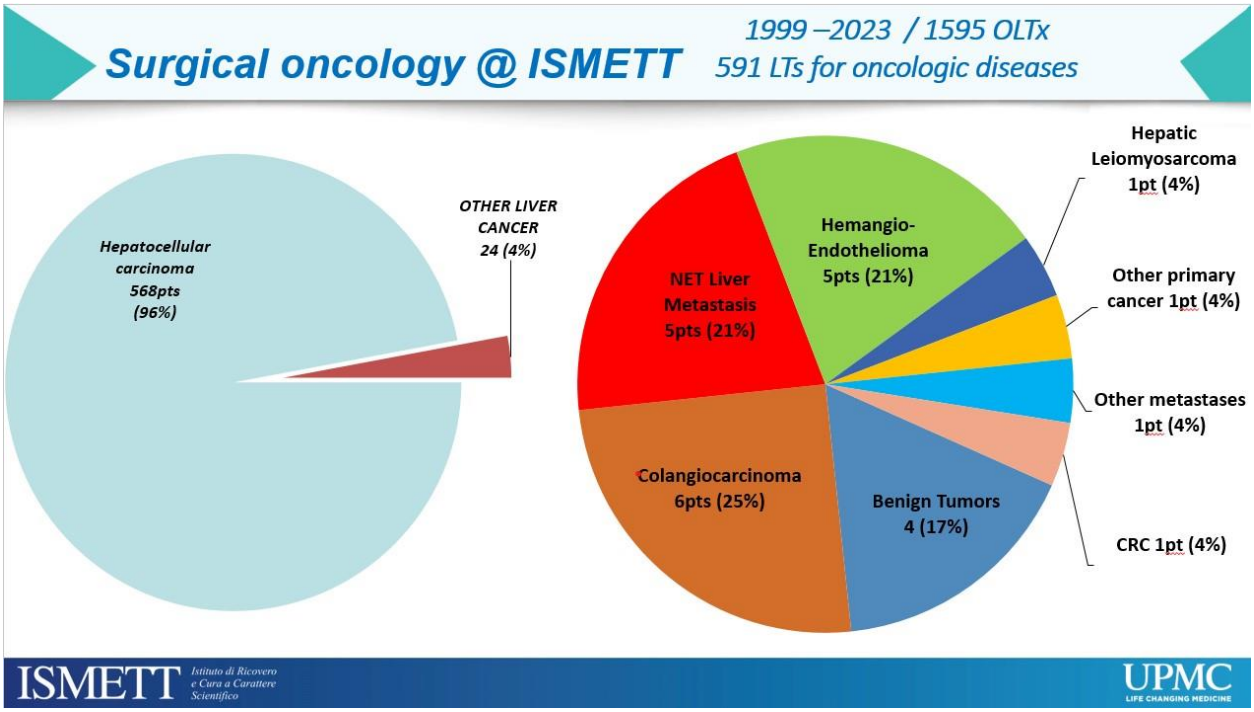



*Figura 1 - Liver trasnplantation 1999-2023 for oncologic disease in IRCCS-ISMETT-UPMC-Italy*

## OLTx for CRLM in IRCCS-ISMETT-UPMC-Italy

A 61-year-old patient with colorectal liver metastases (CRLM) was enrolled in the COlorectal Liver Metastases Transplantation (COLT) protocol. The patient's anthropometric characteristics were as follows: height 1.78 m, weight 78 kg, and a body mass index (BMI) of 19.6 kg/m2. The patient had blood type A+.

The patient had a medical history of left-sided colorectal cancer, histologically classified as stage IV adenocarcinoma, triple wild-type for KRAS, NRAS, and BRAF, with synchronous liver metastases. The patient received neoadjuvant chemotherapy consisting of seven cycles of FOLFOX-Panitumumab and subsequently underwent left hemicolectomy and multiple wedge liver resections for the synchronous liver metastases. Unfortunately, complete eradication of all metastases was not achieved, and the patient received four cycles of adjuvant chemotherapy with

FOLFIRI-Bevacizumab.

