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TESI DI LAUREA

ANALYSIS OF FACTORS ASSOCIATED WITH READMISSIONS AFTER SURGERY IN PATIENTS AFFECTED BY COLORECTAL LIVER METASTASIS.

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1. ABSTRACT

Background: Colorectal cancer represents the third most frequent malignancy in the world. In the course of the natural history of the disease, about 50% of affected patients develop liver metastases (CRLMs). Liver resection represents the gold-standard in the treatment of CRLMs, but only 20-25% of patients are candidates for surgery. About 50% of treated patients have recurrence after liver resection and despite advances in treatment, readmission rates post-procedure remains a significant issue, impacting patient outcome and healthcare costs. This Thesis explores the contributing factors to readmission among patients with colorectal liver metastasis following surgical procedures/resection.

There is sparse information available regarding readmission rates after liver resection for metastatic colorectal cancer (CRLM).

Reducing readmission is key quality improvement target for policy makers. The purpose of the present study was to analyse and identify factors associated with readmission after hepatic resection in CRLM patients.

Aim of the study: Analysis of the patterns of readmission or patients post procedure for complications related to liver resection.

Materials and Methods: Thirty-day readmission after discharge and factors associated with high risk of readmission were examined among patients undergoing hepatic resection. The study employed a retrospective cohort design, utilising data from electronic records and considered population consists of patients with CRLM who underwent surgical treatment purely or combined with ablative treatment or MWA at the UOC of General Surgery 2 - Hepatobiliopancreatic and Liver Transplant Surgery between January 2019 and December 2023. Data were collected regarding population characteristics, primary tumour, metastasis characteristics, laboratory data, surgical procedure characteristics, postoperative complications, and thirty-day postoperative follow-up. Statistical analysis was carried out using Pearson's Chi-square test or Fisher's exact test for categorical variables and Wilcoxon's test for continuous variables; readmission and recurrence curves were calculated using the Kaplan-Meier technique and compared with the log-rank test; prognostic factors of readmission were identified through univariate and multivariate analyses using the Cox proportional hazards model. Overall factors that influenced readmission were evaluated.

Results: Among 266 patients with CRLM, a total of 222 patients (liver resected for CRLM) were selected; among them, the median age was 62.4 years and 118 (53.15%) were men. More than half 128 (57.65%) of surgical resection consisted of involvement of 3 or more liver segments. The median index hospitalisation length of stay (LOS) was 7 days; the majority of

the readmitted patients, early readmission was common as 52.94% (n =18 out of 34), readmitted-within 1 week of discharge.

Among those readmitted, the median LOS for the first hospitalisation was 8 (IQR: 5,12) days.

The majority of the readmission indicators were bile leak and bile obstruction (n =8, 23% and 5, 14% respectively as well as abdominal (gastrointestinal)issues including sub occlusions, abdominal pain, perforations and fistula; n = 6, 17%)

On the multivariate analysis, a major complication perioperatively [Clavien-dindo grade 3 and 4: OR 4.2, 95% Confidence Interval (CI) 1.11-15.86; $p<0.05$] was a strong independent predictor of readmission.

Conclusion: Readmission is common after liver resection and/or ablation in CRLM, occurring in approximately one out of every six patients. People who experienced a postoperative complication are more likely to be readmitted. On the multivariate analysis, the strongest independent predictor of readmission was the presence of a major complication perioperatively [Clavien-dindo grade 3 and 4: OR 4.2, 95% Confidence Interval (CI) 1.11-15.86; $p<0.05$].

This thesis underscores the importance of comprehensive preoperative assessment, optimized perioperative care, and targeted postoperative interventions to mitigate readmission risk among CRLM patients. Strategies aimed at addressing modifiable risk factors and improving care transitions may contribute to reducing readmission rates, enhancing patient outcomes, and optimizing resource utilization.

RIASSUNTO

Background: Il cancro del colon-retto rappresenta la terza neoplasia maligna più frequente al mondo. Nel corso della storia della malattia, circa il 50% dei pazienti affetti sviluppa metastasi epatiche (CRLM). La resezione epatica rappresenta il gold standard nel trattamento delle CRLM, ma solo il 20-25% dei pazienti è candidato all'intervento chirurgico. Circa il 50% dei pazienti trattati presenta una recidiva dopo la resezione epatica e, nonostante i progressi nel trattamento, i tassi di riammissione post-procedura rimangono un problema significativo, incidendo sull'esito del paziente e sui costi sanitari. Questa tesi esplora i fattori che contribuiscono alla riammissione in pazienti con metastasi epatiche colorettali a seguito di procedure chirurgiche/resezioni.

Sono disponibili scarse informazioni sui tassi di riammissione dopo resezione epatica per cancro del colon-retto metastatico (CRLM).

Ridurre la riammissione è un obiettivo chiave per migliore la qualità della sanità. Lo scopo del presente studio è quello di analizzare e identificare i fattori associati alla riammissione post resezione epatica nei pazienti con CRLM.

Scopo dello studio: Analisi dei modelli di riammissione o di pazienti post procedura per complicanzi legate alla resezione epatica.

Materiali e metodi: Sono stati esaminati i pazienti sottoposti a resezione epatica dopo 30 giorni dalla dimissione e i fattori associati ad alto rischio di riammissione. Lo studio ha utilizzato un'analisi retrospettiva, valutando dati provenienti da archivi elettronici. Inoltre, la popolazione considerata è composta da pazienti affetti da CRLM sottoposti a trattamento chirurgico puro o combinato con trattamento ablativo o MWA presso l'UOC di Chirurgia Generale 2 - Chirurgia Epatobiliopancreatica e Trapianto di Fegato tra gennaio 2019 e Dicembre 2023. Sono stati raccolti dati riguardanti caratteristiche della popolazione, come tumore primario, caratteristiche delle metastasi, dati di laboratorio, caratteristiche della procedura chirurgica, complicanzi postoperatorie e follow-up postoperatorio di trenta giorni. L'analisi statistica è stata effettuata utilizzando il test Chi-quadrato di Pearson o il test esatto di Fisher per le variabili categoriali e il test di Wilcoxon per le variabili continue; le curve di riammissione e di recidiva sono state calcolate utilizzando la tecnica di Kaplan-Meier e confrontate con il log-rank test; i fattori prognostici di riammissione sono stati identificati attraverso analisi univariata e multivariata, utilizzando il modello dei rischi proporzionali di Cox. Sono stati dunque valutati i fattori complessivi che hanno influenzato la riammissione.

Risultati: tra 266 pazienti con CRLM, sono stati selezionati un totale di 222 pazienti (resezione epatica per CRLM); tra questi, l'età media era di 62,4 anni e 118 (53,15%) erano uomini. Più della metà delle 128 (57,65%) resezioni chirurgiche consistevano nel coinvolgimento di 3 o più segmenti epatici. La durata media della degenza ospedaliera (LOS) è stata di 7 giorni; nella

maggior parte dei pazienti riammessi, la riammissione precoce è stata comune nel 52,94% (n = 18 su 34) dei casi, entro 1 settimana dalla dimissione.

Tra i riammessi, la LOS mediana per il primo ricovero è stata di 8 giorni (IQR: 5,12).

La maggior parte degli indicatori di riammissione erano perdite biliari e ostruzione biliare (n = 8, 23% e 5, 14% rispettivamente, nonché problemi addominali (gastrointestinali) tra cui sub occlusioni, dolore addominale, perforazioni e fistole; n = 6, 17%)

Nell'analisi multivariata, la presenza di una complicanza maggiore durante il periodo perioperatorio [Clavien-dindo grado 3 e 4: OR 4,2, intervallo di confidenza (CI) al 95% 1,11-15,86; $p<0,05$] era un forte indicatore indipendente per la riammissione.

Conclusione: la riammissione è comune dopo la resezione epatica e/o l'ablazione nella CRLM e si verifica in circa un paziente su sei. Le persone che hanno avuto una complicazione postoperatoria hanno maggiori probabilità di essere riammesse. Nell'analisi multivariata, il più forte indicatore indipendente di riammissione era la presenza di una complicanza maggiore nel periodo perioperatorio [Clavien-dindo grado 3 e 4: OR 4,2, intervallo di confidenza (CI) al 95% 1,11-15,86; $p<0,05$].

Questa tesi sottolinea l'importanza di una valutazione preoperatoria completa, di cure perioperatorie ottimizzate e di interventi postoperatori mirati per mitigare il rischio di riammissione tra i pazienti con CRLM. Le strategie volte ad affrontare i fattori di rischio modificabili e a migliorare le transizioni assistenziali possono contribuire a ridurre i tassi di riammissione, migliorare i risultati dei pazienti e ottimizzare l'utilizzo delle risorse.

2. INTRODUCTION

2.1 COLORECTAL CANCER AND COLORECTAL LIVER METASTASIS

2.1.1. Epidemiology

Colorectal cancer (CRC) is a significant global health concern, with 1.85 million new cases reported annually [1]. It ranks as the second most prevalent cancer diagnosis among women and the third most common in men. In the United States, CRC accounts for 10% of all yearly cancer diagnoses and cancer-related deaths [2]

Projections based on aging, population growth, and human development suggest that colorectal cancer (CRC) cases will increase to 3.2 million by 2040 [3]. In Europe, the incidence of colorectal liver metastasis is slightly above the global average. Research published in the European Journal of Cancer indicates that liver metastases develop in roughly 25-30% of European patients diagnosed with colorectal cancer. [4]

The occurrence of colorectal liver metastasis in Italy aligns with the European average. Research indicates that approximately 25-30% of Italian colorectal cancer patients develop metastases in the liver. [5]

For 2022, Italy projected 48,100 new cases (26,000 men and 22,100 women, showing increases of +1.5% and +1.6% respectively from 2020). Mortality estimates for 2021 were 21,700 deaths, comprising 11,500 men and 10,200 women. Current data shows that net survival rates 5 years post-diagnosis are 65% for men and 66% for women [6]. It's worth noting that these prevalence figures may fluctuate slightly based on the diverse study populations and methodologies employed.

The epidemiological study of readmission patterns among patients with colorectal liver metastases highlights the critical need for holistic patient management, early identification of risk factors, and vigilant post-surgery follow-up. These measures are essential to decrease the frequency of hospital readmissions and enhance overall patient outcomes in this specific group.

2.1.2. Risk factors and screening

Early detection and optimal treatment options for patients with this condition rely on the ability to identify screening indicators and recognize risk factors.

Numerous environmental and lifestyle-related factors can elevate the likelihood of developing CRC. These include:

- overweight,
- physical inactivity,
- excessive consumption of red meat,
- low intake of calcium, intake of fruit, vegetables, and whole grain fibre,
- cigarette smoking,
- alcohol consumption,
- Genetic/hereditary factors include affected first-degree relatives, hereditary genetic syndromes (e.g. Lynch syndrome), history of IBD and DM2.

Prolonged administration of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a decreased likelihood of colorectal cancer (CRC) development; however, it concurrently elevates the risk of gastrointestinal bleeding [7]. Recent research suggests that the intestinal microbiota may also contribute to the aetiology of this neoplasm, with its dysregulation potentially leading to CRC onset [8].

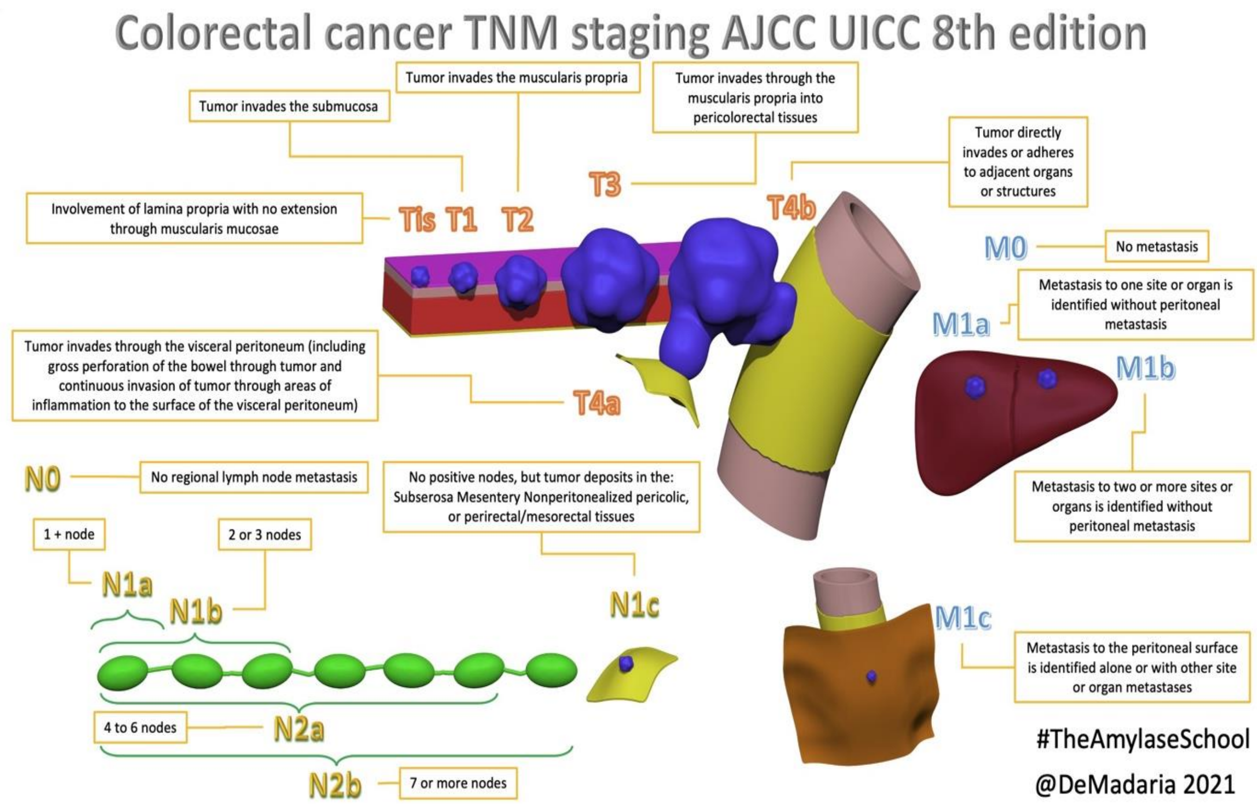
The latest edition (2023) of the National Comprehensive Cancer Network (NCCN) Guidelines outlines the criteria for CRC screening, categorizing the population based on their risk of developing the disease. Notably, in the medium-risk group—comprising individuals without a family history of CRC or chronic inflammatory bowel diseases (IBD)—the recommended age to commence screening has been revised from 50 to 45 years. Additionally, the recommended surveillance interval for patients with one or two small tubular adenomas identified during their initial colonoscopy has been extended from 5 or 7 years to 10 years [9].

In Italy, the responsibility for organizing cancer screening programs lies with the Regions, with the objective of facilitating the early detection of cervical, breast, and colorectal cancers. A national law has classified these screening initiatives as essential public health measures that must be executed by all regions [10].

2.1.3. Staging

Worldwide, the most widely used staging system for CRC is the TNM (Tumour, Node and Metastasis) classification of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) [11] [12]. This is based on four main factors: the location of the primary tumour; the size of the tumour; lymph node involvement and the presence or absence of distant metastases. [13]

Figure 1: TNM classification of American Joint committee on Cancer/ Union for International Cancer Control (AJCC/UICC) 2017



TNM staging can be used to classify the tumor clinically (cT, cN, cM) or pathologically (pT, pN, pM). The latter is determined by the analysis of the tissue removed following surgery and is therefore more accurate and reliable than clinical staging, which is instead based on tests, biopsies, and imaging carried out before surgery

2.1.4. Tumour characterisation

Imaging plays a crucial role in the characterization of tumors to ensure optimal treatment for colorectal liver metastases (CRLM). Various imaging modalities are utilized, including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and fluorine-18-deoxyglucose (FDG) positron emission tomography (PET-CT).

In recent years, contrast-enhanced ultrasound (CEUS) has gained popularity for characterizing liver lesions through a dynamic evaluation of tumor vascularity. CEUS demonstrates a sensitivity of 80% to 90%, which is comparable to that of CT, and it is significantly more effective than conventional grey-scale ultrasound in detecting small CRLMs measuring less than 10 mm [14] [15]. However, CEUS does not provide the comprehensive information necessary for surgical planning when compared to CT or MRI.

Intra-operative ultrasound (IOUS) has a well-established role in identifying lesions and mapping major hepatic vessels during surgical procedures. Studies have indicated that IOUS can detect new lesions in 16% of patients and can influence clinical management in 9% of cases [16]. Furthermore, contrast-enhanced IOUS exhibits greater sensitivity and specificity than traditional IOUS, particularly in identifying "disappearing" lesions following neoadjuvant therapy [17] [18].

CT is regarded as the preferred imaging technique for the detection of liver and extrahepatic metastases. Its high spatial resolution, combined with isotropic pixel size, allows for the reformatted imaging in multiple planes, facilitating improved delineation of tumors and adjacent vascular structures for precise segmental localization [19].

Fluorine-18 FDG PET-CT is recognized for its accuracy and sensitivity in detecting CRLM, particularly for lesions larger than 10 mm [20]. Nonetheless, it may overlook small liver metastases (less than 10 mm) and those arising from certain mucinous adenocarcinomas [21] [22]. Despite these limitations, 18FDG PET-CT continues to be an integral component of our imaging protocol prior to hepatic metastectomy.