During radiologic follow-up, disease stability was observed, specifically in the liver lesions located in:

- segment IV (10 and 6 mm) in close proximity to the middle hepatic vein;
- segment II (8 mm);
- segment V (14, 8, 4 mm) subcapsular region;
- segment VI (7 and 8 mm);
- segment VIII (8, 7, and 8 mm)

In addition, other small, hypodense nodules were detected in the portal phase in the bilobed area that could not be characterized. This case was evaluated by a multidisciplinary team for COLT recruitment and the patient underwent liver transplantation. At the transplant evaluation, the levels of carcinoembryonic antigen (CEA) were 4 ng/mL and carbohydrate antigen 19.9 (CA 19.9) were 4.3 U/mL.

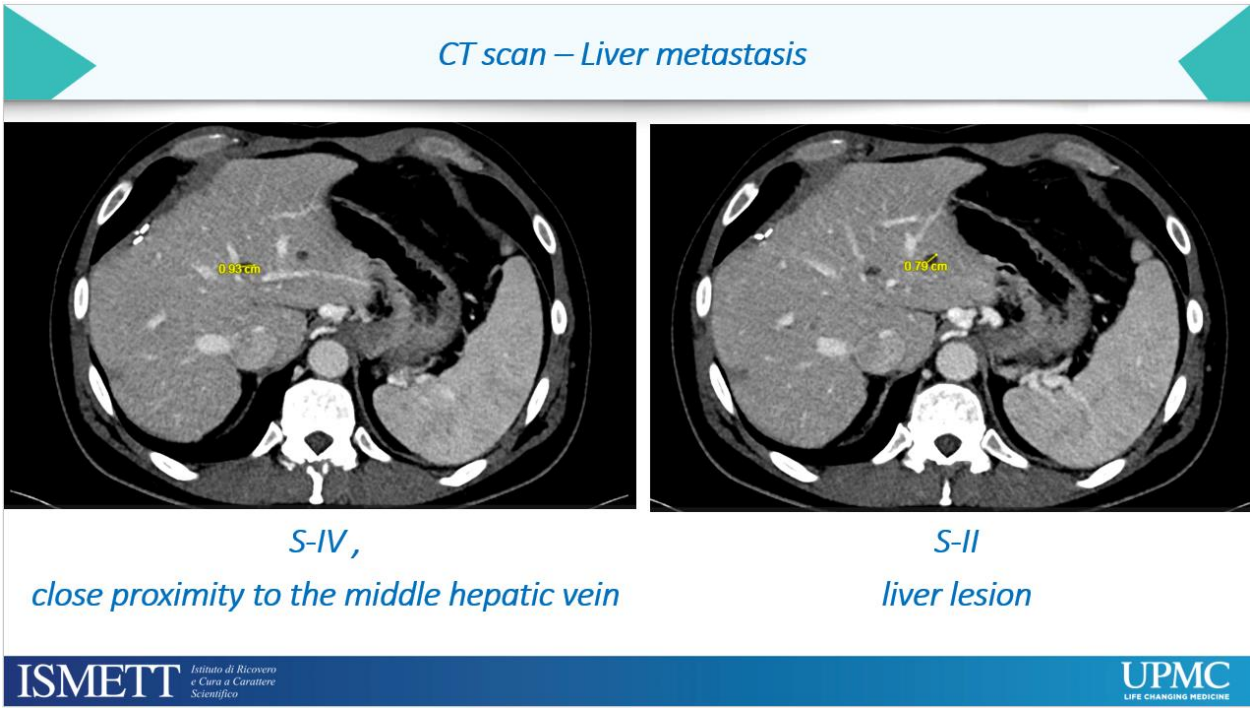



*Figure 7 - CT scan - Liver metastasis*

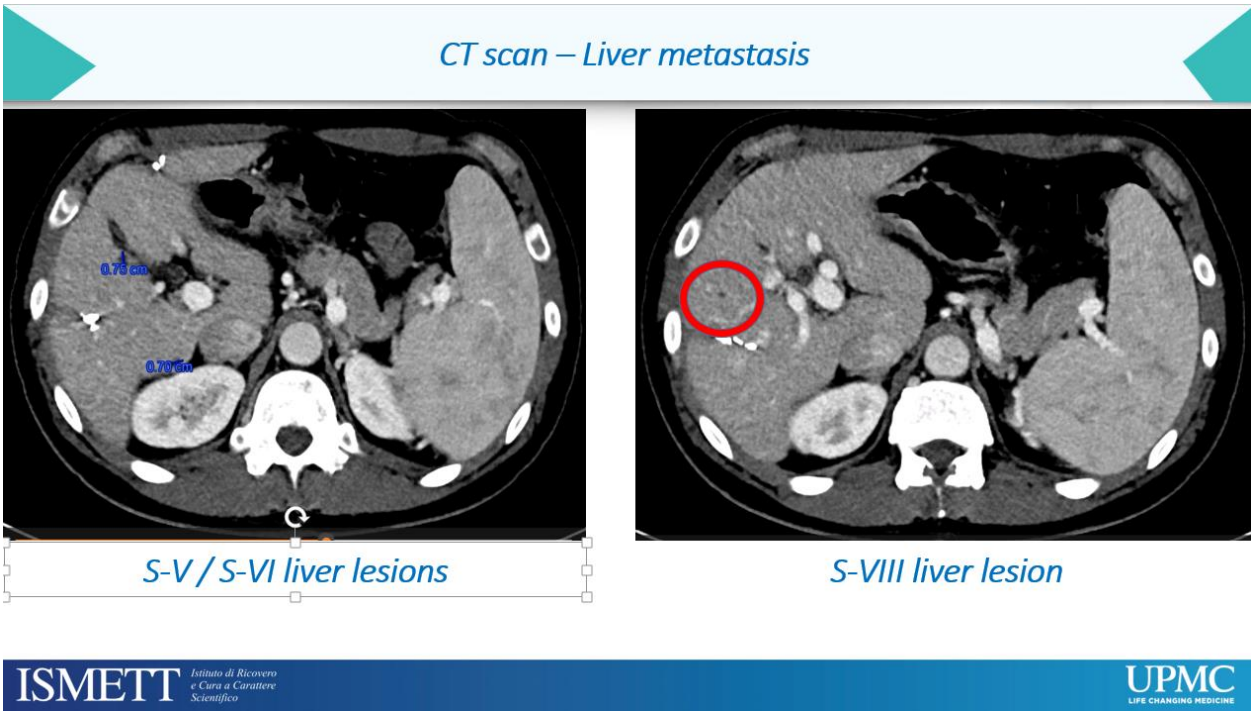



*Figure 8 - CT scan - Liver metastasis*

## Retrospective and Prospective Analysis of Inflammatory Indices in 50 Patients with CRLM and CRC at IRCCS-ISMETT-UPMC

In this study, we present the demographic and clinical characteristics of these patients who underwent surgical treatment for CRLM and/or colorectal resection. Our study aimed to evaluate the efficacy of hepatic resection in this patient population and to assess the impact of demographic and clinical factors on patient outcomes.

| Numeric variables | Range (min-max) | Mean | Median | Standard Deviation |
|---|---|---|---|---|
| **Age** | (44-86) | 66.65 | 66.00 | 9.36 |
| **Height** | (147.00-180.00) | 165.20 | 165.0 | 8.49 |
| **Weight** | (41.80-100.00) | 71.10 | 70.00 | 12.59 |
| **BMI** | (19.10-33.90) | 26.00 | 25.55 | 3.34 |
| **Dimension of the primary tumor (cm)** | (3.00-54.00) | 6.30 | 5.00 | 7.11 |

| Categorical Variables | Levels | Frequence (%) |
|---|---|---|
| **Gender** | Male | 31 (63.33%) |
| | Female | 18 (36.73%) |
| **Primary tumor resection** | Yes | 40 (81.63%) |
| **Colon histology (T)** | ≤3 | 41 (83.67%) |
| | >3 | 6 (12.24%) |
| **Colon histology (N)** | 0 | 9 (18.37%) |
| | 1 | 19 (38.78%) |
| | 2 | 17 (34.69%) |
| | 3 | 2 (4.08%) |
| **M** | No | 27 (55.10%) |
| | Yes | 21 (42.86%) |
| **G** | 1 | 14 (28.57%) |
| | 2 | 27 (55.10%) |
| | 3 | 6 (12.24%) |
| **V** | 0 | 1 (2.04%) |