2.1.5. Prognostic Factors

***Table 1: summarizes the main prognostic factors*.**

Prognostic factors		
Pathologic Characteristics	*Local extension of the tumour*	▪ *The depth of the extension of the tumour independently influences overall survival.*

(Wiggers T et al, 1988. Compton C et al, 2000. Chen SL et al, 2006. Ceelen W et al, 2010. Benson AB 3rd et al, 2004. Pagès F et al, 2005. Petrelli F et al, 2017. Taieb J et al, 2017. Gryfe R et al, 2000)		▪ *The residual tumour after resection (R1-R2) and the circumferential margin influences overall survival.*
	Regional lymph nodes	▪ *One of the major predictors of outcome*
		▪ *At least 12 lymph nodes must be histologically examined to accurately determine lymph node status*
	Tumor regression after neoadjuvant therapy	
	Lymphovascular invasion	
	Perineural invasion	
	Histological type, degree of differentiation and presence of mucin	
	Tumour margin	*Negative predictor: irregular, with infiltrative growth pattern*
	Immune system response	*Positive predictor: tumor-infiltrating lymphocytes*
	Peritumoral fibrosis	*Negative predictor*
	Density of tumour micro-vessels	
	Focal neuroendocrine differentiation	
	Site of the primary tumour	*Positive predictor: left location*
	Deficiency of the mismatch repair system	

	RAS and BRAF *<u>Biological Markers</u>: Mutations in specific genes, such as KRAS, BRAF, and TP53, have been associated with an increased risk of developing colorectal liver metastasis (Gruenberger et al., 2017).* *KRAS is a GTP-binding protein and the first member of the KRAS-BRAF-MEK-MAPK pathway which is activated following binding of ligand to Epidermal Growth Factor Receptor (EGFR).*	*BRAF mutations are associated with decreased efficacy of drugs directed against EGFR*
	Prognostic molecular profile	*Oncotype DX Colon Cancer Assay*
Clinical characteristics (Thirunavukarasu P et al, 2015. Mohd Suan MA et al, 2015)	*Preoperative CEA levels*	*Elevated CEA levels are a negative prognostic factor. The cut off is unclear (≥ 5.0 ng/mL)*
	Intestinal perforation and/or obstruction	

<u>Tumour Microenvironment</u>: The tumour microenvironment, characterized by elements such as angiogenesis, immune cell infiltration, and stromal components, is integral to the onset and advancement of colorectal liver metastasis [23]. Consequently, approaches that leverage the immune system to target both cellular and molecular components within the Liver Microenvironment (LME) have proven to be effective strategies, resulting in highly successful and long-lasting therapeutic outcomes [24].

<u>Liver-Specific Factors:</u> Factors unique to the liver, including liver functionality, the presence of cirrhosis, and the vascular structure, significantly affect the progression and management of colorectal liver metastasis [25].

<u>Treatment-Related Factors:</u> The nature of the treatment administered for the primary colorectal cancer, encompassing surgery, chemotherapy, and targeted therapies, can influence the risk of developing liver metastasis as well as overall survival rates [26].

This aspect serves as a critical predictor of patient prognosis, with TNM staging being indicative of survival outcomes.

Table 2: Five-year survival (Overall Survival, OS) in relation to TNM staging

Stage	TNM staging	OS at 5 years
0	T is N0 M0	>90%
I	T1 -T2 N0 M0	75%
IIa	T3 N0 M0	66.5%
IIb	T4a N0 M0	58.6%
IIc	T4b N0 M0	37.3%
IIIa	T1 -T2 N1a -N1b M0	73.1%
IIIb	T3/T4a N1/N1b M0 T2/T3 N2a M0 T1/T2 N2b M0	46.3%
IIIc	T4a N2a M0 T3/T4a N2b M0 T4b N1/N2 M0	28%
IVa	M1a	5.7%
IVb	M1b	
IVc	M1c	

In addition to the pathological TNM staging, the most important prognostic factors are:

- the presence of lympho-vascular and perineural invasion,
- the presence of extramural tumour deposits, the degree of histological differentiation,
- the preoperative levels of carcinoembryonic antigen in the serum (CEA),
- the instability of microsatellites (MSI) and
- RAS and BRAF mutations as described above.

2.2. LIVER METASTASES

The liver is the most frequent site of metastasis in individuals diagnosed with colorectal cancer, with a significant proportion, at least 25%, developing colorectal liver metastases (CRLM) throughout their disease progression [27] [28].

CRLM is characterized by the presence of malignant tumors in the liver that originate from colorectal cancer.

2.2.1. Colorectal liver metastasis (CRLM) definition

Micro-metastasis occurs when cancer cells from the primary colorectal tumor disseminate into the portal circulation. Cells from gastrointestinal malignancies, particularly those from colorectal cancer, often spread hematogenously through the portal circulation, making the liver the primary site for metastasis. As these hepatic metastases grow and exceed 2mm, they require additional blood supply for sustenance. The metastatic tumors release angiogenic factors to promote neovascularization, thereby obtaining blood supply from the hepatic artery, while normal hepatocytes primarily receive perfusion from the portal circulation [29].

The process of CRLM is categorized into two specific phases: the formation of the premetastatic niche and the post-tumor invasion niche [30].

- The formation of the premetastatic niche is the initial phase, wherein primary tumor cells secrete factors that attract non-parenchymal cells, including Kupffer cells (KC), Hepatic Stellate cells (HeSC), Myeloid-derived suppressor cells (MDSC), and Neutrophils, to facilitate their invasion.
- The post-tumor invasion niche encompasses four distinct phases of the metastatic process:
    - Microvascular phase
    - Pre-angiogenic phase
    - Angiogenic phase
    - Growth phase
- Tumour-derived factors activate the cells of the liver microenvironment (LME) to create a conducive environment for metastatic outgrowth prior to the entry of tumour cells [31]. Colorectal liver metastasis is a prevalent condition among patients with advanced colorectal cancer, with estimates indicating that 25% to 50% of individuals with CRC will develop CRLM during their illness [32] [33].

It is frequently reported that around 50% of individuals diagnosed with colorectal cancer develop liver metastases, which may occur as either synchronous or metachronous disease [34]. Definitions of synchronous and metachronous colorectal liver metastases (CRLM) vary. The Expert Group on OncoSurgery Management of Liver Metastases (EGOSLIM) has established an international consensus statement, which includes the following definitions [35]:

- Synchronous CRLM should be referred to as “synchronously detected liver metastases” when liver metastases are identified at or prior to the diagnosis of the primary tumor.
- Early metachronous metastases are defined as those identified within 12 months following the diagnosis or surgical intervention of the primary tumor.
- Late metachronous metastases are those detected more than 12 months after the diagnosis or surgery of the primary tumor.

- Synchronous CRLM generally exhibit less favorable cancer biology and anticipated survival rates compared to metachronous cases, particularly late metachronous metastases.

In terms of the timing of liver involvement diagnosis, a distinction is made between synchronous liver metastasis (MES), indicating the presence of secondary disease at the time of the primary tumor diagnosis, and metachronous liver metastasis (MEM), which refers to a secondary diagnosis that occurs later than the initial colorectal cancer diagnosis. The term recurrent liver metastasis (RLM) denotes the emergence of a new liver tumor following prior treatment [36]. At the point of diagnosis, approximately 15–25% of colorectal cancer patients present with synchronous distant metastases (Stage IV according to the TNM classification), with the majority located in the liver [37]. A study published in the journal Cancer Epidemiology indicates that the global prevalence of liver metastasis in colorectal cancer patients ranges from 15% to 20% at the time of initial diagnosis [38].

Among patients diagnosed without metastases, it is estimated that 14-34% will develop metachronous metastases within a five-year period [39]. The term oligometastasis, introduced in 1995, has been incorporated into various clinical trials and guidelines. Oligometastatic colorectal cancer (OCRC) is characterized by the presence of distant metastases, limited to a maximum of five lesions across no more than three distant sites, typically including the liver, lungs, peritoneum, lymph nodes, and ovaries [40] [41].

In 2015, the ESMO (European Society of Medical Oncology) guidelines adopted this concept to classify colorectal cancer into two categories: oligometastatic disease and diffuse disease. Patients classified under the oligometastatic category are viewed as potentially curable, with a favorable long-term survival outlook. The primary objective of treatment in these cases is to achieve a state of No Evidence of Disease (NED) through loco-regional interventions. Conversely, for patients with diffuse disease, the focus shifts to disease control and prolonging survival [42].

To accurately predict overall survival, it is crucial to stratify patients according to their recurrence risk. Based on this premise, four clinical risk scores have been established: Fong, Nordlinger, Nagashima, and Konopke [43] [44] [45] [46], which are detailed in Table 3. These scores play a significant role in identifying high-risk patients, for whom neoadjuvant chemotherapy prior to surgery may be beneficial.

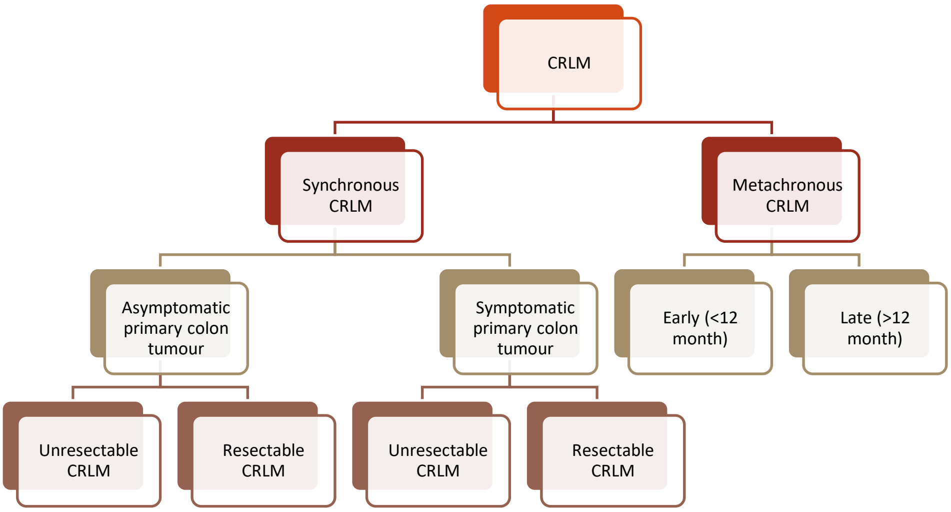
Table 3: Clinical risk score.

Score	Risk factors (1 point each)	Risk level
Fong	Disease-free interval < 12 months Number of Metastasis > 1 Preoperative CEA levels > 200ng/mL Largest liver metastasis > 5cm Positive primary tumour lymph nodes	Low: from 2 to 2 points High: from 3 to 5 points
Nordlinger	Age > 60 Invasion of the serosa by the primary tumour (>pT3) Positive primary tumour lymph nodes Disease-free interval >24 months Number of liver metastases > 3 Largest liver metastasis > 5cm	Low: 0 to 2 pts Intermediate: 3 to 4 pts High 5 to 6 pts
Nagashima	Invasion of the serosa by the primary tumor (>pT3) Positive primary tumor lymph nodes Number of liver metastases ≥ 2 Largest liver metastasis > 5cm Resectable extrahepatic metastases	Low: 0 to 1 pt Intermediate: 2 to 3 pt High: ≥ 4 pt
Konopke	Number of liver metastases ≥ 4 CEA ≥ 200 ng/mL Synchronic hepatic metastastis	Low: 0 pt Intermediate: 1pt High: ≥ 2 pt

2.2.2. Tumour burden assessment for resectability.

The assessment of tumour burden at the time of diagnosis considered the stage, size, and volume of the tumours. Size was defined as the largest diameter of the primary tumour, in addition to the cumulative maximum diameters of all tumours when synchronous tumours or metastatic lesions were identified, in accordance with WHO guidelines [47].

Figure 2: Potential scenario of colorectal liver metastasis, [48]



The determination to proceed with surgical intervention in patients diagnosed with colorectal liver metastases (CRLM) presents a multifaceted challenge, as numerous factors must be evaluated. These include the timing of systemic chemotherapy, whether to administer it with or without anti-EGFR agents, and whether this should occur prior to or following liver resection. Additionally, it is crucial to establish a safe assessment of response before liver resection, ensuring that there is an adequate Functional Remnant Liver (FRL), as well as to determine the sequence of surgical procedures—whether to perform colon resection first, liver resection first, or to conduct a simultaneous combined surgery.

The efficacy of liver resection for CRLM in promoting long-term survival while minimizing complications and readmissions has spurred the exploration of various techniques aimed at enhancing resection rates. In the context of defining 'resectability,' it is essential to differentiate between what is technically achievable and what is oncologically appropriate. Clinical, biochemical, and histopathological factors [48] [49] [50] [51] [52], along with risk assessment tools such as the Fong score [53], have offered valuable guidance in the decision-making process. From a purely technical standpoint, CRLM can be regarded as resectable if clear surgical margins are obtained and if the Future Liver Remnant (FLR) is adequately sized, with sufficient arterial supply, portal venous flow, hepatic venous drainage, and biliary outflow.

The techniques used to increase resectability include:

- downsizing chemotherapy
- portal vein embolization (PVE)
- Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS)

- and the use of ablation technology.

Surgical procedures for colorectal cancer (CRC) may be performed either laparoscopically or through an open approach, and in certain patients, these interventions can occur prior to or concurrently with the resection of the primary tumor. A more comprehensive discussion of these factors is provided. Surgical resection remains the cornerstone of treatment for colorectal liver metastases (CRLM), aiming for a curative outcome in suitable candidates. Research indicates that the resection of colorectal liver metastases (CRLM) can result in significant long-term survival advantages and, in some cases, a complete cure for selected individuals [54].

A study conducted by Simmonds et al. (2016) found that the readmission rate for patients with colorectal liver metastasis who underwent hepatic resection was 20%, with postoperative complications such as infections and bile leaks being the primary causes for readmission [55]. Additionally, O'Connor et al. (2019) reported a 25% readmission rate among patients with colorectal liver metastasis receiving systemic therapy, with readmission reasons including disease progression and complications related to treatment [56].

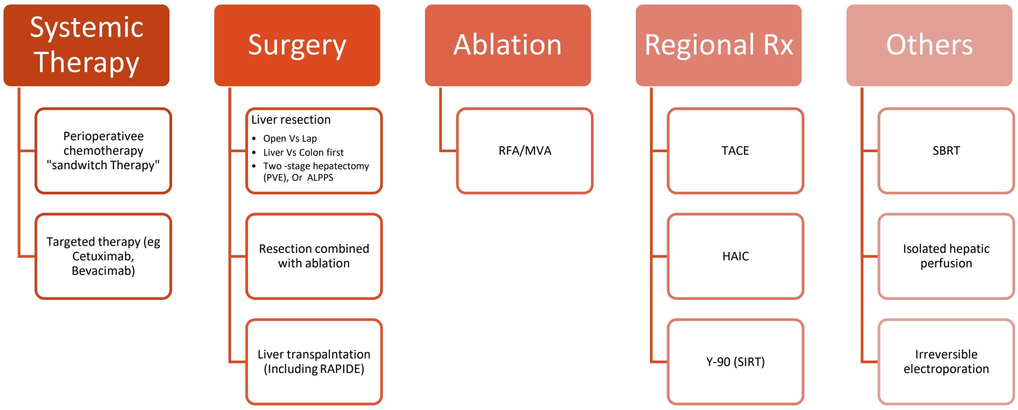
To assess the tumor volume in each patient, the Tumor Burden Score (TBS) can be computed using the following formula: TBS2 = (maximum tumor diameter) ^2 + (number of liver lesions) ^2 [57].

While preoperative imaging can help define tumor burden, the phenomenon of "vanishing metastases" must be considered; neoadjuvant chemotherapy may result in the disappearance of liver metastases. A study involving 325 CRLM lesions identified via contrast-enhanced CT prior to neoadjuvant chemotherapy revealed that only 183 lesions were detectable post-chemotherapy by CT, whereas 309 lesions were identified through intraoperative ultrasound. Lesions that are no longer visible on imaging may still be found during histopathological examination and are likely to recur during follow-up. Consequently, a complete radiological response does not necessarily equate to a complete pathological response.

2.3. TREATMENT

The management of CRLM typically involves a multidisciplinary approach that includes surgery, systemic therapy (Chemotherapy), and local ablative therapies.

Figure 3: Current treatment options. [58] (Journal of gastrointestinal Oncology).



2.3.1. Systemic Therapy

<u>Chemotherapy</u>

From the standpoint of optimizing the likelihood of liver resection, which represents the treatment with the highest potential for long-term survival, these various contexts can be categorized into three general groups, while recognizing that some overlap may exist among them.

(1) Patients with unequivocally unresectable disease;
(2) Those with up-front resectable disease; and
(3) Those patients between these 2 ends of the spectrum, whose disease is deemed initially unresectable, but with the potential of conversion to resectability by downsizing chemotherapy.