| | | |
|---|---|---|
| | 1 | 25 (51.02%) |
| | 2 | 4 (8.16%) |
| **KRAS mutation** | Yes | 20 (40.82%) |
| **NRAS mutation** | Yes | 2 (4.08%) |
| **BRAF mutation** | Yes | 5 (10.20%) |
| **Chemotherapy** | Yes | 43 (87.76%) |
| **Radiotherapy** | Yes | 3 (6.12%) |
| **Liver resection histology (T)** | 1 | 9 (18.37%) |
| | 2 | 19 (38.78%) |
| | 3 | 14 (28.57%) |

| **Comorbidity** | **Frequence (%)** |
|---|---|
| HTN | 34 (69.39%) |
| CRF | 1 (2.04%) |
| Current smokers | 13 (26.53%) |
| Former Smoker | 23 (46.94%) |
| ASA | 9 (18.37%) |
| Oral Anticoagulant Use | 2 (4.08%) |

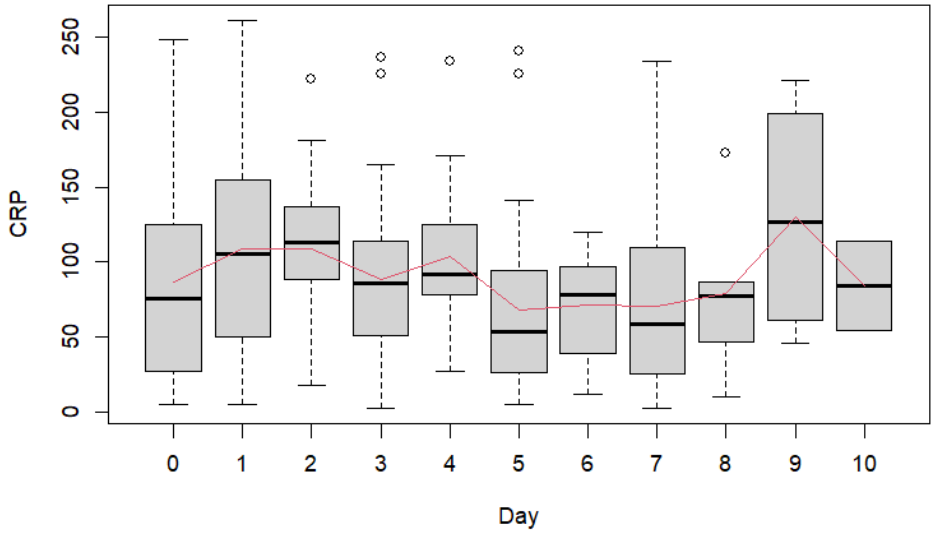
| | **Range (min-max)** | **Mean** | **Median** | **Standard Deviation** |
|---|---|---|---|---|
| **Albumin** | (2.90-4.80) | 3.74 | 3.80 | 0.39 |
| **CEA** | (0.00-240.00) | 33.45 | 12.00 | 55.03 |
| **CA19.9 ng.ml** | (0.00-135.00) | 25.48 | 7.00 | 35.15 |

## C-reactive protein (CRP) and Procalcitonin analysis

| Day | Mean CRP | % missing | Mean Procalcitonin | % missing |
|---|---|---|---|---|
| **0** | 86.57 | 22.45 | 0.39 | 46.94 |
| **1** | 108.67 | 32.65 | 0.01 | 77.55 |
| **2** | 109.19 | 46.94 | 0.41 | 81.63 |
| **3** | 88.76 | 48.98 | 0.25 | 89.80 |
| **4** | 103.65 | 65.31 | 0.60 | 95.92 |
| **5** | 67.93 | 40.82 | 0.10 | 81.63 |
| **6** | 71.29 | 71.43 | - | - |
| **7** | 70.64 | 71.43 | - | - |
| **8** | 78.8 | 89.8 | - | - |
| **9** | 130.25 | 91.84 | - | - |
| **10** | 84.0 | 95.92 | - | - |

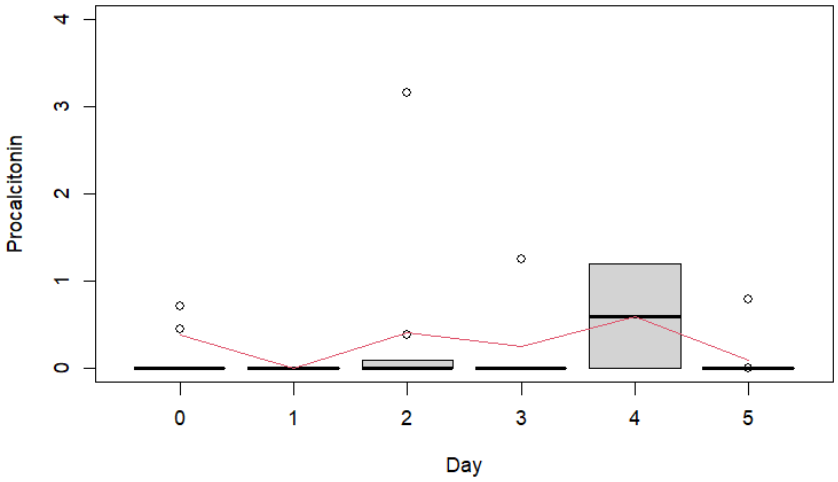
A t-Student test was performed (with significance level of $\alpha \leq 0.05$) to evaluate whether the CRP level changes significantly as days progress. Thus, CRP levels at day 0 and day 5 were compared, since starting from day 6 the percentage of missing values is too high to obtain sufficiently reliable results. With a t-test=1.19, p-value=0.24 and a confidence interval at 95% of [-12.44, 49.72], it can be concluded that mean CRP at day 0 is not significantly different from mean CRP at day 5.

The following boxplot synthesizes CRP values observed each day, with median values indicated by black lines in the boxes, while the red line joins the mean values.




The same analysis was performed for procalcitonin, by comparing day 0 with both day 2 and day 5, since both these days had the lowest percentages of missing values. Mean procalcitonin was no t significantly different from day 0 in both day 2 and day 5, with respectively t-tests of -0.04 and 0.84, p-values of 0.97 and 0.41 and confidence intervals at 95% of [-1.02,0.98] and [-0.42,1.02].

Similarly to CRP, the following boxplot shows the distribution of procalcitonin values during the 6 days observed and their median and mean values during the days. For graphical needs, it was excluded from the plot a procalcitonin value of 8.86 registered at day 0.




## Post-operative analysis

Post-operative variables were analyzed with reference to the two primary endpoints (CRP and procalcitonin) using linear regression models. Here, dependent variables were given by the mean value of CRP and procalcitonin, respectively from day 0 to day 10 and from day 0 to day 5. Results are showed in the following table, and it turns out that none of these variables is significantly correlated to the primary endpoints (p-value>0.05), except the diarrhea that is significantly (and positively) correlated with procalcitonin (p-value=0.004).

| | | **Frequence (%)** | **CRP coefficient** | **CRP p-value** | **Procalcitonin coefficient** | **Procalcitonin p-value** |
|---|---|---|---|---|---|---|
| **Day of bowel movements** | 0 | 8 (16.33%) | 10.12 | 0.16 | 0.14 | 0.21 |
| | 1 | 6 (12.24%) | | | | |
| | 2 | 20 (40.82%) | | | | |
| | 3 | 11 (22.45%) | | | | |
| **Diarrhea** | Yes | 2 (4.1%) | 19.55 | 0.58 | 1.02 | 0.004 |
| **Nausea** | Yes | 2 (4.1%) | 28.99 | 0.41 | -0.17 | 0.76 |
| **Emesis** | Yes | 2 (4.1%) | -1.48 | 0.97 | -0.15 | 0.78 |