The significance of downsizing chemotherapy in the treatment of initially inoperable colorectal liver metastases (CRLM) is well recognized. A systematic review conducted by Lam et al. and others, including Chua TC et al., indicates a response rate of 64%, with 22.5% of patients ultimately eligible for curative liver resection. [59] [60]

However, this success in chemotherapy is accompanied by the paradox of **disappearing metastases**, which poses challenges for the surgical team.

<u>Preoperative Chemotherapy</u>

Chemotherapy may be administered prior to surgical intervention, referred to as neoadjuvant chemotherapy. This approach is intended for patients diagnosed with advanced stages of the disease, aiming to decrease the size of the primary tumor or any metastases to facilitate surgical procedures. Alternatively, chemotherapy can be given post-surgery, known as adjuvant chemotherapy, which seeks to minimize the risk of disease recurrence. In situations where, radical treatment is not feasible, the objective of systemic therapy shifts to alleviating or delaying the onset of disease-related symptoms, enhancing the quality of life, and extending survival. The selection of treatment is influenced by various factors, including the patient's age, overall health, comorbidities, the nature of the disease, and the presence of specific genetic mutations [61].

First-line therapy involves the use of drugs belonging to the Fluoropyrimidine class, which includes 5-Fluorouracil (5-FU) and its prodrug, Capecitabine, which has less toxicity; these are nucleotide analogues whose mechanism of action involves the inhibition of thymidylate synthetase and, ultimately, the synthesis of DNA. [62] [63].

The therapy can be implemented with the addition of Oxaliplatin, a platinum derivative which inhibits DNA synthesis through the formation of cross-links with the molecule; the regimen is called FOLFOX and is associated with a greater response to therapy (Objective Response Rate, ORR) (50.7% vs 22.3%) and with a greater survival free from disease progression (PFS) (9.0 vs 6.2 months , p=0.0003), despite not improving OS (16.2 vs 14.7 months, p=0.12) and having greater toxicity [64].

Oxaliplatin can also be associated with Capecitabine in the so-called XELOX or CAPOX regimen; although this association presents greater toxicity linked to its more frequent administration. [65] [66] [67]

An alternative first-line regimen is FOLFIRI, which involves the association of 5-FU/Leucovorin and Irinotecan, a Topoisomerase I inhibitor, (Bertram G. Padova) [68].

Targeted therapy: The use of biological drugs in the first line of therapy has improved the outcome of affected patients. The choice of the suitable drug is determined by several factors, including the RAS and BRAF status, the location of the tumor and the presence of the primary in the site, and the initial resectability of the metastases, [69].

Among the biological drugs (targeted therapy) used at the front line is Bevacizumab, a recombinant monoclonal antibody that acts as an anti-VEGF, acting as a tumour angiogenesis inhibitor. [70].

Drugs that target EGFR and its signaling cascade include Cetuximab and Panitumumab. KRAS and NRAS are involved in the transduction pathway. [71].

It is also possible to use the triple therapy, which consists of the combination of 5-FU, Irinotecan and Oxaliplatin, commonly known as FOLFOXIRI. This regimen can be used in patients who have good Performance Status and particularly aggressive tumours, including those with RAS and BRAF mutations, poorly differentiated, with ring histology or right colon tumours [72].

In a research conducted by Kepenekian et al., a total of 76 metastases were identified, of which 23 were found to have resolved following preoperative chemotherapy [74]. The marking procedure was associated with four complications: two cases of intrahepatic hematomas, one instance of fiducial migration, and one case of misplacement. After a median follow-up period of 47.7 months, there were no reports of needle-track seeding. Four of the disappearing colorectal liver metastases (CRLM) were surgically resected, resulting in two local recurrences, while other absent lesions were addressed through Thermo-ablation. Consequently, the placement of fiducial markers offers a viable strategy in the management of disappearing CRLM, although there remain concerns regarding the selection criteria for marking specific CRLM, potential procedural complications, and the risk of needle track seeding.

Chemotherapy associated morbidity

A rise in frequency has been observed with the number of medications used [74] [75] and length of hospital stay.

In 2017, the World Health Organization (WHO) launched its global patient safety initiative known as Medication Without Harm. The objective of this initiative is to achieve a 50% reduction in the incidence of severe, preventable harm associated with medication over a five-year period. The primary focus areas include high-risk situations, such as the use of high-risk medications, polypharmacy, and transitional care. Each of these factors has been identified as contributing to the likelihood of hospital readmission within 30 days [76] [77] [78].

Chemotherapy related hepato-toxicity, as this has a significant influence on decision making.

Hepatotoxicity associated with chemotherapy manifests in three primary forms: steatosis, steatohepatitis, and sinusoidal obstruction syndrome.

Steatosis refers to liver alterations characterized by the accumulation of fat within hepatocytes, commonly known as "non-alcoholic fatty liver disease." While this condition is typically benign in the majority of patients, a more severe variant can progress to steatohepatitis, fibrosis, and ultimately cirrhosis [79]. Approximately 30% to 40% of individuals receiving 5-Fluorouracil exhibit reversible steatosis, as evidenced by radiological and histological findings [80] [81]. Although steatosis is linked to a higher incidence of complications following liver resection, it does not correlate with increased mortality rates [82].

Steatohepatitis is believed to result from the "two-hit theory," where the initial damage (steatosis) is exacerbated by a secondary insult involving reactive oxygen species. Irinotecan is the primary medication associated with steatohepatitis, particularly affecting patients with a high body mass index, likely due to pre-existing steatosis. Regarding its implications for liver surgery, patients diagnosed with steatohepatitis experience not only a higher frequency of postoperative complications but also a significantly elevated 90-day mortality rate, with figures of 15% compared to 2% for those without steatohepatitis [83].

Hepatic sinusoidal obstruction syndrome associated with chemotherapy: Sinusoidal obstruction syndrome (SOS) was initially identified in relation to bone marrow transplantation and the use of various cytotoxic drug combinations [84]. In the realm of chemotherapy for colorectal liver metastases, oxaliplatin emerges as the primary agent linked to SOS, with 78% of patients treated with oxaliplatin exhibiting signs of sinusoidal damage [85]. SOS is correlated with heightened morbidity following liver resection, although it does not contribute to increased mortality [86].

Forster et al. reported that 11% of patients encountered adverse drug events (ADEs) within 30 days post-hospital discharge, with roughly one-third of these events being preventable. The likelihood of experiencing ADEs escalates with advancing age due to the pharmacokinetic and pharmacodynamic alterations that take place [87] [88] [89] [90].

2.3.2. Surgical treatment

General considerations

a) Resectability

The evaluation of resectability considers several factors, including the assessment of disease burden, which encompasses the size, quantity, and distribution of colorectal liver metastases (CRLM) [91] [92] [93]. Additionally, it considers the biological characteristics of the disease, such as the rate of progression, the possibility of extrahepatic disease, the timing of metastasis in relation to the primary colorectal tumour, the sidedness of the primary tumour, and the status of RAS/BRAF mutations and microsatellite instability (MSI) [94]. Furthermore, technical factors are also evaluated, including the relationship with vascular inflow, outflow, and biliary drainage [95].

Table 4: Resectability classifications.

Classification	Definition
Resectable	If CRLM can be completely resected, where two adjacent liver segments can be spared, adequate vascular inflow, and biliary drainage can be preserved, and the volume of the FLR will be adequate. (at least 20% of the total liver volume) [96].
Borderline	If CRLM can potentially be completely resected, but there maybe be technical and/or biological challenges. i.e., reduced odds of achieving R0 resection and/or numerous metastases, evidence of disease progression (possible extrahepatic disease) [97]
Unresectable	If CRLM cannot be resected due to burden of disease (i.e., greater than 70% of the liver involved or more than 6/8 segments, invasion of both portal veins or hepatic veins. [98]

Factors determining CRLM resectability:

I. Size and number of nodules

The quantity of tumors has been identified as an independent prognostic factor in various studies, irrespective of the treatment administered [99].

Liver resection (LR) is advised when it can potentially cure colorectal liver metastases (CRLM), yet there are no definitive guidelines regarding the permissible number of nodules. When there are more than five CRLM nodules, the condition is classified as unresectable or marginally resectable, as hepatectomy alone is insufficient in such cases. Additionally, the presence of over five nodules has been recognized as an independent negative prognostic indicator [100] [101].

The guidelines established by the European Society of Medical Oncology categorize more than five CRLM nodules as a marginally resectable condition [102]. A virtual residual liver volume of less than 30% serves as a criterion for determining unresectable disease [103].

While some studies have documented synchronous ablation of up to twelve tumors, the majority focus on the treatment of solitary lesions [104].

II. Relationship of the lesion(s) with major hepatic vessels and segmental localisation of the lesions in the liver

Surgical intervention for colorectal liver metastases (CRLM) is always conducted with the aim of achieving a cure; there is no indication for debulking procedures [105]. Consequently, the surgical approach is focused on ensuring the complete excision of the tumor while maintaining an adequate amount of healthy liver tissue to mitigate the risk of postoperative liver dysfunction or failure [106]. Resection of CRLM is not feasible when the disease burden exceeds 70% of the liver or involves more than six segments, as well as in cases of invasion of both portal veins or all hepatic veins [107]

Significant complications may arise, including damage to the main bile ducts, which can lead to strictures, cholangitis, and abscess formation [108].

III. Response after neoadjuvant chemotherapy

Chemotherapy has the potential to transform conditions that were initially deemed unresectable; this approach is referred to as "conversion therapy." In this context, the use of combinations of three drugs or doublets alongside a biological agent appears to facilitate this outcome more effectively. In instances of isolated liver disease, chemotherapy enables the "conversion" of a significant proportion of patients, exceeding 50%, thereby making surgical intervention a viable option. [109]

IV. Anticipated remnant liver volume.

The liver possesses a remarkable ability to regenerate, allowing for the removal of up to 80% of a healthy, non-cirrhotic liver [110]. However, liver failure may occur due to insufficient volume and function following resection, with mortality rates reaching as high as 80% [111]. This has led to a significant interest in evaluating liver function, particularly in predicting the functionality of the future remnant liver (FRL), to enhance safety during liver resection procedures.

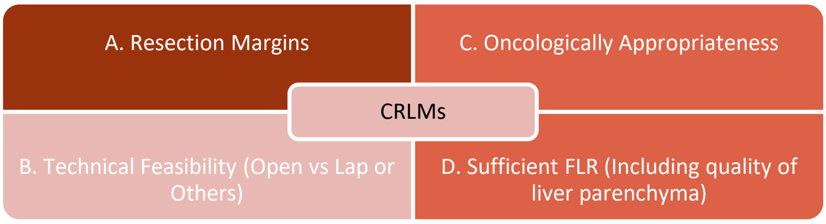
Advanced imaging technologies, such as 3-D volumetric software, facilitate precise calculations of the volumes of specific liver segments, enabling the assessment of the FRL either as an absolute measurement or as a proportion of the total liver volume. While volume measurements can be beneficial for patients with entirely healthy livers—where a minimum FRL of 25% is recommended—in cases involving suboptimal liver parenchyma, volume may not accurately reflect functional capacity [112] [113]. This is particularly true for patients suffering from conditions such as steatosis, chemotherapy-induced liver damage, or those who have undergone portal vein embolization (PVE) or associating liver partition and portal vein embolization for staged hepatectomy (ALPPS).

- Non-tumoreal liver quality – cirrhotic or not- cirrhotic mandatory to check hep b/c before chemo, NASH, or CASH liver

Various conditions such as cirrhosis, fibrosis, cholestasis, steatosis, and steatohepatitis can hinder the liver's ability to regenerate. The effectiveness of future liver remnant (FRL) is thus contingent upon the integrity of the liver parenchyma. Current recommendations for extended hepatectomies suggest an FRL of at least 20% to 25% in healthy individuals, over 30% in those with chemotherapy-related liver damage and exceeding 40% in patients with cirrhosis.

Considering these factors, there are four essential aspects to evaluate prior to determining the resectability of colorectal liver metastases (CRLM), as illustrated in the accompanying figure.

Figure 4: Essential aspects to evaluate resectability.



A. **<u>Resection margins</u>:**

There is a general agreement that the presence of positive margins following the resection of colorectal liver metastases (CRLM) is associated with a poor prognosis [114]. While traditional guidelines have recommended a liver resection margin of 1 cm for CRLM, a Propensity Score Case-Match study conducted by Hamady et al. in 2014 demonstrated that a cancer-free resection margin of just 1 mm resulted in a 33% five-year overall disease-free survival rate, indicating that increasing the margin width does not confer additional benefits in terms of disease-free survival.

Although R0 resection is undoubtedly the preferred approach, the acceptance of R1 resection may be warranted in select patients, particularly for lesions located near critical structures that cannot be removed or when it is necessary to preserve liver parenchyma [115].

In 2015, EGOSLIM posited that achieving safe resection margins remains a principal objective of treatment, with a suggested minimum surgical clearance margin of 1mm deemed adequate [116] Nevertheless, the optimal surgical margin for colorectal liver metastases (CRLM) continues to be a subject of contention. Meta-regression analyses have indicated that while a margin exceeding 1mm correlates with improved prognosis relative to submillimeter margins, targeting a margin greater than 1cm could yield even more favorable oncological results and should be pursued when feasible [117].

Furthermore, research shows no statistically significant distinctions among different types of resections regarding positive margins, recurrence rates, or overall survival [118].

A systematic review conducted in 2017, which compared conventional and parenchyma-sparing resections (PSR), revealed that preserving liver parenchyma does not affect oncological outcomes. Additionally, it found no significant differences in blood loss, length of hospitalization, incidence of R0 resections, or mortality. Nevertheless, anatomic resection was linked to a higher incidence of postoperative liver failure, with rates of 8% compared to 2%. A 2019 review further suggested that PSR is associated with reduced procedural duration, decreased blood loss, fewer transfusions, and lower rates of postoperative complications, while maintaining the same overall survival and disease-free survival rates [119]

B. Technical Feasibility

The use of Laparoscopic Liver Resection (LLR) has seen a significant rise over the past ten years, with studies documenting both minor and major liver resections [120] [121]. The Oslo CoMET trial [122] conducted a comparison between laparoscopic and open parenchymal-sparing liver resections for minor cases involving 280 patients. The findings revealed a notable decrease in complications within 30 days for the laparoscopic method, alongside a reduced average hospital stay of 3 days compared to 4 days for the open approach. No significant differences were observed in resection margin status or overall survival rates between the two techniques.

Although the initial operative costs for the laparoscopic method were higher, these expenses were balanced by the reduced recovery and hospital durations, leading to no overall cost disparity between the two approaches. The success of Minimally Invasive Surgery (MIS) for liver resection is heavily influenced by the lesion's location and its proximity to critical structures such as the portal vein, hepatic artery, bile ducts, and hepatic veins. Often, lesions may be found in various sites, necessitating that laparoscopic HPB surgeons develop individualized strategies to achieve R0 resection for all lesions while ensuring adequate future liver remnant (FLR) for the patient's immediate postoperative survival.

C. Oncological appropriateness

Numerous scoring systems have shown a significant correlation with prognosis and long-term survival; however, they still serve as a rudimentary framework for identifying patients who may benefit from the resection of colorectal liver metastases (CRLM). The clinical risk score developed by Fong et al. in 1999 was the pioneering effort to offer guidance in selecting suitable candidates for liver resection. Since then, various other scoring systems have emerged, including those by Ress M et al. (2008), Yamaguchi T et al. (2008), Kattan MW (2008), Damm R et al. (2016), Hill CR (2012), Sasaki K et al. (2018), and Brudvik KW et al. (2019).

If CRLM resection can achieve an R0 status, survival rates remain consistent regardless of the number of lesions present; however, the primary challenge lies in the feasibility of performing liver resection. It was previously believed that an increased number and size of lesions correlated with a poorer prognosis for CRLM.

D. Sufficient Future Liver Remnant (FLR)

The positioning of the lesion(s) in relation to essential inflow structures, such as the bile duct, portal vein, and hepatic artery, as well as outflow structures like the hepatic veins, plays a crucial role in determining the surgical approach. Tumors located peripherally can typically be resected with relative ease, provided the liver parenchyma is of sufficient quality. Generally, patients with colorectal liver metastases (CRLM) possess liver parenchyma capable of tolerating resection, unless they have undergone excessive systemic chemotherapy, which may lead to Chemotherapy-Associated Liver Injury (CALI).

In most cases, small wedge resections are considered safe. However, if tumors are situated deep within the liver parenchyma and in proximity to major hepatic veins, portal veins, or biliary structures, a more extensive liver resection will be required to achieve an R0 resection. In such instances, it is imperative to carefully evaluate the size of the Future Liver Remnant (FLR) and the liver's functional capacity following resection. As previously noted, up to 70% to 75% of a non-cirrhotic liver can be resected, provided that the remaining liver volume constitutes 25% to 30% of the total liver volume [123] [124]. The safety margin for patients with non-cirrhotic livers significantly improves when a smaller resection is performed.

A more comprehensive assessment of hepatocyte quality and functionality can be conducted through the indocyanine green (ICG) clearance test. This dye is exclusively eliminated by hepatocytes and subsequently excreted into the biliary system. The level of ICG remaining in the bloodstream after a specified period post-injection serves as a valuable indicator for evaluating the risk associated with significant liver resection.