**Glasgow Prognostic Score (GPS)**

GPS was calculated evaluating levels of pre-treatment CRP (day 0), that was considered "elevated" if >10mg/L, and hypoalbuminemia, if albumin concentration<3.5g/dL. Thus, the following GPS score were assigned:

- GPS=0 if the patient did not show any evidence of CRP elevation and hypoalbuminemia (CRP <10 and albumin>3.5)
- GPS=1 if patient had only one of the two abnormal values (CRP>10 or albumin <3.5)
- GPS=2 if both abnormal values were present.

| | **No** | **Yes** |
|---|---|---|
| **CRP >10** | 1 (2.04%) | 37 (75.51%) |
| **Hypoalbuminemia** | 29 (67.35%) | 10 (20.41%) |

Also mGPS was calculated, using the following criteria:

- GPS=0 if the patient did not show any evidence of CRP elevation and hypoalbuminemia (CRP <10 and albumin>3.5)
- GPS=1 if patient had CRP>10 and albumin >3.5 (only CRP abnormal value)
- GPS=2 if both abnormal values were present or if CRP<10 and albumin<3.5 (only hypoalbuminemia was present).

Since for the only patient with CRP>10 the albumin concentration was missing, GPS and mGPS exactly matched.

The association between GPS score and some clinicopathologic features was evaluated. Specifically, a t-Student test was used to study the relationship with the age and a chi-squared test was used to study the relationship with sex, tumor location and depth of tumor. Results are shown below.

| | | **GPS 1 (n=25)** | **GPS 2 (n=7)** | **test** | **p-value** |
|---|---|---|---|---|---|
| **Age** | | 66.08 (±8.39) | 66.43 (±13.20) | -0.07 | 0.95 |

| | | | | | |
|---|---|---|---|---|---|
| **Sex** | Male | 16 (32.65%) | 2 (4.08%) | 1.54 | 0.22 |
| | Female | 9 (18.37%) | 5 (10.20%) | | |
| **Location** | Right colon | 10 (20.41%) | 4 (8.16%) | 1.63 | 0.80 |
| | Left colon | 2 (4.08%) | 1 (2.04%) | | |
| | Transverse colon | 2 (4.08%) | 0 | | |
| | Right colonic flexure | 0 | 0 | | |
| | Rectus sigmoid | 10 (20.41%) | 2 (4.08%) | | |
| **Depth of tumor** | 2 | 6 (12.25%) | 1 (2.04%) | 1.64 | 0.44 |
| | 3 | 16 (32.65%) | 3 (6.12%) | | |
| | 4 | 3 (6.12%) | 2 (4.08%) | | |

None of these association is statistically significant (p-value>0.05).

## C-reactive protein/albumin ratio score (CAR)

The first step to evaluate CAR score was to calculate the ratio between CRP (day 0) and albumin concentration. Then, the CAR score was dichotomized using its average (2.40) as cut-off and assigning 1 (High) if the ratio was greater then the average, 0 (Low) otherwise. The same analysis as GPS were performed to study the relationship between CAR score and some clinicopathologic features. Also in this case, none of the association studied was statistically significant (p-value>0.05).

| | | **CAR 0 (n=16)** | **CAR 1 (n=16)** | **test** | **p-value** |
|---|---|---|---|---|---|
| **Age** | | 65.25 (±11.49) | 67.06 (±6.97) | -0.54 | 0.59 |
| **Sex** | Male | 7 (14.26%) | 7 (14.26%) | 0 | 1 |
| | Female | 9 (18.37%) | 9 (18.37%) | | |
| **Location** | Right colon | 6 (12.24%) | 8(16.33%) | 1.95 | 074 |
| | Left colon | 1 (2.04%) | 2 (4.08%) | | |

| | | | | | |
|---|---|---|---|---|---|
| | Transverse colon | 1 (2.04%) | 1 (2.04%) | | |
| | Right colonic flexure | 0 | 0 | | |
| | Rectus sigmoid | 7 (14.28%) | 5 (10.20%) | | |
| **Depth of tumor** | 2 | 2 (4.08%) | 5 (10.20%) | 3.11 | 0.21 |
| | 3 | 9 (18.37%) | 10 (20.41%) | | |
| | 4 | 4 (8.16%) | 1 (2.04%) | | |

## Fong Score

Fong score ranges from 0 to 5 and it depends on the following conditions, assigning 1 point for each that is considered true.

- Nodal status of primary tumor >1
- The disease-free interval from the primary to the discovery of the liver metastases is <12 months
- Number of metastases >1
- Preoperative CEA level >200 ng/ml
- Size of the largest metastasis >5cm

The following Tables show the number of patients for which these conditions were true and the number of patients for each level of Fong score.

| | **N (%)** |
|---|---|
| **Nodal status** | 38 (77.55%) |
| **Disease free interval** | 22 (44.90%) |

| | |
|---|---|
| **Number of metastases** | 26 (53.06%) |
| **CEA** | 2 (4.08%) |
| **Size of largest metastasis** | 7 (14.29%) |

| Fong score | N (%) |
|---|---|
| **0** | 3 (6.12%) |
| **1** | 12 (24.49%) |
| **2** | 10 (20.41%) |
| **3** | 12 (24.49%) |
| **4** | 2 (4.08%) |

## Discussion of statistical analysis and findings:

This study analyzed inflammatory markers, such as C-reactive protein (CRP) and procalcitonin, in 50 patients with colorectal cancer liver metastasis (CRLM) and colorectal cancer (CRC) who underwent surgical treatment at IRCCS-ISMETT-UPMC. Our findings indicate that there were no significant differences in mean CRP and procalcitonin levels across different time points during the observation period. Additionally, none of the post-operative variables were significantly correlated with the primary endpoints (CRP and procalcitonin) except for diarrhea, which was positively correlated with procalcitonin (p-value=0.004). Furthermore, we evaluated the Glasgow Prognostic Score (GPS), modified GPS (mGPS), C-reactive protein/albumin ratio score (CAR), and Fong score as potential prognostic indicators. Our analysis showed no statistically significant association between these scores and various clinicopathological features such as age, sex, tumor location, and depth of the tumor (p-

value>0.05).

The current study emphasizes the importance of investigating inflammatory markers in patients with CRLM and CRC, but further research is needed to better understand their prognostic value and relationship with patient outcomes. As our understanding of the role of inflammation in cancer progression and prognosis deepens, these findings may contribute to the development of more effective therapeutic strategies and improved patient care.

## Conclusion:

Our findings indicate that hepatic resection is a safe and efficacious treatment modality for patients presenting with colorectal liver metastases (CRLM) and/or colorectal cancer (CRC). The majority of patients exhibited improvements in overall survival and disease-free survival rates following the surgical intervention.

This study aimed to evaluate the effectiveness of hepatic resection in a patient cohort with CRLM and/or CRC and to investigate the influence of demographic and clinical factors on patient outcomes. The analysis of demographic and clinical variables demonstrated a broad range of values for age, height, weight, BMI, and primary tumor size. Categorical variables revealed a higher prevalence of male patients and primary tumor resection, as well as a significant association between diarrhea and procalcitonin levels. The assessment of inflammatory markers, specifically C-reactive protein (CRP) and procalcitonin, showed no significant correlation between post-operative variables and CRP or procalcitonin levels, except for a positive relationship between diarrhea and procalcitonin levels. Additionally, the study evaluated Glasgow Prognostic Score (GPS), modified Glasgow Prognostic Score (mGPS), C-reactive protein/albumin ratio (CAR), and Fong score but found no statistically significant associations between these scores and clinicopathological features. Overall, this study offers valuable insights into the demographic and clinical characteristics of patients with CRLM and CRC and their outcomes following hepatic resection, which may guide future research and clinical practice in this area.

In conclusion, our study underscores the significance of surgical intervention in managing patients with CRLM and/or CRC presenting with liver metastases. The results of this study may furnish valuable guidance for clinicians in the treatment and management of this patient population.

## List of figures:



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