Imamura et al. introduced the Makuuchi decisional algorithm, which utilizes ICG retention at the 15-minute mark, as follows: In certain complex scenarios where liver resection is technically feasible and oncologically appropriate, yet the remaining liver volume is considered insufficient (i.e., less than 25% of the total liver volume), strategies to enhance the future liver remnant (FLR) may be necessary. The methods available for increasing the FLR can be categorized into:

- Portal vein embolization (PVE) combined with staged hepatectomy;
- Portal vein ligation (PVL) along with staged hepatectomy;
- Association of Liver Partition with Portal vein ligation for Staged hepatectomy (ALPPS).

Surgical resection remains the primary treatment for patients with colorectal liver metastases (CRLM); however, only 25-30% of these patients are deemed resectable and thus eligible for surgical intervention. The resectability of a liver tumor is primarily assessed based on the estimated residual liver volume (Future Liver Remnant, FRL), which is a critical predictor of postoperative liver failure and mortality. [125]

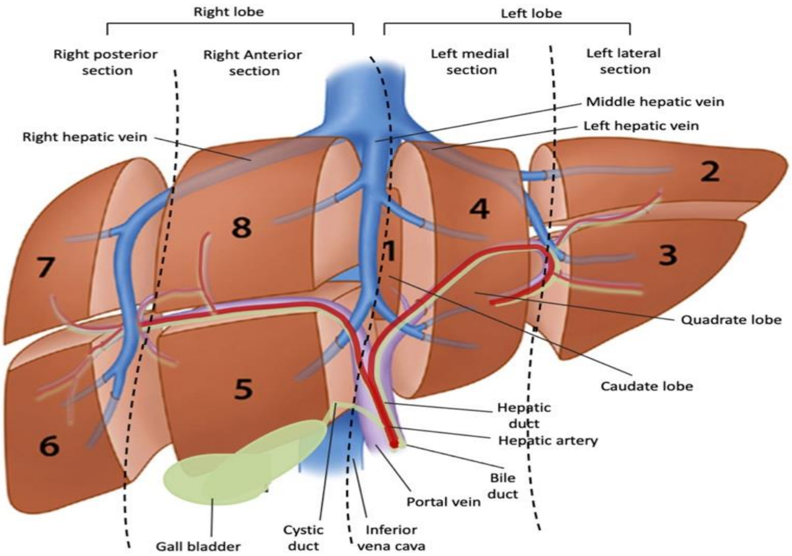
Liver Anatomy

Understanding the liver's anatomy is crucial for an effective surgical approach. Claude Coinaud, a French surgeon, was the first to articulate the functional anatomy of the liver, focusing on the intrahepatic distribution of the peduncle's components, particularly the branches of the portal vein [126]. He categorized the liver into two "hemilivers," which were further subdivided into sections: right lateral, right paramedian, left lateral, and left paramedian, based on the secondary divisions of the portal vein branches (COUINAUD C., 1954).

The right sectors are further classified into upper (VII and VIII) and lower (V and VI) segments. On the left side, the falciform ligament separates the liver into a medial area, consisting of an upper (II) and a lower (III) segment, while segment IV, located laterally to the falciform ligament, is divided into an upper (IVa) and a lower (IVb) portion. Segment I is situated posteriorly, adjacent to the inferior vena cava. Each segment possesses its own Glissonian peduncle, which includes a branch of the hepatic artery for arterial supply, a branch of the portal vein for venous drainage, and a duct for bile excretion [127]. A thorough understanding of liver anatomy is vital for the proper planning of surgical procedures.

The division into segments is summarized in the image below. (Hepatic segments – internet, 2023)

Figure 5: Anatomy of the liver (COUINAUD C., 1954)

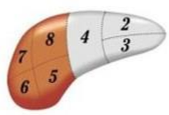


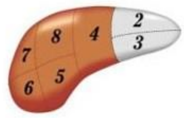
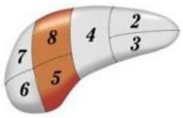
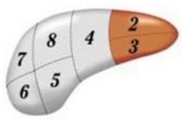
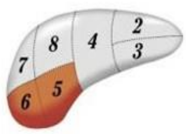
Types of liver resection

CRLMs resection types are categorised via two forms of resection:

A. anatomical or Typical. The former is also called "regular" hepatectomies and are defined as such when a portion of liver parenchyma is resected respecting the anatomical subdivision of the liver segments according to Coinaud; in this case we talk about hepatectomies (right or left), sectorectomies and segmentectomies.
B. Atypical or non-anatomical hepatectomies, on the contrary, involve the resection of a portion of liver parenchyma without following its anatomical subdivision [128]. In this case we are talking about the so-called “Parenchymal-Sparing Resection” (PSR), the extent of which is determined by the location and size of the CRLM.

Table 5: Principal types of hepatic resections. (Wakabayashi G et al, 2022. Strasberg SM et al, 2000 and 2005. Nagino M et al, 2021.)

Right Hepatectomy		Removal of the entire right lobe of the liver (segments 5,6,7,8) +/- 1

Left hepatectomy		Removal of the left hemiliver (segments 2, 3, 4)
Right hepatectomy enlarged		Removal of the right hemiliver and the fourth segment
Left hepatectomy enlarged		Removal of the entire left hemiliver and the right anterior sector (segments 8 and 5)
Anterior right sectorectomy		Removal of the segments 8 and 5
Posterior right sectorectomy		Removal of segment s 6 and 7
Segmentectomy 4		Isolated removal of segment 4
Sectorectomy left lateral or left lobectomy		Removal of the left anatomical lobe i.e. segments 2 and 3
Bisectomy		Removal of two segments of the liver that are not vascularized by the same branch of the portal vein
Segmentectomy		Removal of a single segment
"Wedge" or ''Acuneo" resection	Resection that does not follow the anatomical division of the liver and involves the removal of a part of the liver measuring less than a segment	

Resection that does not follow the anatomical division of the liver and involves the removal of a part of the liver measuring less than a segment

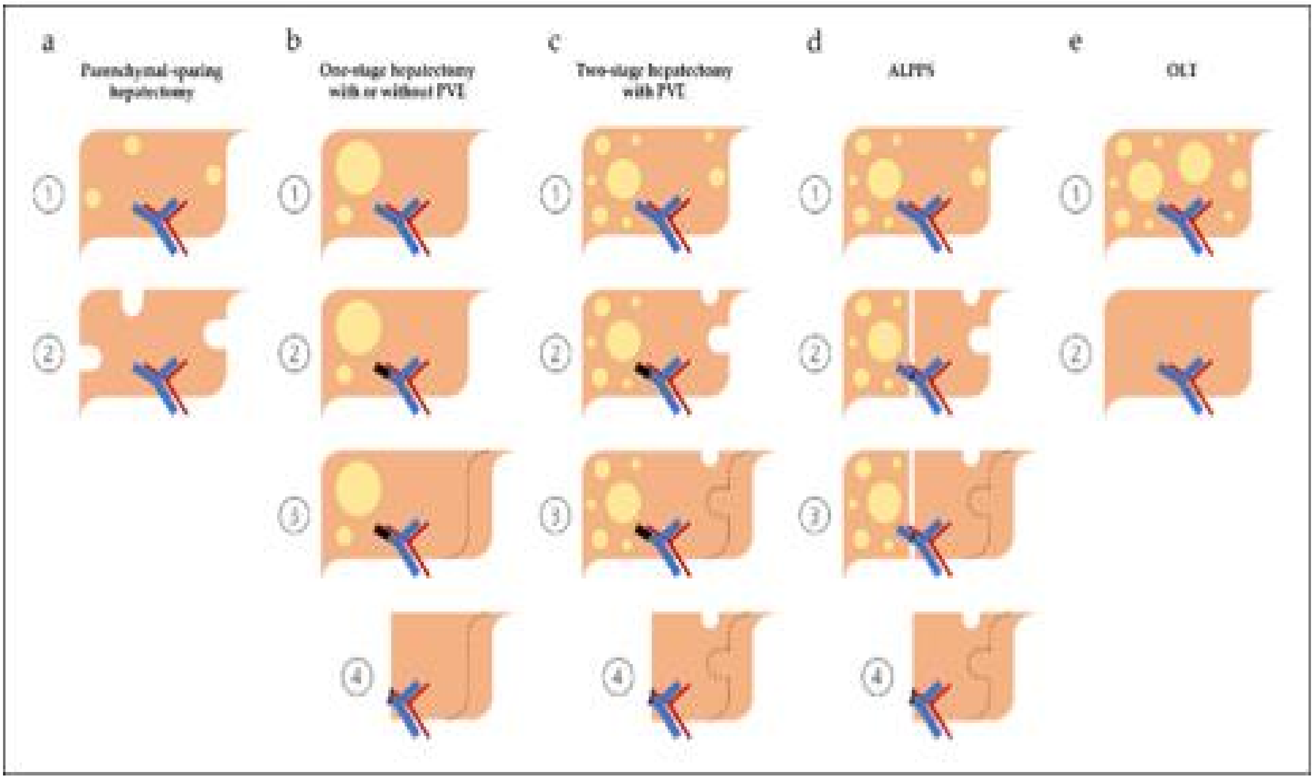
Historically, contraindications for a patient to qualify for surgical intervention included the existence of extrahepatic disease, lymph node involvement in the hepatic pedicle, and a resection margin measuring less than one centimetre. Presently, the criteria for resectability necessitate a complete resection with surgical margins that are free of tumour (R0), while preserving at least two liver segments and ensuring a future liver remnant (FRL) of no less than 20% of the original liver volume in non-cirrhotic patients [129].

R0 resections and repeat liver resections are recognized as the sole curative approaches, yielding a 5-year survival rate ranging from 15% to 50%. R1 resections, where the margins are not microscopically clear of disease, may also contribute to improved survival outcomes. The quantity of liver metastases is no longer deemed a disqualifying factor, provided the procedure is conducted by skilled surgeons. A negative resection margin, even if only millimetric, is regarded as a favourable prognostic indicator [130].

Surgical strategies for CRLM

The figure below shows the several hepatic resection sequence approaches for CRLM once the assessment of medical fitness has been established for a surgical operation.

Figure 6: Hepatic resection sequence approaches for CRLM (Gabriel D. Ivey et al., 2022)



A variety of hepatic resection procedures for colorectal liver metastases (CRLM) can be considered following an evaluation of the patient's medical fitness and the selection of an appropriate treatment strategy. The recent diversification of surgical techniques is attributed to advancements in the understanding of segmental anatomy [131], the significance of inflow occlusion techniques such as the Pringle manoeuvre [132], and the application of low central venous pressure anaesthesia [133]. These surgical interventions are tailored to achieve a complete resection of all radiographically detectable disease, including those liver metastases that may not be visible but pose a risk of recurrence [134] [135], while also aiming to maximize future liver remnant (FLR) and maintain the integrity of vascular inflow, outflow, and biliary drainage.

Parenchymal-Sparing Hepatectomy approach

Parenchymal-sparing hepatectomy, commonly referred to as non-anatomic liver resection, is based on the principle of conserving non-tumorous liver tissue. This surgical approach involves the excision of tumors while minimizing the removal of healthy hepatic parenchyma, eliminating the necessity for pre-operative interventions aimed at inducing liver hypertrophy, such as portal vein embolization (PVE), portal vein ligation (PVL), or liver venous deprivation (LVD). This technique is indicated for both unilobar and bilobar disease.

Parenchymal-sparing resection facilitates the preservation of a substantial reserve of liver parenchyma, which is particularly beneficial in cases where there is a risk of liver damage due to chemotherapy, thereby potentially enhancing the likelihood of recovery in the event of recurrence [136].

One-Stage Hepatectomy with or without PVE/HVE approach

One-stage hepatectomy refers to a liver resection procedure that may be conducted with or without preoperative interventions aimed at promoting hypertrophy of the future liver remnant (FLR). In cases where preoperative hypertrophy is necessary due to a diminished FLR (specifically, less than 30%), procedures such as portal vein embolization (PVE), potentially in conjunction with hepatic vein embolization (HVE), may be utilized.

Once adequate hypertrophy has been achieved, the hepatectomy can proceed. It is important to note that patients undergoing one-stage hepatectomy may present with multifocal disease, and this approach can be integrated with parenchymal-sparing hepatectomy of the FLR in instances of bilobed disease. However, patients exhibiting bilobed disease who require FLR hypertrophy are generally not treated with the one-stage hepatectomy approach.

Two-Stage Hepatectomy approach

A two-stage hepatectomy refers to a method of liver resection that occurs in two distinct phases. In the initial procedure, the designated future liver remnant (FLR) is surgically cleared of any malignancy. After the tumor has been excised from the FLR, the contralateral portal vein is either ligated or embolized to encourage the growth of the FLR. Once adequate hypertrophy of the FLR is achieved, a second liver resection is conducted to eliminate the remaining diseased liver tissue. This approach leverages the liver's inherent regenerative abilities, providing patients with extensive bilobed disease an opportunity for potential cure.

The application of this technique has significantly increased since the year 2000, following the publication of the first series of two-stage hepatectomy in patients with unresectable bilateral colorectal liver metastases (CRLM) by Adam R et al.

Two-stage hepatectomy is frequently executed using either combined or reversed strategies for synchronous disease, or independently (with or without perioperative systemic therapy) for metachronous disease. In cases where combined resection for synchronous disease is selected, the excision of the primary colorectal cancer is generally performed concurrently with the first-stage liver resection.

Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) approach.

The associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a variant of the two-stage hepatectomy procedure. Similar to the traditional two-stage approach, the primary objective of the initial surgery is to eliminate disease from the designated future liver remnant (FLR). Subsequently, the contralateral portal vein is ligated, and the division of the right and left hemilivers occurs without affecting the remaining vascular and biliary structures. Once adequate hypertrophy is attained, which generally occurs more rapidly than with portal vein embolization (PVE), the second liver resection is conducted to excise the remaining diseased liver tissue.

Evidence suggests that when performed in specialized centers on appropriately selected patients, ALPPS may offer advantages over conventional two-stage hepatectomy [137] [138].

ALPPS is frequently utilized in a combined approach for synchronous diseases or as a standalone procedure (with or without perioperative systemic therapy) for metachronous diseases. In cases where combined resection for synchronous disease is indicated, the resection of the primary colorectal cancer is typically executed during the first-stage liver resection.

Liver Transplantation approach

Orthotopic liver transplantation (OLT) involves the complete removal of a diseased liver, which is then substituted with a healthy liver, either partially or entirely, sourced from a deceased or living donor. This procedure is infrequently performed for colorectal liver metastases (CRLM); however, increasing evidence, particularly from European institutions with extensive donor networks, indicates that it may offer survival advantages for certain patients.

The exploration of transplantation as a viable option for individuals with CRLM stems from the persistent risk of recurrence following liver resection aimed at curative intent. Approximately two-thirds of patients who undergo such resections will face recurrence, with around fifty percent occurring in the remaining liver tissue. When assessing eligibility for transplantation, it is crucial to consider significant poor prognostic indicators, including right-sided disease, BRAF and RAS mutational status, chemotherapy progression, and the N2 nodal status of the primary tumor.

Transplantation is generally discouraged for patients exhibiting BRAF V600E mutations, although it may be contemplated for those with RAS mutations, despite their unfavorable prognostic implications.

Furthermore, transplantation is not advisable if there is any indication of radiological or biochemical disease progression during the six months of necessary bridging therapy. The presence of N2 nodal disease in the primary tumor serves as a relative exclusion criterion.

Hepatic Arterial Infusional Chemotherapy approach

Hepatic arterial infusional chemotherapy (HAIC) is a locoregional therapeutic approach that involves the direct administration of chemotherapeutic agents into the hepatic artery. This method is specifically intended for patients with colorectal liver metastases (CRLM) who are not candidates for surgical resection or ablation and have shown no response to first-line systemic chemotherapy [139].

Although HAIC is not a liver resection technique, it may be utilized post-hepatectomy as an adjuvant treatment for liver-directed chemotherapy [140]. Historically, it has frequently been employed to convert patients with initially unresectable CRLM into candidates for surgical resection [141].

Repeat Hepatectomy for Recurrence approach

Hepatic recurrence after curative intent hepatectomy for colorectal liver metastases (CRLM) occurs in approximately 33% of cases [142]. In certain patients, a repeat hepatectomy can lead to enhanced overall survival, provided there is an adequate amount of healthy liver tissue remaining [143] [144].

Laparoscopic (Minimally invasive liver resection) approach

Surgical resection can take place via laparotomy or laparoscopically.

The application of minimally invasive liver surgery (MILR) has demonstrated outcomes that are comparable to those achieved through traditional open techniques regarding oncological radicality, irrespective of tumor location and resection extent. This approach offers significant advantages, including reduced intraoperative blood loss, diminished postoperative pain, lower rates of complications, shorter hospital stays, and improved quality of life [145]. Additionally, it is associated with a decreased incidence of biliary fistulas and a lower rate of wound infections [146].

The minimally invasive technique presents several benefits over the open method, such as enhanced visualization of small intrahepatic blood vessels and a notable reduction in bleeding risk during parenchymal sectioning, attributed to the buffering effect of pneumoperitoneum. However, it does have drawbacks, including the absence of tactile feedback due to the inability to physically touch the liver and challenges in rapidly controlling blood loss in the event of sudden hemorrhage. Nevertheless, this issue can be effectively addressed through the minimally invasive application of the Pringle maneuver [147] [148] [149].

In centers with substantial experience, laparoscopic and robotic surgeries for colorectal liver metastases (CRLM) are considered safe and can yield oncological outcomes that are equivalent to those of open surgical methods [150] [151] [152]. The minimally invasive approach is a viable option for many cases that would typically require open surgery, although the complexity may increase depending on the size and location of the CRLM [152]. Similar to other minimally invasive procedures compared to their open counterparts, minimally invasive resections are frequently linked to reduced blood loss and shorter hospital stays [153]. Furthermore, combined minimally invasive surgeries for colorectal and liver excision are both feasible and safe, provided that the surgical team possesses expertise in both areas [154].

Ablation

Liver resection is widely regarded as the optimal treatment for colorectal liver metastases (CRLM); however, a significant number of patients are deemed ineligible for surgical intervention due to factors such as the unresectable characteristics of the disease, the existence of extrahepatic disease, or the presence of comorbid conditions in the patient [155] [156]. To increase the pool of patients who might qualify for surgery, various locoregional therapies have been developed over the years, with local ablation therapy being among the most frequently employed. This encompasses techniques such as radiofrequency ablation (RFA) and microwave ablation (MWA), both of which utilize elevated temperatures (around

60° C) to induce destruction of the tumour and adjacent liver tissue through coagulative necrosis [157] [158].

The adoption of RFA has markedly risen since the early 1990s and has gained formal recognition as a therapeutic option since the early 2000s, attributed to its efficacy and minimal morbidity [159] [160] [161]. Nevertheless, its application has recently seen a decline in favor of MWA. The MWA antenna produces heat directly within the tumor tissue at higher temperatures, resulting in a larger and more uniform ablation zone. In contrast, the RFA antenna creates necrosis through direct heat application, which does not effectively propagate throughout the tissue, leading to limited penetration and a consequently heterogeneous ablation zone [162]. Consequently, MWA is capable of safely addressing larger nodules while providing improved long-term outcomes, with reduced heat dissipation effects associated with nearby large-calibre vessels. [163] [164] [165].

There are technical limitations to the ablation tool, the energy applied, and the technique used. In any case, the goal must be complete of the tumour; otherwise, it is common to have a recurrence. Some authors consider ablation of tumours larger than 40mm to be contraindicated [166].

2.3.3. Comparison between resection and thermal ablation

In comparison to surgical resection, the ablation of colorectal liver metastases (CRLM) tends to result in fewer complications [167] [168]. However, survival outcomes, such as overall survival and disease-free survival, may be inferior following ablation compared to resection [169]. This discrepancy in survival rates may be attributed to the enhanced local control associated with ablation [170]. It is important to acknowledge the significant risk of selection bias present in these studies, as they often compare hepatectomy for resectable CRLM with ablation for unresectable cases [172] [172] [173] [174] [175] [176] [177]

A meta-analysis examining local ablative therapies for resectable CRLM, which included radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation (CA), and irreversible electroporation (IRE) with curative intent across 860 patients, demonstrated that local recurrence (LR) was reduced, leading to improved disease-free survival (DFS) and overall survival (OS) compared to other local ablative treatments [178].

Multiple studies suggest that local tumor control achieved through ablation is comparable to that of resection, provided that adequate margins are maintained during both procedures [179] [180]. The decision to opt for ablation instead of resection may be influenced by specific clinical scenarios [181].

A. unresectable tumors due to hepatic tumor burden or extrahepatic disease;
B. resectable tumors in patients unsuitable for resection;
C. small (<3 cm), resectable tumors that would have required major hepatectomy and the patient chose to undergo ablation;
D. patient preference after objectively discussing the pros and cons of potential treatment options;
E. Tumors located in segments IVa, VII and VIII, defined as lesions posterior;
F. Relationship of the lesions to the hepatic vasculature that can be evaluated intraoperatively with ultrasound and drive ablation rather than resection.

Ablation may be utilized alongside resection surgery to address unresectable colorectal liver metastases (CRLM). The incorporation of ablation into hepatectomy offers benefits such as the preservation of functional liver tissue and a decreased likelihood of post-hepatectomy liver failure.

In a study involving 53 patients, the combination of microwave ablation (MWA) and hepatectomy did not demonstrate a significant difference in overall survival when compared to hepatectomy alone (median overall survival: 28 months versus 39 months; p = 0.43) [182]. Additionally, one case series indicated a 5-year overall survival rate of 40.4% for MWA used as an adjunct to hepatectomy in cases of unresectable CRLM [183]. Moreover, a novel sequential treatment approach, which involves an initial incomplete resection followed by postoperative completion percutaneous ablation for lesions that were intentionally left untreated, has been shown to enhance local tumor control (5-year local tumor recurrence: 31.7% versus 62.4%; p = 0.03) and to result in fewer complications compared to intraoperative ablation, while not revealing significant differences in overall survival at the 5-year mark (53.2% versus 41.8%; p = 0.407) [184].

In another investigation, a Propensity Score Matching analysis was conducted involving 1,384 patients, with 692 (50%) undergoing liver resection (LR) alone and 692 (50%) receiving LR combined with intraoperative ablation (IA) for CRLM. The findings indicated that the use of IA in conjunction with LR was linked to reduced postoperative morbidity compared to LR alone. These outcomes suggest that IA combined with LR represents a safe strategy that may broaden the pool of patients eligible for curative treatment [185].

2.3.4. Comparison of readmission and/ or recurrence patterns after resection and ablation

Patients diagnosed with colorectal liver metastases (CRLM) experience a recurrence in the non-resected liver segment in over 50% of instances [186]. Surgical resection is considered the gold standard for the management of CRLM, significantly enhancing patient survival rates and, in certain cases, leading to a complete cure. To reduce surgical risks, traditional guidelines have advocated for a delayed approach to CRLM resection rather than simultaneous procedures. However, recent research has demonstrated that simultaneous resection is equally safe and offers comparable long-term outcomes. With advancements in modern medical facilities and the principles of minimally invasive techniques, thermal ablation has emerged as a viable alternative for treating CRLM.

A retrospective study evaluated the perioperative safety and long-term outcomes of patients who underwent simultaneous treatment for primary colorectal cancer (CRC) and CRLM, specifically comparing the efficacy of ablation versus surgical resection for CRLM. This investigation included 68 patients (23 in the resection cohort and 45 in the ablation cohort) who received either ablation or surgical resection of CRLM alongside CRC resection from 2011 to 2016. The findings indicated that patients undergoing ablation required fewer blood transfusions (8 vs. 2, $p = .023$) and had shorter postoperative hospital stays (10.93 ± 4.26 vs. 7.39 ± 1.09 days, $p = .005$) compared to those who underwent resection, while the overall and specific morbidity rates were similar across both groups [187].

In a single-centre retrospective analysis, the recurrence patterns following laparoscopic and percutaneous microwave ablation (MWA) for CRLM were examined in 51 patients, encompassing a total of 79 ablated nodules. With a median follow-up period of 18 months (ranging from 9.9 to 26 months), the overall recurrence rate was found to be 64.7% (33 patients), with local tumour progression (LTP) at 27.4% (14 patients), intrasegmental recurrence (ISR) at 25.4% (13 patients), intrahepatic relapse (IHR) at 17.6% (9 patients), and extrahepatic relapse (EHR) at 5.8% (3 patients), resulting in a no evidence of disease (NED) rate of 35.2% (18 patients) [188].

2.4. READMISSIONS ASSOCIATED WITH CRLM

2.4.1. Readmission associated with CRLM post-surgical resection.

The reduction of post-operative hospital stays is of significant medical and economic importance, prompting extensive efforts across various surgical disciplines to achieve this objective. Consequently, advancements in post-operative care and modifications within healthcare institutions have led to a decrease in the median duration of hospitalization following liver resection.

This evolution in post-operative management necessitates the monitoring of complications in patients who have been discharged, which previously would have manifested during their initial hospital stay. There is a notable lack of data regarding the incidence and progression of these late complications following liver surgery, as they were typically monitored in inpatients during their primary post-operative period, and the duration of post-operative days was seldom documented. [189]

2.4.2. Complications and Surgical Site Infections

A significant factor influencing readmission rates among patients with colorectal cancer liver metastasis is the emergence of postoperative complications, particularly surgical site infections.

Research indicates that such surgical complications markedly elevate the chances of readmission after liver metastasis surgeries, resulting in extended hospital stays and heightened healthcare expenses [190]. The mortality rate associated with liver failure post-resection can reach as high as 80% Van den Broek MA et al., which has led to increased interest in evaluating liver function, especially in predicting the functionality of the future remnant liver (FRL), to enhance safety following liver resections. In 2011, the International Study Group of Liver Surgery (ISGLS) established a standardized definition and classification for Post Hepatectomy Liver Failure (PHLF) after reviewing over 50 studies.

According to ISGLS, PHLF is characterized by a decline in the liver's synthesis, excretion, and detoxification capabilities, indicated by elevated INR and bilirubin levels, occurring on or after the fifth postoperative day [191]. The reported incidence of PHLF is approximately 10% [192] [193], and it is recognized as a leading cause of mortality, with 25% of patients succumbing to PHLF within the first month after surgery [194]. Evaluating the adequacy of hypertrophy of the FRL in relation to readmission poses significant challenges.

A systematic review of portal vein embolization (PVE) indicated a major complication rate leading to non-resectability of 0.4% and a mortality rate of 0.1%; however, it is likely that complications in the existing literature are underreported. Furthermore, comprehensive accounts of the reasons for the inability to advance to curative liver resection are often absent in published studies. A systematic review of cohort series reveals an overall failure rate of 18.7% in proceeding to curative liver resection following PVE, with the majority of these failures attributed to the progression of liver disease.

2.4.3. Disease Progression and Recurrence:

The recurrence of colorectal cancer or progression of liver metastases can also result in readmission of patients following initial surgical procedures. Monitoring and surveillance are crucial in detecting disease progression early and initiating appropriate interventions to prevent readmission. There was no data or study suggesting 30day recurrence of CRLM.

2.4.4. Comorbidities

Comorbidity is an important determinant of medical and surgical patients [195]. One frequent tool used to measure comorbid conditions is the Charlson Comorbidity Index, but some studies suggest that it does not reliably predict short term Mortality [196] [197].

Table 6: the Charlson Comorbidity Index

Comorbidity	Score
Prior myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic Ulcer disease	1
Mild liver disease	1
Diabetes	1
Cerebrovascular (hemiplegia) event	2
Moderate-to-severe renal disease	2
Diabetes with chronic complications	2
Cancer without metastases	2
Leukaemia	2
Lymphoma	2
Moderate or severe liver disease	2
Metastatic solid tumour	3
Solid tumour	6
Immune-deficiency syndrome (AIDS)	6

Previous studies indicate that the rate of hospital readmission within 30 days post-discharge is elevated among patients with comorbidities [198] [199]. Individuals with existing comorbid conditions, such as diabetes, hypertension, or cardiovascular diseases, may face an increased risk of readmission following procedures for colorectal cancer liver metastasis.

Research conducted by Chutwichai T et al. on the time-varying effects of comorbidities on mortality after liver transplantation within the NHS in England revealed that diabetes mellitus was the most prevalent comorbidity, affecting 23.9% of patients. Chronic pulmonary disease and chronic renal disease followed, with prevalences of 9.9% and 7.7%, respectively. Notably, the influence of comorbidities present at the time of transplantation evolves over time; specifically, renal disease, pulmonary disease, and diabetes were found to have no significant effect on mortality, contrary to earlier findings.

2.4.5. Health Care System related readmission factors

Healthcare system-related factors, such as non-follow up for compliance with postoperative care instructions, failure to follow-up with healthcare providers, and lack of social support, can increase the likelihood of readmission following colorectal cancer liver metastasis procedures. Education and support programs are essential in helping patients navigate the postoperative period and minimize the risk of readmission [200].

2.4.6. Patient related readmission factors – age and sex

In several western countries including Italy, the frequency of 30day readmission is approximately one in five [201] [202] [203]. Patients aged 65 or older account for approximately 56% of these early readmissions and close to 60% of the associated costs according to the Swedish Association of Local Authority and Regions, Health care and Numbers 2018.

A rise in frequency has been further observed with the number of previous discharges male sex and age (elderly)

3. PURPOSE OF THE STUDY

The aim of this study is to analyse the factors associated with readmission of patients with liver metastases from colorectal cancer.

Specifically, the primary end point is to evaluate procedure-related patient readmission pattern and the economic implication on the healthcare system with the aim to reduce readmission as a key quality improvement target for policy makers for the benefit of the patient population.

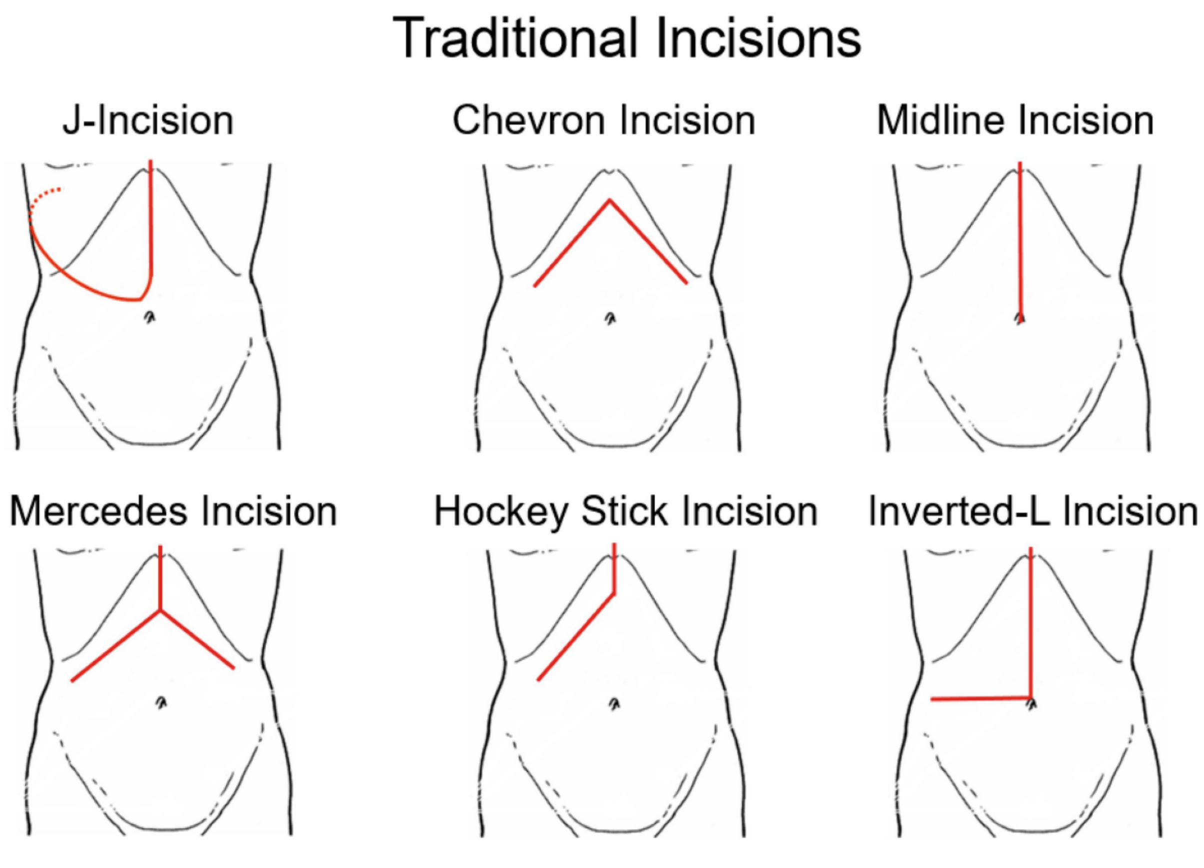
4. MATERIALS AND METHODS

4.1. Surgical Procedure

The surgical procedures were performed by the General Surgery team 2 of the Hospital - University of Padua in laparotomy or laparoscopy. In both cases the patient is subjected to general anesthesia and is in a supine position; after disinfection of the skin and the operating field, the incision is made.

In the case of surgery performed via laparotomy, a different type of incision is made depending on the segment to be resected, with the aim of exposing as much as possible the area on which it is necessary to operate. The main incisions used are summarized in the image below [204].

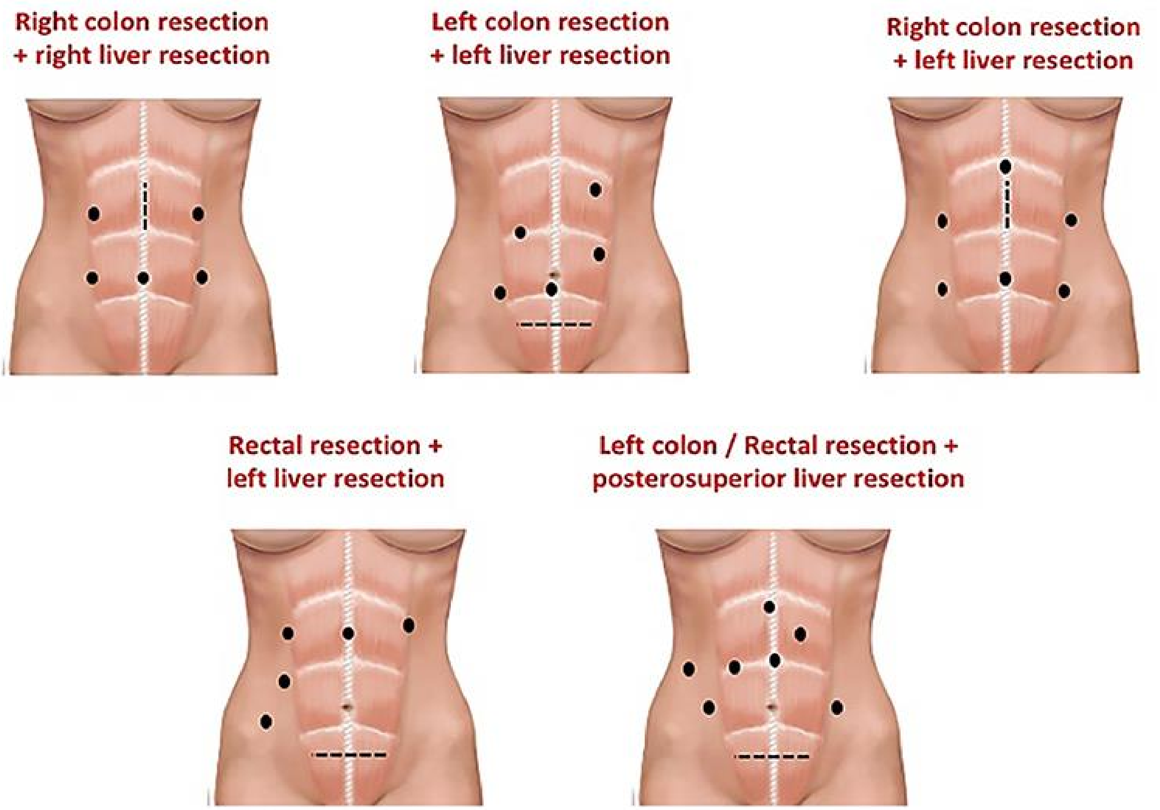
Figure 7: Traditional surgical incision in laparotomy.



4.2 Minimally Invasive Liver Resection Surgery

As regards the laparoscopic technique, a first supraumbilical midline mini-incision is made to allow access to the first 12mm trocar according to the Hasson technique; pneumoperitoneum is then induced, maintaining the insufflation pressure between 8 and 12 mmHg. After the introduction of the scope, the abdominal cavity is explored for extrahepatic disease. The second 15mm trocar is then inserted into the right hypochondrium, which is used to insert the ultrasound probe; a careful ultrasound is then carried out to allow adequate intraoperative staging, confirm the neoplastic localization and compare the results with the preoperative imaging, identify lesions that were not visible on imaging and check relationships with the major vascular structures of the liver.

Figure 8: Trocar placement to perform a combined resection. [205]



Other trocars are introduced, the position of which varies depending on the location of the lesion and the physical conformation of the patient. The instruments necessary for surgical resection of the liver parenchyma are inserted through the trocars; the haemostatic control is carried out thanks to the Pringle maneuver and the surgical piece is then inserted into the Endobag and extracted thanks to a Pfannenstiel-type incision.

An accurate haemostatic control and exploration of the abdominal cavity are carried out to identify any bleeding, including at the level of the abdominal wall where the trocars and probes have been inserted. A tubular drain is inserted near the treated area to monitor bleeding and ascites in the post-operative period. If there are no complications, it will be removed on the first or second post-operative day. The trocar in the hypochondrium is removed, the gas inlet is blocked, and the other trocars are removed. Finally, the various accesses are risked with the direct synthesis of the fascia of the rectus abdominis muscle and the synthesis of the skin is carried out with detached stitches in absorbable material or staples. Vital parameters, urine output and blood count must be monitored immediately after the operation (within 4 hours of the operation).

4.3 Choice of study population

Between January 2019 and December 2023, for this single-center retrospective study, a database use was prospectively maintained. The population considered is made up of subjects who have undergone resection surgery or combined treatment of resection and microwave thermal ablation for the treatment of liver metastases from colorectal cancer at the General Surgery Complex Operational Unit 2 - Surgery Hepatobiliopancreatic and Liver Transplants of the Hospital - University of Padua.

Other than demographic and surgical details, complications within 30 days after surgical details, complications within 30days after surgery as well as 90day mortality were recorded in the study database.

Data for complications occurring >30 days post operatively would skew the impression of post-operative morbidity, because many patients would have already commenced systemic chemotherapy, that is, adjuvant chemotherapy. We identified patients who were evaluated within 30days after surgery and were readmitted within those 30 days.

We used a well-established system (Clavien dindo) for scoring surgical complications that has been described previously [206]. type of complication (general, infectious, haemorrhagic, cardiovascular, pulmonary, neurological, gastrointestinal, renal), hepatic or biliary complications (portal vein thrombosis, biliary dehiscence, post-operative liver failure, ascites) according to ISGLS classification [207].

Table 7: International Study Group for Liver Surgery (ISGLS) definition for biliary leak

Definition	Bile leakage is defined as fluid with an elevated bilirubin level in the abdominal drain or intra-abdominal fluid on or after post-operative day three or the need for radiological intervention (i.e. interventional drainage) owing to biliary collections or re-laparotomy due to biliary peritonitis. The elevated bilirubin level in the drain or intraabdominal fluid is defined as a bilirubin concentration at least three times higher than the serum bilirubin level measured at the same time.
Grade	**A.** Bile leakage requiring no or little change in patients' clinical management
	B. Bile leakage requiring a change in patients clinical management (e.g. additional diagnostic or interventional procedures) but manageable without a re-laparotomy. OR: a **Grade A** bile leakage lasting for > 1 week
	C. **Bile leakage requiring re-laparotomy**

Briefly, complications were graded from 1 to 5, where 1 and 2 usually indicate management with either oral or intravenous pharmacologic treatment; and where grade 3 indicates procedures requiring involvement of intervention al radiology or gastroenterology, or revision in the operating room. Grade 4 indicates treatment in the intensive care unit for organ dysfunction or permanent disability as sequel of the complication; grade 5 indicates patient death.

Table 8: Definition of the grading system of complications used for this study.

Grade	Criteria
0	No complication
1	Oral antibiotics, bowel rest, basic monitoring, supportive care
2	IV antibiotics, total parenteral nutrition, drainage not required, prolonged tube feedings, transfusions, arrhythmia treated with intravenous medication, chest tube insertion.
3	Intervention radiology drainage, intensive care unit admission, intubation, pace maker placement, bronchoscopy
4	Chronic disability, organ resection, entero-diversion, ICU
5	Death due to complication

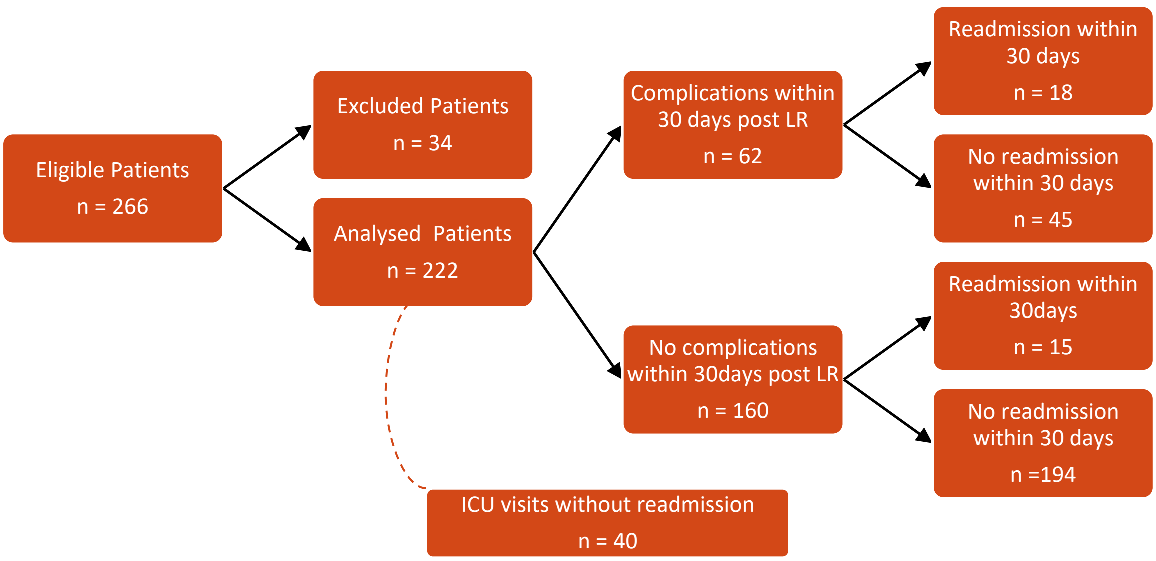
Surgical and post-operative care. The standard approach to liver resection at the General Surgery Complex Operational Unit 2 - Surgery Hepatobiliopancreatic and Liver Transplants of the Hospital - University of Padua has been described in detail already. Post-operative management was carried out per pathway protocols, ensuring that all aspects of recovery were met. These features included management of fluid replacement, diet, mobilisation, physical therapy, venous thromboembolisation prophylaxis, and pain management. Per pathway, patients where eligible for discharge from day 5-7, depending on the procedure. The compliance with pathways was generally high, although individual exemptions especially in the case of complications were possible. Finally, the decision regarding the day of discharge was at the discretion of the treating clinician.

4.4. Inclusion criteria

- Patients of both sexes;
- Age over 18 years;
- Operated at Padova polyclinic Hospital between January 2019 and December 2023;
- CRC with synchronous or metachronous metastases;
- Radiological and/or pathological confirmation of the presence of CRLM;
- Undergo resection of the primary tumour with adequate margins resection, not necessarily in conjunction with the first liver surgical procedure;
- Surgical procedure carried out in an oncological manner;
- Patients who have been operated on with either a laparotomy or laparoscopic and MWA

The final study cohort consisted of 224 patients who had undergone one liver resection and/or surgical ablation in this time frame.

Figure 9: Patient Eligible for this Analysis



4.5. Exclusion criteria

- Liver transplant patients (n = 21)
- 2 Stage procedure patients. From the initial dataset (n = 7 patients) other patients were excluded because they underwent >1 operative resection in that time period, either for recurrent liver metastasis or in the course of 2 stage approach. We considered readmission from the date of the 2nd intervention.

- Patients with incomplete data on hospital course and post-operative discharge were excluded from analysis (n = 15)
- Patients treated or readmitted from another hospital that were not transferred to this hospital were not documented in this database.

4.6. Data collection

The following data was collected anonymously and entered into a database:

- Standard patient demographic and clinicopathological characteristics were collected including age, gender, patient ID in the centre, BMI; possible smoking, comorbidities (diabetes mellitus, hypercholesterolemia, arterial hypertension, previous myocardial infarction or heart failure, previous ischemic attacks transient or cerebrovascular pathologies, COPD and chronic renal failure), ECOG PS at the diagnosis of metastasis, ASA score.

- Data regarding the primary tumor: date of diagnosis, location (cecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum), pre-operative chemo (Neoadjuvant) or radiotherapy, type and approach to the procedure.

- Data regarding metastases: date of first diagnosis, synchronous or metachronous metastases, number of metastases at diagnosis, location, size, maximum diameter, vascular invasion or proximity to major vascular structures, CEA, possible neoadjuvant therapy;

- Preoperative laboratory data; platelets, INR, bilirubin (total and direct), creatinine, and CEA.

- Data regarding the operation: date, time elapsed between operation and discharge, surgical approach (laparotomy or laparoscopic), type of operation performed (resection only or combined resective and ablative treatment), segments resected, type of resection and surgical complexity (surgical complexity was defined as greater when ≥ hepatic segments), number of nodules per segment resected, vascular occlusion maneuvers (Pringle) and their duration, ablation of the resection section, possible lymphadenectomy, biliary or vascular reconstruction, ablative treatment with microwaves, segments treated with MWA and number of nodules treated , size of metastases, sum of total resection time.

- Information on the surgical procedure: duration of the operation, Estimated blood loss and any transfusions of blood, possible intraoperative death;

- Post-operative complications: type of complication (general, infectious, haemorrhagic, cardiovascular, pulmonary, neurological, gastrointestinal, renal), hepatic or biliary complications (portal vein thrombosis, biliary dehiscence, post-operative liver failure, ascites) according to ISGLS classification (Mahribi A et al, 2022), degree of complication according to the Clavien-Dindo classification (Dindo D et al, 2004), stay in the Intensive Care Unit and duration, length of hospital stay, possible readmission for complications at 30 and 90 days, possible death at 30 and 90 days ;

- Follow-up: last visit (date of last visit and readmission), possible death and cause of death, current status (diagnosis at readmission) (pain, emesis, fever, nausea, neutropenia, pneumonia and sepsis).

4.7. STATISTICAL ANALYSIS

Values for categorical variables were expressed as totals and percentages whereas for continuous variables they were described as medians and interquartile ranges (IQR). Statistical analyses were performed using Pearson's chi-squared test or Fisher's test for categorical variables and the Wilcoxon rank sum test for continuous variables.
The length of follow-up was calculated from the date of surgery to the date of patient death (overall survival—OS) or the latest follow-up. The duration of follow-up was expressed as median (interquartile ranges).

Factors of readmission and survival were identified through univariate and multivariate analyses using the Cox proportional hazards model.

A propensity score matching (PSM) was made to make the two groups homogeneous.
Some variables were not balanced within the two study groups according to statistical test (refer to descriptive table), thus, to make the two populations more homogeneous a "propensity score-matching" (PSM) analysis was carried out. The analysis was performed with MatchIt, which made pairing, subset selection, and subclassification to create treatment groups balanced on included covariates. The matching method was "optimal" and the distance measure was computed by logistic regression with a probit link function.

A *p-value* < 0.05 was considered to indicate statistical significance; variables with a *p-value* < 0.1 were considered of marginal statistical significance. Statistical analyses were performed using R, RStudio 4.4.1 (2024).

5. RESULTS

5.1 Characteristics of the cohort.

All patients considered in this study were CRLM, therefore the indication for surgery for all patients was resection or locoregional therapy such us MWA of liver lesions due to CRLM (n=222).

Between January 2019 and December 2023, the 222 patients in our study cohort underwent a liver resection and/or surgical ablation for CRLM at the General Surgery team 2 of the Hospital - University of Padua. The demographic and surgical details of these patients are summarized in the table below.

Table 9: Demographics

Variable		Total cohort (n = 222) M=20	No readmission (n=168) M= 0	Readmission (n=35) M=0	P - Value
Age (years), median (IQR)		62.4 (54-69.85)	62.6(54.1-70.15)	61.5 (53.95-68.5)	0.665
Male Gender (%)		118/222 (53.15)	97/168 (57.73)	21/35 (60)	0.895
Body Mass Index (kg/m2), Median (IQR)		24.9 (22.4-27.7)	24.8 (22.2-27.7)	25.2 (23.4-27.6)	0.6402
Comorbidities, number (%)	No	151/222(68.01)	127/168 (75.56)	24/35 (68.57)	
	Yes	71/222(31.98)	60/168 (35.71)	11/35 (31.42)	0.989
Number of comorbidities, (%)	1	71/222 (31.98)	60/168 (35.71)	11/35 (31.42)	
	2 or more	14/222(6.30)	11/168 (6.54)	3/35 (8.57)	
Laboratory Values (pre - operative), median, (IQR)	Creatinine	0.9 (0.72-1.275)	0.84 (0.71-1.125)	1.05 (0.93-59)	0.043
	Tot. Bilirubin (mg/dl)	0.69 (0.5-2.075)	0.66 (0.495-1.47)	1.5 (0.54-5.45)	>0.9
	Platelets	205.5 (153.25-253.25)	204 (154-247)	212 (151-281)	0.2
	INR	1.03 (0.99-1.1)	1.03 (0.995-1.105)	1 (0.985-1.045)	0.13

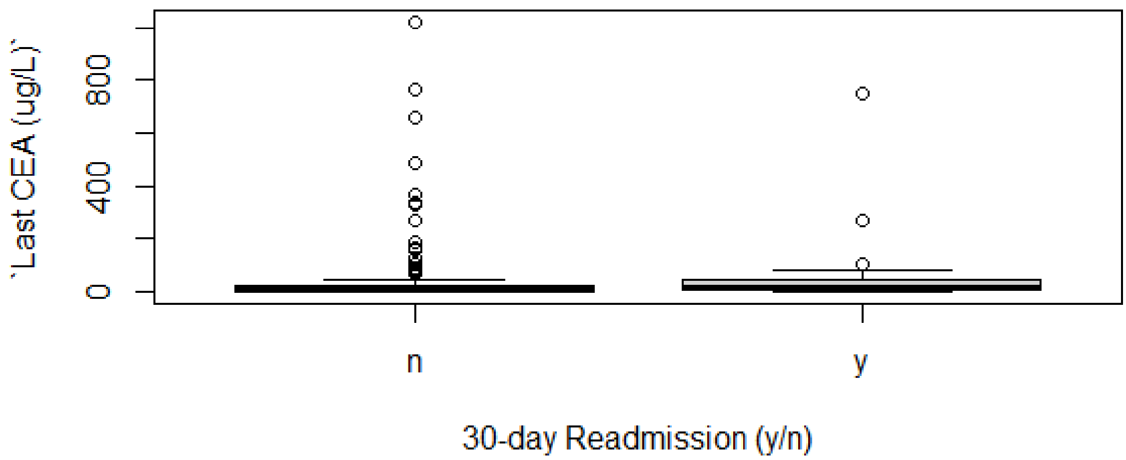
	CEA (ug/L), median (IQR)	7.6 (3-24.725)	6.9 (3-23.535)	15.8 (5.3-44.76)	
ASA, no., (%)	1 & 2	76/222 (34.23)	63/168 (37.5)	13/35 (37.14)	0.056
	3 & 4	75/222 (33.78)	67/168 (39.88)	8/35 (22.85)	0.0335
Smoking/Potus, no., (%)		34/222 (15.31)	30/168 (17.85	4/35 (11.42)	

INR, International normalised ratio; IQR, interquartile ratio; N/A, not applicable; Tot. Bilirubin, Total Bilirubin; CEA, Carcinoembryonic Antigen

Average age of all resected patients in this study was 62.4(IQR:54,69.85) and the male gender resected was 60% of this cohort. The last CEA preoperatively for all patients in this study was median of 7.6 (IQR 3,24.725)

The majority of the patients had normal pre-operative INR levels (Median: 1).

Figure 10: Association of Last CEA with readmission



n = no readmission, y = yes for readmission.

5.2 Patients and operative details

Surgical resection consisted of either minor (n = 140), major (n=62) or technically major (n = 10) and 9 patients had missing data on which resection was done. The median operative time was 330 min (IQR: 215, 445).

There were 56 major liver resections involving >3 segments, in 8 patients a technically major resection and/or ablation was performed, and 131 patients had a minor liver resection, that is, <3 segments or only MWA. More than 50 % of the patients (n = 125, 56.3%) in this cohort had a concurrent/additional non -hepatic procedure, often involving MWA (n = 116), cholecystectomy (n = 42, adhesionlysis (n = 12), lymphadenectomy or extrahepatic biliary tract resection, among others.

The majority of the patients underwent laparoscopic (n = 164, 73.87%) liver resection, and Robotic resection (n = 3, 1.35%) was the least performed. Of all patients that underwent laparoscopic resection, 18 (10.9%) of 164 patients, were converted to open surgical approach for reasons of adhesions (n=8), radicality (n =5), diffuse disease (n = 2), and others (n = 3).

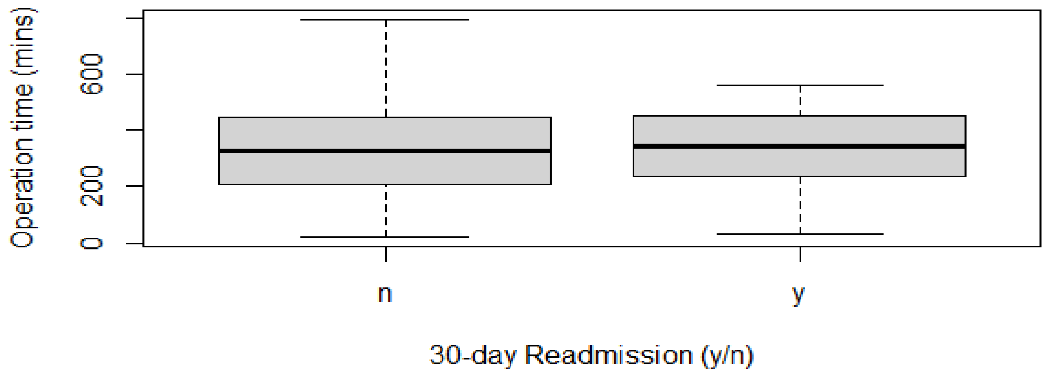
Table 10: Operative procedures

Variable		Total cohort (n = 222) M=20	No readmission (n=168) M= 0	Readmission (n=35) M=0	P- Value
Operation time (mins), median (IQR)		330 (215,445)	330 (210, 445)	345 (238.75,440)	0.755999
Number of previous LR, median (IQR)		1 (1-2)	1 (1-1)	1 (1-2)	0.00348
Concurrent procedure, no., (%)		125/222(56.3)	108/168 (64.28)	17/35 (48.57)	
Surgical approach, no., (%)	OPEN	50/222 (22.52)	35/168 (20.83)	15/35 (42.86)	0.015
	Laparoscopic	164/222 (73.87)	145/168 (86.3)	19/35 (54.29)	
	Robotic	3/222 (1.35)	3/168 (1.79)	0/35 (0)	
	Other	5/222 (2.25)	4/168 (2.38)	1/35 (2.86)	
Number of liver segments involved, no., (%)	< 3	94/222 (42.34)	81/168 (48.21)	13/35 (37.14)	0.0247
	=/>3	128/222 (57.65)	106/168 (63.1)	22/35 (62.86)	

LR- Liver Resection, m- missing data, IQR- Interquartile Range

Majority of the patients (n = 128, 57.65%) in this cohort had liver resection involving 3 or more liver segments. There was no difference in the incidence of readmission no readmission with operation time for this cohort.

Figure 11: Association of Operation time with readmission



n = no readmission, y = yes for readmission.

5.3 Postoperative complications and readmissions.

Post-operative complications were common (n = 61), however, the majority of complications were minor (Clavien Dindo I-II), (n= 50), table below.

The median ICU LOS was 1day (IQR: 0,2) and the median overall hospital LOS was 7days (IQR: 4.5,11). The perioperative 90day mortality rate was 1.8% (n=4).

Within 30 days of surgery, 61 patients developed 1 medical or surgical complication, either during the primary stay or after discharge, leading to readmission. 34 patients required readmission within 30 days to treat complications; of those, 18 already had a complication during the primary stay and 16 had no complication during the primary stay.

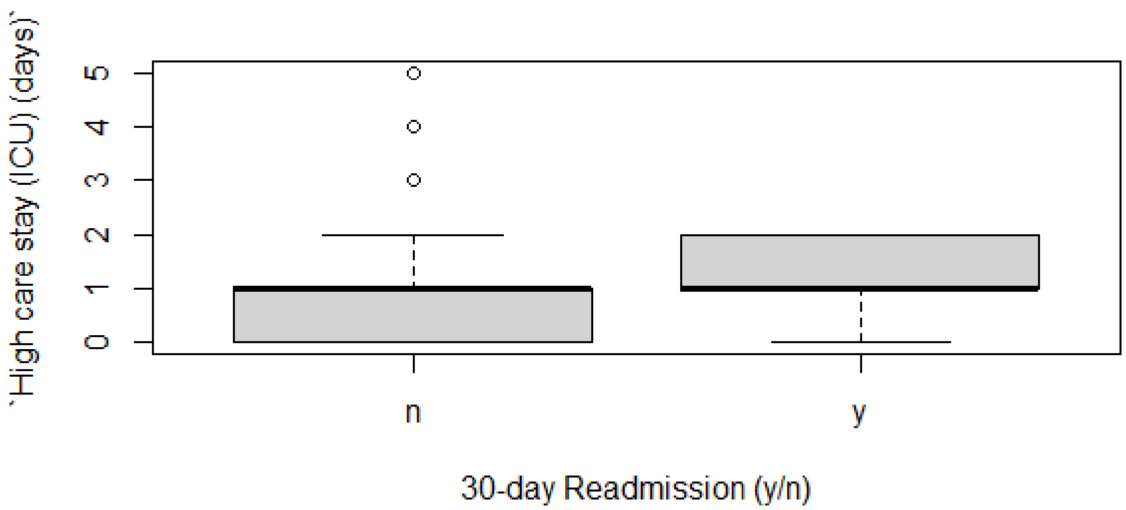
Table 11: postoperative complications and readmissions.

Variable	**Total cohort (n = 222) M=20**	**No readmission (n=168) M= 0**	**Readmission (n=35) M=0**	P-Value
ICU (days), median (IQR)	1 (0-2)	1 (0-1)	1 (1-2)	0.83
Total hospital stays (days), median (IQR)	7 (4.5-11)	7 (4-11)	8 (5-12)	0.28
Number of Patients in ICU, no., (%)	45/222 (20.27)	38/168 (22.61)	7/35 (20)	

Complications, number, (%)	No complications	142/222 (63.96)	125/168 (74.4)	17/35 (48.57)	Ref
	Clavien Dindo I-II	50/222 (22.52)	36/168 (21.43)	14/35 (40)	0.00992
	Clavien Dindo III - IV	11/222 (4.95)	7/168 (4.17)	4/35 (11.42)	0.03424
	Death	4/222 (1.80)	4/168 (2.38)	0/35 (0)	

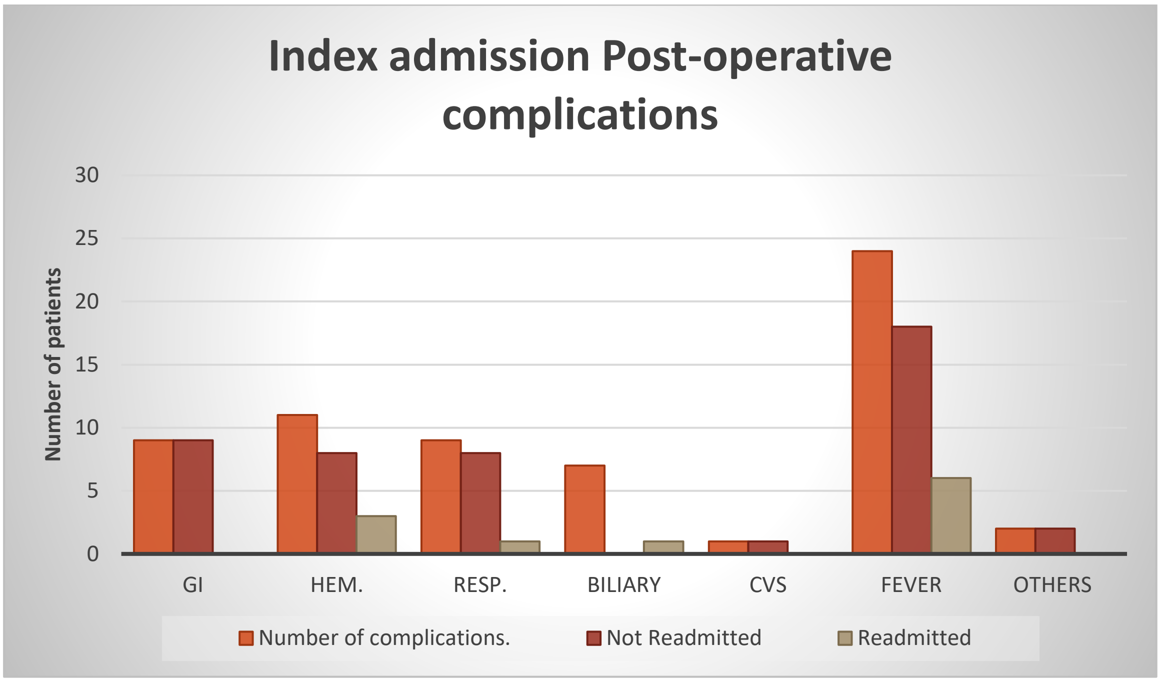
38 patients were evaluated in the Intensive Care Unit (ICU) without requiring readmission.

Figure 13: Assciation of ICU stay and readmission



Fever was the commonest post-operative complaint noted in CLRM liver resected patients whereas biliary complications like bile leak and bile obstuction were not common during index admission as much as other gastroninterstinal, hematologic and respiratory complications.

Figure 14: Post-operative complications at index patient admission



5.4 Readmission analyses

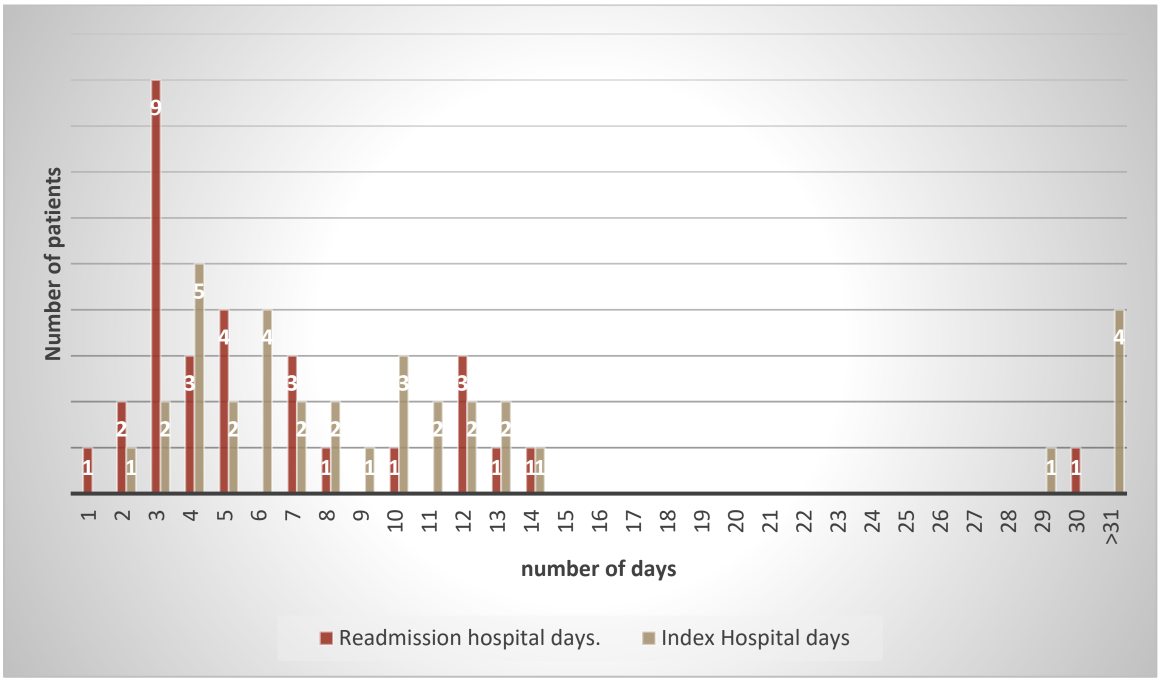
The all-cause readmission rate within 30 days from index hospitalisation discharge was 15.3% (n = 34). Stratified by procedure type, 8.1% of patients who underwent less than a minor hepatectomy were readmitted whereas 6.7% of patients who underwent a greater hepatectomy were readmitted (n = 15). The median time to readmission was 8 days (IQR: 5,12)

Table 12: Readmission analyses

Variable		Total cohort (n = 222) M=20	No readmission (n=168) M= 0	Readmission (n=35) M=0	
Comorbidities (%)		64/222 (28.82)	53/168 (31.54)	11/35 (31.42)	0.989
	CVS (%)	42/222 (18.91)	36/168 (21.42)	6/35 (17.14)	0.57
	Diabetes (%)	20/222 (9)	16/168 (9.52)	4/35 (11.43)	0.8
	Renal (%)	10/222 (4.5)	7/168 (4.17)	3/35 (8.57)	0.3
	Respiratory (%)	3/222 (1.35)	3/168 (1.78)	0/35 (0)	>0.9

The primary duration of stay was different in patients that had one admission versus those who were readmitted later (median of 7 vs 8 days; Not surprisingly, patients who were readmitted had a longer total duration of stay (median, 8 days;(range 5-12) than all other patients.

Figure 15: Grapth showing the frequeny number of days of index admission and readmission



Among those patients readmitted, early readmission was common as 52.94% (n = 18 out of 34 patients who were readmitted). Patients were readmitted within 1 week of discharge (figure above). Among the patients readmitted, the median LOS for the first hospitalisation was 8 (IQR:5,12) days. Of note, 7 (20.58%) required a second operation owing to peri-operative complications whereas no patients experienced in-hospital mortality after readmission.

Figure 16: Number of days between index discharge and readmission

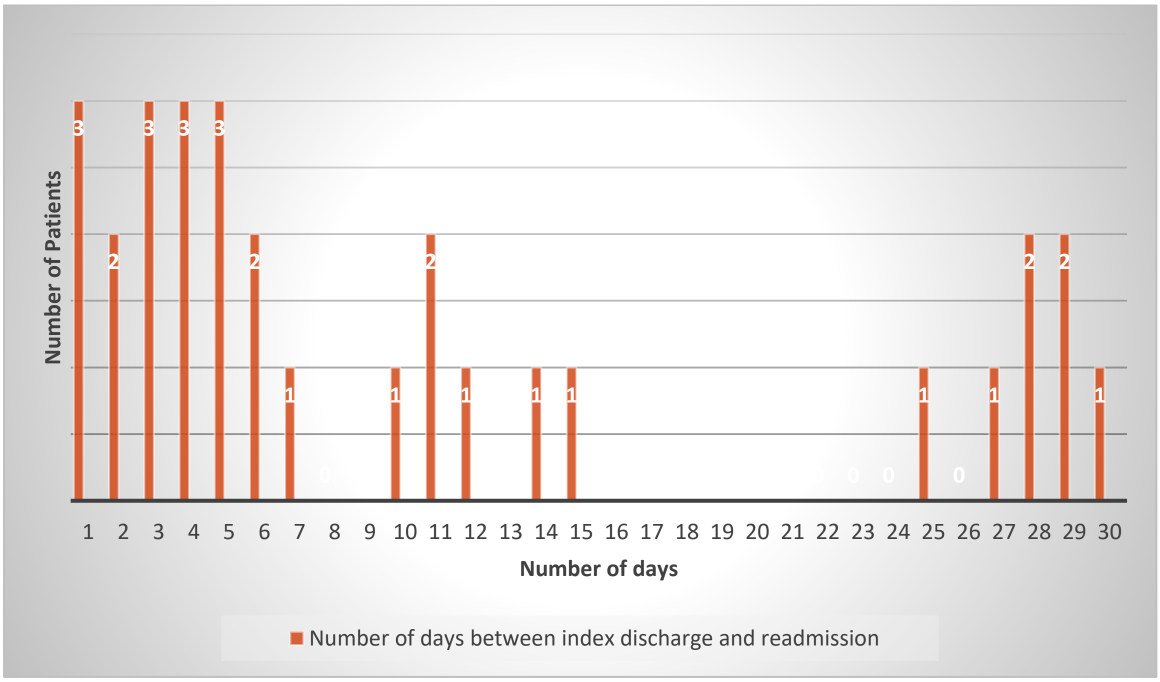
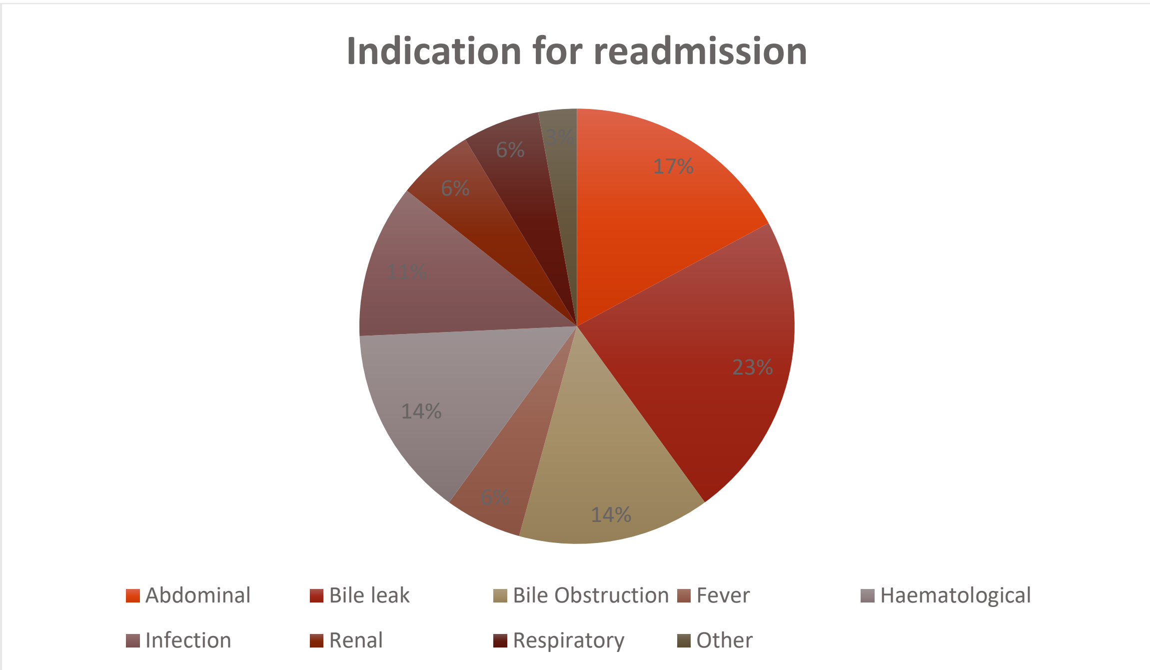


Figure 17: Indications for readmissions after a hepatectomy



The majority of the readmissions were for bile leak and bile obstruction (n = 8, 23%, and 5, 14% respectively), as well as abdominal (gastrointestinal) issues (n = 6, 17%) including sub-occlusion, abdominal pain, perforation and fistula.

Table 13: Logistic regression analysis of variables associated with 30-day readmission

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	**P-Value**	**OR**	**95% CI**	**P-Value**
Age > =62	0.92	0.45-1.91	0.828			
Male gender	1.05	0.50-2.21	0.895			
BMI > = 25	1.32	0.48-3.59	0.587			
ASA 1	Ref					
ASA 2	0.09	0.007-1.06	0.056			
ASA 3	0.06	0.005-0.81	0.0335			
ASA 4	0	0-Inf	0.9859			
How many times has the patient been re-resected (Liver)? > 1	2.93	1.26 – 6.78	0.0122	3.26	1.20 - 8.85	0.0204
Operation time (mins) > 330	1.01	0.47 - 2.16	0.975			
High care stays (ICU) (days) >= 1	4.24	0.49 – 36.66	0.18974			
30-day post-operative Complication = Yes	1.10	0.19 – 6.21	0.91			
Post-operative Bile leak = No	0.30	0.09 – 0.94	0.0386	0.17	0.03 - 0.87	0.0337
Procedure_number First	Ref					
Procedure_number Second	2.41	1.12 – 5.21	0.0247			
Procedure_number Third	5.73	1.16 – 28.31	0.0321			
Comorbidity	0.99	0.45 – 2.18	0.989			
CVS (Comorbidity)	0.76	0.29 – 1.97	0.57			
Other Minor comorbidity	1.42	0.29 – 6.82	0.6617			
Previous Liver Resection	2.06	0.93 – 4.54	0.0748			
Previous MWA = No	0.08	0.01 – 0.46	0.0048	0.05	0.004 - 0.59	0.018
Synchronous Liver Mets = No	0.05	0.005 – 0.49	0.0099	0.17	0 – 32.82	0.508
Neo-adjuvant chemotherapy	0.6	0.10 – 3.55	0.576			
Grade of complication (Clavien Dindo): No complication	Ref					
Grade of complication (Clavien Dindo): Grade I-II	2.86	1.28 – 6.35	0.0099			
Grade of complication (Clavien Dindo): Grade III-IV	4.2	1.11 – 15.86	0.0342			

Biliary stent	6.83	1.27 – 36.58	0.0248			
Complexity of resection: Missing data	Ref					
Complexity of resection: Minor	0.48	0.09 – 2.55	0.388			
Complexity of resection: Major	1.00	0.18 – 5.53	10.4			
Complexity of resection: Technically major	0.43	0.03 – 5.98	0.529			

OD *– Odds Ratio,* ***CI****- Confidence Interval.*

Several clinical factors were associated with an increased risk of readmission after a hepatic resection. While patient male gender [odds ratio (OR) 1.05, 95% confidence interval (CI) 0.50 - 2.21], older age (OR 0.92, 95% CI 0.45 - 1.91) and the presence of multiple medical comorbidities (OR 0.99, 95% CI 0.45 – 2.18) were not associated with an increased risk of readmission (all P > 0.05), other patient-specific factors including if the patient has been re-resected more than one time (OR 2.93, 95% CI 1.26 – 6.78) were associated with a higher likelihood of readmission (P < 0.05). In contrast, an ASA score equal to 3 with a score equal to 1 as reference level (OR 0.06, CI 0.005 – 0.81) is associated with a lower likelihood of readmission (P < 0.05).

Interestingly, no pathological or operative factors were associated with an increased risk of readmission. In particular, an operative time greater than median (OR 1.01, 95% CI 0.47 – 2.16) and the complexity of the resection (taking patients with missing information about the complexity as reference level, a minor complexity lead to OR 0.48, 95 % CI 0.09 – 2.55, a major complexity lead to OR 1.00, 95 % CI 0.18 – 5.53, and a technically major complexity lead to OR 0.43, 95 % CI 0.03 – 5.98) did not impact a patient's likelihood of readmission (P > 0.05).

A number of post- operative factors were not associated with an increased risk of read-mission. These post-operative factors included an ICU LOS ≥ 1 days (OR 4.24, 95% CI 0.49 – 36.66) and the presence of a 30-day post-operative complication (OR 1.10, 95 % CI 0.19 – 6.21), resulting in P > 0.05.

Patients experiencing a major complication during the index hospitalization were also at a much higher risk for readmission (Clavien–Dindo grade 3 and 4: OR 4.2, 95% CI 1.11 – 15.86; P < 0.05).

In fact, about half of readmitted patients (n = 18, 51.4%) had had a peri-operative complication prior to readmission.

6. DISCUSSION

Unplanned readmissions following hospitalization are prevalent and impact patients across various medical and surgical disciplines. The rates of readmission are significant as they may act as an indirect indicator of the quality of care provided by healthcare professionals and institutions. Consequently, it is crucial to analyse the identified the common causes, trends, and factors linked to readmissions to enhance the quality of patient care.

Moreover, research indicates that readmissions can adversely affect both short- and long-term survival rates, as well as the quality of life reported by patients. Patients who undergo complex surgical interventions are particularly vulnerable to readmission. Previous investigations have explored readmission rates, patterns, and contributing factors in patients following colorectal, mixed hepatobiliary, and pancreatic resections. The current study is noteworthy as it specifically analyzes the factors associated with readmission in patients undergoing hepatic resections for colorectal liver metastases (CRLM).

A prior study that identified 9,957 individuals aged 66yrs and older in USA reported a readmission rate of 16.4% among patients undergoing mixed hepatopancreatobiliary resections, utilizing population-based national data by Eric B Schneider. [207]

In this study, a 30-day all-cause readmission rate of 15.2% was observed among patients undergoing only hepatic resection at a prominent tertiary HPB institution, the General Surgery Complex Operational Unit 2 - Surgery Hepatobiliopancreatic and Liver Transplants at the Hospital - University of Padua.

Notably, several patient and perioperative factors were identified that correlated with an increased risk of readmission. Specifically, patients who experienced a complication during their initial hospitalization faced a two-fold higher risk of readmission.

Analysing factors that are associated with readmission is crucial as it may help guide management in these high-risk patients, as well as potentially identify areas to target to decrease readmission. Unsurprisingly a major hepatectomy (=/> 3 segments) was associated with a higher readmission rate, differently than previously reported [208]. While the reason for this is probably multi-factorial, it may be as a result of the fact that more and more hepatic resections are ‘parenchymal sparing’ in nature (e.g. not ‘formal’ hemi-hepatectomies), yet still can be technically major in nature and, on occasion, lead to more blood loss because of being non-anatomic dissections.

A variety of factors including increasing index hospitalization LOS and the presence of post-operative complications have previously been reported to be associated with increased readmission after a number of different surgical procedures [209] [210] [211] [212]. Given that these previous studies included patients undergoing a variety of surgical operations, the data may not be generalizable to patients undergoing a hepatectomy. In this study, patients with post-operative major complications (*P*-value 0.0343) were more likely to be readmitted than those with minor complications (*P*-value 0.00992). Among those readmitted, the median LOS for the first hospitalisation was 8 (IQR: 5,12) days.

The majority of the readmission indicators were bile leak and bile obstruction (n =8, 23% and 5, 14% respectively as well as abdominal (gastrointestinal)issues including sub occlusions, abdominal pain, perforations and fistula; n = 6, 17%). There was no similar study found to analyse the indications of readmission in patients undergoing hepatic surgical resection for CRLM.

In one recent study examining readmission in patients after a hepatectomy, Barbas *et al*. observed a 90-day readmission rate of 14.4% that was nearly identical to the incidence of readmission reported in the present study for a similar cohort of patients [208]. In Contrast to this study, we examined thirty-day readmission and observed a rate of 15.2%.

While the present study showed that patients who experienced a major post- operative complication during the index hospitalization were at a much higher risk of readmission (Clavien–Dindo grade 3 and 4: OR 4.2, 95% CI 1.11–15.86; $P > 0.001$), it failed to find an independent association between readmission risk in male gender [odds ratio (OR) 1.05, 95% confidence interval (CI) 0.50 - 2.21], older age (OR 0.92, 95% CI 0.45 - 1.91) and the presence of multiple medical comorbidities (OR 0.99, 95% CI 0.45 – 2.18) with an increased risk of readmission. The reason for these disparate results may be related to differences in the incidence of morbidity after a hepatectomy that can often impact both age and readmission.

Whereas biliary complications like bile leak and bile obstruction were not common during index admission as much as other gastrointestinal, hematologic and respiratory complications, they were the most frequent cause of readmission in this study.

In the study by Barbas *et al*., the authors found that patients who experienced a major complication and who had an index hospitalization > 7 days were at highest risk for readmission [208]. similar to this study. Evidently, readmitted patients had an index admission median LOS of 8 (5,12) days compared to the general cohort 7 (4.5,11) days. It appears clear that early discharge of appropriate patients is safe and does not necessarily lead to increased readmission. In fact, several groups have recently advocated fast- track or enhanced recovery programmes after a liver resection and have noted that it was safe and effective, as well as did not result in higher rates of readmission [213].

There are several limitations that need to be considered when interpreting the data. First, as with all retrospective studies of this nature, selection bias was possible. If a patient had been selected differently (e.g. older, sicker patients), the incidence of readmission may have been higher. Also noted that there was incomplete data in patient database, this could have skewed the incidence of readmission. Given that the data were based on the experience of one specialized HPB centre, the data may not be generalizable to other institutions or patient populations. It is reassuring, however, that the data noted herein independently confirmed a comparable incidence of readmission among HPB patients previously reported by other researchers.

Lastly, the data are limited to patients who were readmitted only to General Surgery team 2 of the Hospital - University of Padua. About half of the patients admitted at this centre are not residents Veneto region. While it is possible that patients sought care and were readmitted at other institutions, it is relatively unlikely as most patients remain in the local area for 1–2 weeks after surgery. While the number of patients readmitted to outside hospitals is likely minimal, such a detection bias would have – if anything – resulted in an underestimation of the incidence of readmission.

7. CONCLUSION

In conclusion, readmission after a hepatic resection is common and occurs in approximately one out of every six patients. Patients who experience a post-operative complication are over five times more likely to be readmitted. In a cost analysis, readmission has a negative impact for the health system and resources.

This thesis underscores the importance of comprehensive preoperative assessment, optimized perioperative care, and targeted postoperative interventions to mitigate readmission risk among CRLM patients. Strategies aimed at addressing modifiable risk factors and improving care transitions may contribute to reducing readmission rates, enhancing patient outcomes, and optimizing resource utilization in this patient population

Further prospective studies are needed to evaluate potential methods to reduce these unplanned readmissions.

GLOSSARY

2-FU	5-Fluorouracil
AJJC	American Joint Committee on Cancer
ALPPS	Association of Liver Partition with Portal vein ligation for Staged hepatectomy
ASA	American society of Anaesthesiologists
BMI	Body Mass Index
BRAF	B-Raf proto-oncogene
CA	cryoablation
CALI	Chemotherapy-Associated Liver Injury
CAPOX	Capecitabine and Oxaliplatin
CASH	chemotherapy-associated steatohepatitis
CEA	Carcinoembryonic antigen
CEUS	contrast-enhanced ultrasound
CI	Confidence Interval
cM	Clinical metastasis
cN	Clinical nodes
COPD	Chronic Obstructive Pulmonary disease
CRLM	Colorectal Liver Metastasis
cT	Clinical Tumour (grading)
CT	Computerised Tomography
DFS	Disease-free survival
DM	Diabetes
ECOG	Eastern cooperative Oncology Group
eGFR	Estimate Glomerular Filtration Rate
EGOSLIM	Expert Group on OncoSurgery Management of Liver Metastases
ESMO	European Society of Medical Oncology
EHR	Extrahepatic relapse
FDG	Fluorine-8-deoxyglucose
FOLFOX	Leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin
FRL	Future Remnant Liver
HESC	Hepatic Stellate Cells
HVE	hepatic vein embolization
IBD	inflammatory bowel diseases
ICG	indocyanine green
ICU	Intensive Care Unit
ID	Identity
IHR	Intrahepatic relapse
IOUS	Intra-operative ultrasound
IQR	Inter quartile range
ISGLS	International Study Group for Liver Surgery
KC	Kupffer cells
LLR	Laparoscopic Liver Resection
LME	Liver micro environment

MDSC	Myeloid -derived suppressor cells
MEM	Metachronous liver metastasis
MES	Synchronous liver metastasis
MILR	minimally invasive liver surgery
MIS	Minimally Invasive Surgery
MSI	microsatellite instability
LVD	Liver venous deprivation
MRI	Magnetic resonance Imaging
MSI	magnetic resonance imaging
MWA	Microwave Ablation
NASH	Nonalcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NED	No Evidence of Disease
NHS	National health System
NSAIDS	Nonsteroidal Anti-inflammatory Drugs
OLT	Orthotopic liver transplantation
ORC	Oligometric colorectal cancer
OCRC	Oligometastatic colorectal cancer
OS	Overall survival
PET	positron emission tomography
PHLF	Post Hepatectomy Liver Failure
PSR	Parenchymal-Sparing Resection
PSM	propensity score matching
PVE	portal vein embolization
PVL	Portal vein ligation
RLM	Recurrent liver metastasis
RO	Zero Residual
SOS	Sinusoidal obstruction syndrome
TBS	Tumour Burden Score
TNM	Tumour Nodes Metastasis
UICC	Union for International Cancer Control
WHO	World health Organisation
ADEs	Adverse Drug Events
RFA	Radiofrequency ablation

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